PIMD: 35475386

Corpus callosum damage to account for cognitive, affective, and social-cognitive dysfunctions in multiple sclerosis: A model of callosal disconnection syndrome?

The corpus callosum (CC) is the major commissure interconnecting the two hemispheres and is particularly affected in multiple sclerosis (MS). In the present review, we aimed to investigate the role played by callosal damages in the pathogenesis of MS-related dysfunctions and examine whether a model of callosal disconnection syndrome is a valid model for MS. For this purpose, we will first review structural and functional evidence of callosal pathology in MS. Second, we will account for the potential role of CC abnormalities in MS-related dysfunctions. Finally, we will report data concurring with a "multiple disconnection hypothesis" that has been proposed to explain those dysfunctions, and we will examine evidence pointing toward MS as a "callosal disconnection syndrome." We will end by discussing the contribution of this interpretation to the understanding of MS and MS-related deficits.

PIMD: 35452961

Magnetic resonance imaging criteria at onset to differentiate pediatric multiple sclerosis from acute disseminated encephalomyelitis: A nationwide cohort study.

MRI of the nervous system is the critical in distinguishing pediatric MS from acute disseminated encephalomyelitis (ADEM). Our aim was to propose MRI criteria to distinguish MS from monophasic ADEM based on the first MRI and to validate previously proposed MRI criteria.A neuroradiologist undertook retrospective evaluation of the MRI at the first demyelinating event in children (<18 years) with medical record-validated MS and ADEM in Denmark during 2008-15. We used forward stepwise logistic regression to identify MRI categories that differed significantly between MS and ADEM. We estimated accuracy statistics for all MRI criteria to distinguish MS from ADEM.The monophasic ADEM cohort (n=46) was nationwide and population-based during 2008-15; the median age at onset of 5.3 years (range 0.8–17.2) and children had at least five years of follow-up to ensure a monophasic disease course. Children with MS (n=67) had a median age at onset of 16.3 years (range 3.3–17.9). Having at least two categories best distinguished MS from monophasic ADEM by an area under the curve of 83% to 89%: (a) corpus callosum long axis perpendicular lesion; (b) only well-defined lesions; (c) absence of basal ganglia or thalamus lesion OR, (a) corpus callosum long axis perpendicular lesion; (b) only well-defined lesions; (c) absence of diffuse large lesions; (d) black holes. The Callen, KIDMUS, and IPMSSG criteria performed well. The McDonald 2017, Barkhof, MAGNIMS, and Verhey criteria had poorer performance.This study provides Class II evidence that MRI has good performance in differentiating MS from monophasic ADEM at onset.

PIMD: 35422470

Mouse models of immune dysfunction: their neuroanatomical differences reflect their anxiety-behavioural phenotype.

Extensive evidence supports the role of the immune system in modulating brain function and behaviour. However, past studies have revealed striking heterogeneity in behavioural phenotypes produced from immune system dysfunction. Using magnetic resonance imaging, we studied the neuroanatomical differences among 11 distinct genetically modified mouse lines (n = 371), each deficient in a different element of the immune system. We found a significant and heterogeneous effect of immune dysfunction on the brains of both male and female mice. However, by imaging the whole brain and using Bayesian hierarchical modelling, we were able to identify patterns within the heterogeneous phenotype. Certain structures-such as the corpus callosum, midbrain, and thalamus-were more likely to be affected by immune dysfunction. A notable brain-behaviour relationship was identified with neuroanatomy endophenotypes across mouse models clustering according to anxiety-like behaviour phenotypes reported in literature, such as altered volume in brains regions associated with promoting fear response (e.g., the lateral septum and cerebellum). Interestingly, genes with preferential spatial expression in the most commonly affected regions are also associated with multiple sclerosis and other immune-mediated diseases. In total, our data suggest that the immune system modulates anxiety behaviour through well-established brain networks.

PIMD: 35406658

Development of a Chemical Cocktail That Rescues Mouse Brain Demyelination in a Cuprizone-Induced Model.

Oligodendrocytes are glial cells located in the central nervous system (CNS) that play essential roles in the transmission of nerve signals and in the neuroprotection of myelinated neurons. The dysfunction or loss of oligodendrocytes leads to demyelinating diseases such as multiple sclerosis (MS). To treat demyelinating diseases, the development of a therapy that promotes remyelination is required. In the present study, we established an in vitro method to convert human fibroblasts into induced oligodendrocyte-like cells (iOLCs) in 3 days. The induced cells displayed morphologies and molecular signatures similar to oligodendrocytes after treatment with valproic acid and exposure to the small molecules Y27632, SU9516, and forskolin (FSK). To pursue the development of a cell-free remyelination therapy in vivo, we used a cuprizone-induced demyelinated mouse model. The small molecules (Y27632, SU9516, and FSK) were directly injected into the demyelinated corpus callosum of the mouse brain. This combination of small molecules rescued the demyelination phenotype within two weeks as observed by light and electron microscopy. These results provide a foundation for exploring the development of a treatment for demyelinating diseases via regenerative medicine.

PIMD: 35398999

Brain atrophy patterns in multiple sclerosis patients treated with natalizumab and its clinical correlates.

Multiple sclerosis (MS) is defined as a demyelinating disorder of the central nervous system, witnessing over the past years a remarkable progress in the therapeutic approaches of the inflammatory process. Yet, the ongoing neurodegenerative process is still ambiguous, under-assessed, and probably under-treated. Atrophy and cognitive dysfunction represent the radiological and clinical correlates of such process. In this study, we evaluated the effect of one specific MS treatment, which is natalizumab (NTZ), on brain atrophy evolution in different anatomical regions and its correlation with the cognitive profile and the physical disability.We recruited 20 patients diagnosed with relapsing-remitting MS (RR-MS) and treated with NTZ. We tracked brain atrophy in different anatomical structures using MRI scans processed with an automated image segmentation technique. We also assessed the progression of physical disability and the cognitive function and its link with the progression of atrophy.During the first 2 years of treatment, a significant volume loss was noted within the corpus callosum and the cerebellum gray matter (GM). The annual atrophy rate of the cortical GM, the cerebellum GM, the thalamus, the amygdala, the globus pallidus, and the hippocampus correlated with greater memory impairment. As for the third and fourth years of treatment, a significant atrophy revolved around the gray matter, mainly the cortical one. We also noted an increase of the thalamus volume.Atrophy in RR-MS patients treated with NTZ is regional and targeting highly cognitive regions mainly of the subcortical gray matter and the cerebellum. The cerebellum atrophy was a marker of physical disability progression. NTZ did not accelerate the atrophy process in MS and may play a neuroprotective role by increasing the thalamus volume.

PIMD: 35397753

Advanced diffusion-weighted imaging models better characterize white matter neurodegeneration and clinical outcomes in multiple sclerosis.

White matter (WM) atrophy is relevant in multiple sclerosis (MS), but the methods of analysis currently used are not specific for microstructural changes. The aims of this study were to assess the use of advanced diffusion-weighted imaging (DWI) techniques proposed as measures of baseline and longitudinal WM atrophy in MS and to analyze whether these measures helped explain MS clinical disability (including cognitive impairment) better than volumetric and diffusion tensor (DT)-derived measures.3DT1-weighted and DWI sequences were applied to 86 MS and 55 healthy controls (HC) at baseline and after one-year. Intra-cellular volume (v) maps were computed from neurite orientation dispersion and density imaging model. Voxel-wise fiber-bundle cross-section (FCS) atrophy in MS compared to HC was estimated. Maps of fractional anisotropy and mean diffusivity were also obtained from DWI for a comparison with the proposed advanced DW-derived measures (v and FCS).Both at baseline and after 1-year, only FCS measure showed a significant atrophy in relapsing-remitting (RR) MS compared to HC and in progressive MS compared to RRMS, mainly located in specific WM tracts (corticospinal tract, splenium of the corpus callosum, left optic radiation, bilateral cingulum, middle cerebellar peduncle and anterior commissure, p value < 0.05). Global baseline FCS and v were the selected predictors of clinical (R-sq = 0.33, p = 0.007) and cognitive scores (R-sq = 0.29, p = 0.0014) in a linear regression model.Voxel-based FCS was able to detect WM tracts atrophy in MS clinical phenotypes with greater anatomical specificity compared to other measures (volumetric and DT-derived measures of WM damage). FCS and v measured at baseline in the WM were the best predictors of clinical disability and cognitive impairment.

PIMD: 35380252

Astroglial and oligodendroglial markers in the cuprizone animal model for de- and remyelination.

Myelin loss with consecutive axon degeneration and impaired remyelination are the underlying causes of progressive disease in patients with multiple sclerosis. Astrocytes are suggested to play a major role in these processes. The unmasking of distinct astrocyte identities in health and disease would help to understand the pathophysiological mechanisms in which astrocytes are involved. However, the number of specific astrocyte markers is limited. Therefore, we performed immunohistochemical studies and analyzed various markers including GFAP, vimentin, S100B, ALDH1L1, and LCN2 during de- and remyelination using the toxic murine cuprizone animal model. Applying this animal model, we were able to confirm overlapping expression of vimentin and GFAP and highlighted the potential of ALDH1L1 as a pan-astrocytic marker, in agreement with previous data. Only a small population of GFAP-positive astrocytes in the corpus callosum highly up-regulated LCN2 at the peak of demyelination and S100B expression was found in a subset of oligodendroglia as well, thus S100B turned out to have a limited use as a particular astroglial marker. Additionally, numerous GFAP-positive astrocytes in the lateral corpus callosum did not express S100B, further strengthening findings of heterogeneity in the astrocytic population. In conclusion, our results acknowledged that GFAP, vimentin, LCN2, and ALDH1L1 serve as reliable marker to identify activated astrocytes during cuprizone-induced de- and remyelination. Moreover, there were clear regional and temporal differences in protein and mRNA expression levels and patterns of the studied markers, generally between gray and white matter structures.

PIMD: 35372341

Clemastine Induces an Impairment in Developmental Myelination.

Abnormalities in myelination are associated to behavioral and cognitive dysfunction in neurodevelopmental psychiatric disorders. Thus, therapies to promote or accelerate myelination could potentially ameliorate symptoms in autism. Clemastine, a histamine H1 antagonist with anticholinergic properties against muscarinic M1 receptor, is the most promising drug with promyelinating properties. Clemastine penetrates the blood brain barrier efficiently and promotes remyelination in different animal models of neurodegeneration including multiple sclerosis, ischemia and Alzheimer's disease. However, its role in myelination during development is unknown. We showed that clemastine treatment during development increased oligodendrocyte differentiation in both white and gray matter. However, despite the increase in the number of oligodendrocytes, conduction velocity of myelinated fibers of decreased in clemastine treated mice. Confocal and electron microscopy showed a reduction in the number of myelinated axons and nodes of Ranvier and a reduction of myelin thickness in . To understand the mechanisms leading to myelin formation impairment in the presence of an excess of myelinating oligodendrocytes, we focused on microglial cells that also express muscarinic M1 receptors. Importantly, the population of CD11c microglia cells, necessary for myelination, as well as the levels of insulin growth factor-1 decrease in clemastine-treated mice. Altogether, these data suggest that clemastine impact on myelin development is more complex than previously thought and could be dependent on microglia-oligodendrocyte crosstalk. Further studies are needed to clarify the role of microglia cells on developmental myelination.

PIMD: 35362723

Phenytoin promotes the proliferation of oligodendrocytes and enhances the expression of myelin basic protein in the corpus callosum of mice demyelinated by cuprizone.

Oligodendrocyte loss and myelin sheet destruction are crucial characteristics of demyelinating diseases. Phenytoin promotes the proliferation of endogenous neural precursor cells in the ventricular-subventricular zone in the postnatal brain that help restore the oligodendroglial population. This study aimed to evaluate whether phenytoin promotes myelin recovery of the corpus callosum of demyelinated adult mice. CD1 male mice were exposed to a demyelinating agent (0.2% cuprizone) for 8 weeks. We assembled two groups: the phenytoin-treated group and the control-vehicle group. The treated group received oral phenytoin (10 mg/kg) for 4 weeks. We quantified the number of Olig2 + and NG2 + oligodendrocyte precursor cells (OPCs), Rip + oligodendrocytes, the expression level of myelin basic protein (MBP), and the muscle strength and motor coordination. The oligodendroglial lineage (Olig2 + cells, NG2 + cells, and RIP + cells) significantly increases by the phenytoin administration when compared to the control-vehicle group. The phenytoin-treated group also showed an increased expression of MBP in the corpus callosum and better functional scores in the horizontal bar test. These findings suggest that phenytoin stimulates the proliferation of OPCs, re-establishes the oligodendroglial population, promotes myelin recovery in the corpus callosum, and improves motor coordination and muscle strength.

PIMD: 35326340

An Equivocal SCC Lesion-Antiepileptic-Induced CLOCC.

We present a case of a woman who reported to the emergency unit due to recurrent episodes of severe headache and collapse. MRI examination revealed no relevant findings apart from small meningioma of the right parietal region. The patient was diagnosed with epilepsy and received outpatient treatment, which was changed due to poor toleration. A follow-up MRI was performed which revealed an isolated, focal lesion of the splenium of the corpus callosum. The patient underwent extensive laboratory testing and antiseizure medications were started again. Another MRI indicated substantial regression of the splenium of the corpus callosum (SCC) lesion. Both the complete clinical image and results of the diagnostic evaluation spoke in favor of cytotoxicity of the corpus callosum associated with anti-epileptic drug treatment. Pathologies involving the corpus callosum include congenital, demyelination, infection, neoplasm, trauma and vascular changes. Isolated, non-specific lesions of the splenium of corpus callosum usually indicate multiple sclerosis; however, other pathologies should be considered. Anti-epileptic drugs may evoke cytotoxic lesions of the corpus callosum (CLOCCs).

PIMD: 35310094

Diffusion Tensor Imaging Revealed Microstructural Changes in Normal-Appearing White Matter Regions in Relapsing-Remitting Multiple Sclerosis.

Axons and myelin sheaths are the physical foundation for white matter (WM) to perform normal functions. Our previous study found the metabolite abnormalities in frontal, parietal, and occipital normal-appearing white matter (NAWM) regions in relapsing-remitting multiple sclerosis (RRMS) patients by applying a 2D H magnetic resonance spectroscopic imaging method. Since the metabolite changes may associate with the microstructure changes, we used the diffusion tensor imaging (DTI) method to assess the integrity of NAWM in this study.Diffusion tensor imaging scan was performed on 17 clinically definite RRMS patients and 21 age-matched healthy controls on a 3.0-T scanner. DTI metrics including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were extracted from 19 predefined regions of interest (ROIs), which were generated by removing a mask of manually drawn probabilistic lesion map from the Johns Hopkins University white-matter atlas. The mean values of FA, MD, AD, and RD were compared between different groups in the same ROIs.A probabilistic lesion map was successfully generated, and the lesion regions were eliminated from the WM atlas. We found that the RRMS patients had significantly lower FA in the entire corpus callosum (CC), bilateral of anterior corona radiata, and right posterior thalamic radiation (PTR). At the same time, RRMS patients showed significantly higher MD in the bilateral anterior corona radiata and superior corona radiata. Moreover, all AD values increased, and the bilateral external capsule, PTR, and left tapetum NAWM show statistical significance. What is more, all NAWM tracts showed increasing RD values in RRMS patients, and the bilateral superior corona radiata, the anterior corona radiata, right PTR, and the genu CC reach statistical significance.Our study revealed widespread microstructure changes in NAWM in RRMS patients through a ready-made WM atlas and probabilistic lesion map. These findings support the hypothesis of demyelination, accumulation of inflammatory cells, and axonal injury in NAWM for RRMS. The DTI-based metrics could be considered as potential non-invasive biomarkers of disease severity.

PIMD: 35285112

Ermin deficiency leads to compromised myelin, inflammatory milieu, and susceptibility to demyelinating insult.

Ermin is an actin-binding protein found almost exclusively in the central nervous system (CNS) as a component of myelin sheaths. Although Ermin has been predicted to play a role in the formation and stability of myelin sheaths, this has not been directly examined in vivo. Here, we show that Ermin is essential for myelin sheath integrity and normal saltatory conduction. Loss of Ermin in mice caused de-compacted and fragmented myelin sheaths and led to slower conduction along with progressive neurological deficits. RNA sequencing of the corpus callosum, the largest white matter structure in the CNS, pointed to inflammatory activation in aged Ermin-deficient mice, which was corroborated by increased levels of microgliosis and astrogliosis. The inflammatory milieu and myelin abnormalities were further associated with increased susceptibility to immune-mediated demyelination insult in Ermin knockout mice. Supporting a possible role of Ermin deficiency in inflammatory white matter disorders, a rare inactivating mutation in the ERMN gene was identified in multiple sclerosis patients. Our findings demonstrate a critical role for Ermin in maintaining myelin integrity. Given its near-exclusive expression in myelinating oligodendrocytes, Ermin deficiency represents a compelling "inside-out" model of inflammatory dysmyelination and may offer a new paradigm for the development of myelin stability-targeted therapies.

PIMD: 35280835

Locomotor and histological changes in a cuprizone-induced animal model of multiple sclerosis: comparison between alpha-tocopherol and fingolimod.

Fingolimod is a sphingosine 1-phosphate receptor modulator used to treat multiple sclerosis (MS). Alpha-tocopherol (AT) has been found to improve motor function in an animal model of MS. In the present study, the effects of AT and fingolimod on the locomotor function and histological evidence of demyelination were compared in a cuprizone-induced rat model of MS.Female Sprague-Dawley rats (8 weeks) were fed with 0.2% (w/w) cuprizone diet for 5 weeks followed by intraperitoneal injections of fingolimod (3 mg/Kg; group F, n = 10) and alpha- tocopherol (100 mg/Kg; group A, n = 10). Vehicle-treated rats (group V, n = 10) were treated intraperitoneally with 1% ethanol in saline on weeks 6 and 7. Open field and beam walking tests were carried out every 10 days. The mean area of demyelination in the corpus callosum was quantified using Luxol fast blue stained histological sections of the forebrain.The mean speed of movement was increased by 54% and 50% in groups F and A compared to group V. Total distance moved was increased by 61% and 52.7% in groups F and A compared to group V. Mean time to walk the beam was reduced in group A by 52% compared to group V. Mean frequency of crossing lines from the inner squares to outer squares was reduced in groups A and F compared to group V. Mean area of demyelination in corpus callosum showed 62% reduction in group A compared to group V.Both fingolimod and AT treatments improved the locomotor function. However, AT treatment reduced the areas of demyelination in higher proportion and improved motor coordination and exploratory behavior.

PIMD: 35265555

Adult-onset Mild Encephalitis/Encephalopathy with a Reversible Splenial Lesion Induced by MRSA Endocarditis.

Mild encephalitis/encephalopathy and a reversible splenial lesion (MERS) is a clinicoradiological syndrome with an unknown pathogenic mechanism, which usually involves children. Thus, adult-onset MERS is quite rare.A 71-year-old man, undergoing haemodialysis due to diabetes-induced chronic kidney disease, manifested a persistent fever and disorientation. Blood culture detected methicillin-resistant (MRSA), while echocardiography revealed vegetation in the aortic and mitral valves. Magnetic resonance imaging of the head revealed a fluid-attenuated inversion recovery-high, diffusion-weighted image-high lesion in the splenium of the corpus callosum, with a number of emboli. Accordingly, the patient was diagnosed with MERS induced by MRSA endocarditis.Neurological impairment by MERS can be reversible. However, the differential diagnosis of the disease includes ischaemic lesions, multiple sclerosis, malignant lymphoma, acute disseminated encephalomyelitis, and posterior reversible encephalopathy. Clinicians should consider these diseases when MERS is suspected.Adult-onset mild encephalitis/encephalopathy and a reversible splenial lesion (MERS) is quite rare, and physicians should be aware of it as a differential diagnosis of a diffusion-weighted image-high lesion in the splenium of the corpus callosum.Methicillin-resistant (MRSA) has rarely been reported as a triggering factor for MERS.

PIMD: 35263930

Tumefactive Demyelinating Brain Lesion Developing after Administration of Adenovector-Based COVID-19 Vaccine: A Case Report.

Postmarketing surveillance of COVID-19 vaccination reveals that the COVID-19 vaccine administration is associated with several rare but serious neurological complications.We report a case of new-onset tumefactive demyelinating brain lesion that developed after administration of an adenovector-based COVID-19 vaccine. A middle-aged female presented with recent right hemiparesis, which was noticed 2 days after she received the first dose of the vaccine. Magnetic resonance imaging (MRI) revealed a large subcortical T2/FLAIR hyperintensities involving corpus callosum as well. The patient responded to oral methylprednisolone. At 4 weeks, a follow-up MRI revealed a reduction in size of the lesion.To conclude, adenovector-based COVID-19 vaccination may be associated with a tumefactive demyelinating lesion.

PIMD: 35245521

Ceramide kinase knockout ameliorates multiple sclerosis-like behaviors and demyelination in cuprizone-treated mice.

Changes in sphingolipid metabolism regulate and/or alter many cellular functions in the brain. Ceramide, a central molecule of sphingolipid metabolism, is phosphorylated to ceramide-1-phosphate (C1P) by ceramide kinase (CerK). CerK and C1P were reported to regulate many cellular responses, but their roles in immune-related diseases in vivo have not been well elucidated. Thus, we investigated the effects of CerK knockout on the onset/progression of multiple sclerosis (MS), which is a chronic neurodegenerative disease accompanied by the loss of myelin sheaths in the brain. MS-model mice were prepared using a diet containing the copper chelator cuprizone (CPZ). Treatment of 8-week-old mice with 0.2% CPZ for 8 weeks resulted in motor dysfunction based on the Rota-rod test, and caused the loss of myelin-related proteins (MRPs) in the brain and demyelination in the corpus callosum without affecting synaptophysin levels. CerK knockout, which did not affect developmental changes in MRPs, ameliorated the motor dysfunction, loss of MRPs, and demyelination in the brain in CPZ-treated mice. Loss of tail tonus, another marker of motor dysfunction, was detected at 1 week without demyelination after CPZ treatment in a CerK knockout-independent manner. CPZ-induced loss of tail tonus progressed, specifically in female mice, to 6-8 weeks, and the loss was ameliorated by CerK knockout. Activities of ceramide metabolic enzymes including CerK in the lysates of the brain were not affected by CPZ treatment. Inhibition of CerK as a candidate for MS treatment was discussed.

PIMD: 35221622

Neuroimaging Features and Associated Factors in Multiple Sclerosis Patients: A Perspective from a Private Care Center in Addis Ababa, Ethiopia.

Brain and spine magnetic resonance image (MRI) have an invaluable importance in diagnosing multiple sclerosis (MS) in low prevalence countries such as Ethiopia. The objective of our study was to characterize the neuroimaging features and associated factors in Multiple sclerosis patients in Addis Ababa, Ethiopia.A cross-sectional observational study was conducted in 30 multiple sclerosis patients at Yehuleshet Specialty Clinic, Addis Ababa, Ethiopia. Both descriptive and analytical statistics were used to analyze the data.We have enrolled 30 patients with confirmed multiple sclerosis and clinically isolate syndrome. The mean age was 34.7 years (1SD=8.9). Female accounted 86.7%. The mean duration of illness was 3.4 years (1SD=3.1) (range: 1 - 11 years). Relapsing and remitting variant was the commonest sub type (66.7%). Alcohol use and head injury were the commonest identified risk factors reported by the patients. Classical radiological features of MS such as white matter lesions involving juxtacortical, U-fiber, corpus callosum (CC), and Dawson's finger projections pattern were observed in 46.7%, 23.3%, 70%, and 40% respectively. Cervical and thoracic cords were affected in 40% and 6.7% respectively. Global cortical and CC atrophy was observed in 16.7% and 6.7% respectively. Advanced age was associated with lesions of corpus callosum when adjusted for duration of illness and history of head injury (AOR 1.13, 95% CI 1.01-1.28, p=0.04).Typical neuroimaging features of MS were prevalent among Ethiopian MS patients. Age was an independent predictor of lesions involving corpus callosum. Global cortical atrophy was common among Ethiopian MS patients.

PIMD: 35216779

Quantification of normal-appearing white matter damage in early relapse-onset multiple sclerosis through neurite orientation dispersion and density imaging.

Background Neurodegeneration is a major contributor of neurological disability in multiple sclerosis (MS). The possibility to fully characterize normal appearing white matter (NAWM) damage could provide the missing information needed to clarify the mechanisms beyond disability accumulation. Objective In the present study we aimed to characterize the presence and extent of NAWM damage and its correlation with clinical disability. Methods We applied Diffusion Tensor Imaging (DTI) and Neurite Orientation Dispersion and Density Imaging (NODDI) in a cohort of 27 early relapse-onset MS patients (disease duration < 5 years) compared to a population of 26 age- and sex-matched healthy controls (HCs). All patients underwent a neurological examination, including the Expanded Disability Status Scale (EDSS). Results MS patients showed lower fractional anisotropy (FA) and higher mean diffusivity (MD) values in the main WM bundles, such as the corticospinal tract, corpus callosum, superior and middle cerebellar peduncles, posterior thalamic radiation (which includes optic radiation), cingulum and external capsule. All brain areas with reduced FA/increased MD also displayed a reduction in neurite density index (NDI). However, comparing individual voxels of the WM skeleton between MS and HCs, a higher number of NDI significant voxels was disclosed compared to FA/MD (56.4% vs 11.2%/41.2%). No significant correlations were observed between DTI/NODDI metrics and EDSS. Conclusions Our findings suggest that NDI may allow for a better characterization and understanding of the microstructural changes in the NAWM since the early relapsing-remitting MS phases. Future longitudinal studies including a larger cohort of patients with different clinical phenotypes may clarify the association between NODDI metrics and disability progression.

PIMD: 35195220

"Stable" vs. "silent progressive multiple sclerosis": a real-world retrospective clinical imaging Brazilian study.

Clinical and imaging are required to characterize activity and progression in MS. The parameters for activity are well defined but not those for progression. The ideal aim for long-term treatment is that neither clinical nor imaging signs of disease should be present, and also no brain atrophy.To conduct a comparative clinical-imaging study focusing on MRI brain volumetry.174 consecutive relapsing-remitting MS patients (McDonald 2001) were studied, focusing on activity and progression. Annual clinical evaluations (relapse rate and EDSS) and MRI data, along with the annualized evolution of the corpus callosum index (CCI), were compared.Out of 174 patients, 148 were considered clinically "stable" based on EDSS. However, 33 (22.2%) out of this group showed annualized reductions in CCI of more than 0.5%, which was the cutoff for defining significant brain atrophy.Among apparently "stable" relapsing-remitting MS patients, 1/5 showed significant brain atrophy over a follow-up period of at least 7 years. We consider it reasonable to suggest that MRI volume sequences should be included in follow-up protocols, so as to provide information on the real treatment response status.

PIMD: 35186315

Quantitative MRI findings indicate diffuse white matter damage in Susac Syndrome.

Susac Syndrome (SuS) is an autoimmune endotheliopathy impacting the brain, retina and cochlea that can clinically mimic multiple sclerosis (MS).To evaluate non-lesional white matter demyelination changes in SuS compared to MS and healthy controls (HC) using quantitative MRI.3T MRI including myelin water imaging and diffusion basis spectrum imaging were acquired for 7 SuS, 10 MS and 10 HC participants. Non-lesional white matter was analyzed in the corpus callosum (CC) and normal appearing white matter (NAWM). Groups were compared using ANCOVA with Tukey correction.SuS CC myelin water fraction (mean 0.092) was lower than MS(0.11, $p = 0.01$) and HC(0.11, $p = 0.04$). Another myelin marker, radial diffusivity, was increased in SuS CC(0.27μm2/ms) compared to HC(0.21μm2/ms, $p = 0.008$) and MS(0.23μm2/ms, $p = 0.05$). Fractional anisotropy was lower in SuS CC(0.82) than HC(0.86, $p = 0.04$). Fiber fraction (reflecting axons) did not differ from HC or MS. In NAWM, radial diffusivity and apparent diffusion coefficient were significantly increased in SuS compared to HC($p < 0.001$ for both measures) and MS($p = 0.003$, $p < 0.001$ respectively).Our results provided evidence of myelin damage in SuS, particularly in the CC, and more extensive microstructural injury in NAWM, supporting the hypothesis that there are widespread microstructural changes in SuS syndrome including diffuse demyelination.

PIMD: 35165979

Cortical and white matter lesion topology influences focal corpus callosum atrophy in multiple sclerosis.

Corpus callosum (CC) atrophy is a strong predictor of multiple sclerosis (MS) disability but the contributing pathological mechanisms remain uncertain. We aimed to apply advanced MRI to explore what drives the often nonuniform callosal atrophy.Prospective brain 7 Tesla and 3 Tesla Human Connectom Scanner MRI were performed in 92 MS patients. White matter, leukocortical, and intracortical lesions were manually segmented. FreeSurfer was used to segment the CC and topographically classify lesions per lobe or as deep white matter lesions. Regression models were calculated to predict focal CC atrophy.The frontal and parietal lobes contained the majority (≥80%) of all lesion classifications in both relapsing-remitting and secondary progressive MS subtypes. The anterior subsection of the CC had the smallest proportional volume difference between subtypes (11%). Deep, temporal, and occipital white matter lesions, and occipital intracortical lesions were the strongest predictors of middle-posterior callosal atrophy (adjusted $R = .54\text{-}.39$, $P < .01$).Both white matter and cortical lesions contribute to regional corpus callosal atrophy. The lobe-specific lesion topology does not fully explain the inhomogeneous CC atrophy.

PIMD: 35158445

Myelin imaging measures as predictors of cognitive impairment in MS patients: A hybrid PET-MRI study.

Cognitive impairment is one of the concerns of Multiple Sclerosis (MS) and has been related to myelin loss. Different neuroimaging methods have been used to quantify myelin and relate it to cognitive dysfunctions, among them Magnetization Transfer Ratio (MTR), Diffusion Tensor Imaging (DTI), and, more recently, Positron Emission Tomography (PET) with C-PIB.To investigate different myelin imaging modalities as predictors of cognitive dysfunction.Fifty-one MS patients and 24 healthy controls underwent clinical and neuropsychological assessment and MTR, DTI (Axial Diffusion-AD and Fractional Anisotropy-FA maps), and C-PIB PET images in a PET/MR hybrid system.MTR and DTI(FA) differed in patients with or without cognitive impairment. There was an association of DTI(FA) and DTI(AD) with cognition and psychomotor speed for progressive MS, and of C-PIB uptake and MTR for relapsing-remitting MS. MTR in the Thalamus (β= -0.51, p = 0.021) and Corpus Callosum (β= -0.24, p = 0.033) were predictive of cognitive impairment. DTI-FA in the Caudate (β= -26.93, p = 0.006) presented abnormal predictive result.Lower myelin content by C-PIB uptake was associated with worse cognitive status. MTR was predictive of cognitive impairment in MS.

PIMD: 35123534

Neuroradiological differentiation of white matter lesions in patients with multiple sclerosis and Fabry disease.

White matter lesions (WML) in multiple sclerosis (MS) differ from vascular WML caused by Fabry disease (FD). However, in atypical cases the discrimination can be difficult and may vary between individual raters. The aim of this study was to evaluate interrater reliability of WML differentiation between MS and FD patients.Brain MRI scans of 21 patients with genetically confirmed FD were compared to 21 matched patients with MS. Pseudonymized axial FLAIR sequences were assessed by 6 blinded raters and attributed to either the MS or the FD group to investigate interrater reliability. Additionally, localization of WML was compared between the two groups.The median age of patients was 46 years (IQR 35-58). Interrater reliability was moderate with a Fleiss' Kappa of 0.45 (95%CI 0.3-0.59). Overall, 85% of all ratings in the MS group and 75% in the FD group were correct. However, only 38% of patients with MS and 33% of patients with FD were correctly identified by all 6 raters. WML involving the corpus callosum ($p < 0.001$) as well as juxtacortical ($p < 0.001$) and infratentorial lesions ($p = 0.03$) were more frequently observed in MS patients.Interrater reliability regarding visual differentiation of WML in MS from vascular WML in FD on standard axial FLAIR images alone is only moderate, despite the distinctive features of lesions in each group.

PIMD: 35111601

Perivascular space is associated with brain atrophy in patients with multiple sclerosis.

Perivascular space (PVS) is associated with neurodegenerative and neuroimmune diseases. Multiple sclerosis (MS) is traditionally a neuroimmune disease. However, studies show neurodegeneration also plays a vital role in MS. At present, most studies conclude severer PVS in MS is an imaging marker of neuroinflammation, while a 7T MRI study suggests that PVS in MS is associated with neurodegeneration.In this study, 82 MS patients (n=82) and 32 healthy controls (n=32) were enrolled. The following indexes were measured: the number, size and distribution of PVS, the PVS score, corpus callosum index (CCI), corpus callosum area (CCA), the ratio of the corpus callosum to the cranium (CCR), aligned third ventricle width (a3VW), and unaligned third ventricle width (u3VW).The PVS score (4 3, P=0.041), PVSs number (103.280±45.107 87.625±30.139, P=0.035), and enlarged perivascular spaces (EPVSs) number (9 1, P<0.001) of MS patients were significantly higher than in the healthy controls. PVSs number (23.5 13) and EPVSs number (1 0) in the basal ganglia (BG), and EPVSs number (3 0) in centrum semiovale (CSO) of MS patients were significantly higher than in the healthy controls, P<0.001. In MS patients, PVS was correlated with age and hypertension but not to the extended disability status scale (EDSS) score and other clinical data. In MS patients, PVS score was correlated with CCA (rs=0.272; P=0.013) and the CCR (rs=0.219; P=0.048), and PVSs number was correlated with CCA (rs=0.255; P=0.021), the correlation disappeared after adjusting hypertension and age. In MS patients in remission, PVSs number was correlated with CCA (rs=0.487; P=0.019), CCR (rs=0.479; P=0.021), and PVS score was correlated with CCA (rs=0.453; P=0.03). After adjustment of hypertension and age, the total number of PVSs was correlated with CCA (rs=0.419; P=0.049).The PVS load in MS patients was heavier than healthy people, especially in BG and CSO. PVS was not correlated with EDSS in MS patients. The PVS of MS patients was associated with CCA and CCR, and PVSs number was independently related with CCA in MS patients in remission.

PIMD: 35103140

Primary Progressive Multiple Sclerosis in a Portuguese Patient With Neurofibromatosis Type 1.

Neurofibromatosis type 1 (NF1) is a frequent genetic neurocutaneous syndrome and multiple sclerosis (MS) is an acquired demyelinating disease of the central nervous system. The association of both these diseases is rare. In this case report, we describe a 25-year-old man with gait impairment, upper limbs tremor, slurred speech, and urinary symptoms in the form of urinary urgency and incontinence. These symptoms started a year earlier and had a progressive course. Examination revealed scattered café-au-lait spots, right ptosis, bilateral horizontal and vertical nystagmus, mild dysarthria, quadriparesis with generalized hyperreflexia and bilateral Babinski signs, upper limb tremor, bilateral proprioceptive errors, bilateral appendicular dysmetria, and severe gait ataxia. Brain MRI showed lesions involving the deep and subcortical white matter, as well as thalami, with no enhancement after administration of gadolinium, suggestive of focal areas of signal intensity (FASI) in the setting of NF1. There were also oval lesions in the periventricular white matter, perpendicular to the ventricles and involving the corpus callosum, which were atypical for FASI. Spinal MRI also demonstrated several lesions, which mildly enhance after administration of gadolinium. Cerebrospinal fluid (CSF) examination revealed mild lymphocytic pleocytosis (18/μL), mildly elevated protein (0.53 g/L), normal glucose, and positive oligoclonal IgG bands. Extensive laboratory workup, including microbiological CSF studies, aquaporin-4-IgG, myelin-oligodendrocyte glycoprotein-IgG, autoimmune screening, and viral serology, was negative. The genetic study revealed a new mutation in the NF1 gene that was not previously reported. We intend to discuss the genetic and autoimmune mechanisms by which MS and NF1 appear to be related and draw attention to this association because a timely diagnosis of MS is important to prevent further disability in NF1 patients.

PIMD: 35091079

Abnormal oxidative metabolism in the cuprizone mouse model of demyelination: An in vivo NIRS-MRI study.

Disruptions in oxidative metabolism may occur in multiple sclerosis and other demyelinating neurological diseases. The impact of demyelination on metabolic rate is also not understood. It is possible that mitochondrial damage may be associated with many such neurological disorders. To study oxidative metabolism with one model of demyelination, we implemented a novel multimodal imaging technique combining Near-Infrared Spectroscopy (NIRS) and MRI to cuprizone mouse model. The cuprizone model is used to study demyelination and may be associated with inhibition of mitochondrial function. Cuprizone mice showed reduced oxygen extraction fraction (-39.1%, $p \leq 0.001$), increased tissue oxygenation (6.4%, $p \leq 0.001$), and reduced cerebral metabolic rate of oxygen in cortical gray matter (-62.1%, $p \leq 0.001$). These changes resolved after the cessation of cuprizone exposure and partial remyelination. A decrease in hemoglobin concentration (-34.4%, $p \leq 0.001$), but no change in cerebral blood flow were also observed during demyelination. The oxidized state of the mitochondrial enzyme, Cytochrome C Oxidase (CCO) increased (46.3%, $p \leq 0.001$) while the reduced state decreased (-34.4%, $p \leq 0.05$) significantly in cuprizone mice. The total amount of CCO did not change significantly during cuprizone exposure. Total CCO did decline after recovery both in control (-23.1%, $p \leq 0.01$) and cuprizone (-28.8%, $p \leq 0.001$) groups which may relate to age. A reduction in the magnetization transfer ratio, indicating demyelination, was found in the cuprizone group in the cerebral cortex (-3.2%, $p \leq 0.01$) and corpus callosum (-5.5%, $p \leq 0.001$). In summary, we were able to detect evidence of altered CCO metabolism during cuprizone exposure, consistent with a mitochondrial defect. We observed increased oxygenation and reduced metabolic rate associated with reduced myelination in the gray and white matter. The novel multimodal imaging technique applied here shows promise for noninvasively assessing parameters associated with oxidative metabolism in both mouse models of neurological disease and for translation to study oxidative metabolism in the human brain.

PIMD: 35088352

Bridging the callosal gap in gait: corpus callosum white matter integrity's role in lower limb coordination.

Bilateral coordination of the lower extremities is an essential component of mobility. The corpus callosum bridges the two hemispheres of the brain and is integral for the coordination of such complex movements. The aim of this project was to assess structural integrity of the transcallosal sensorimotor fiber tracts and identify their associations with gait coordination using novel methods of ecologically valid mobility assessments in persons with multiple sclerosis and age-/gender-matched neurotypical adults. Neurotypical adults (n = 29) and persons with multiple sclerosis (n = 27) underwent gait and diffusion tensor imaging assessments; the lower limb coordination via Phase Coordination Index, and radial diffusivity, an indirect marker of myelination, were applied as the primary outcome measures. Persons with multiple sclerosis possessed poorer transcallosal white matter microstructural integrity of sensorimotor fiber tracts compared to the neurotypical adults. Further, persons with multiple sclerosis demonstrated significantly poorer bilateral coordination of the lower limbs during over-ground walking in comparison to an age and gender-matched neurotypical cohort. Finally, bilateral coordination of the lower limbs was significantly associated with white matter microstructural integrity of the dorsal premotor and primary motor fiber bundles in persons with multiple sclerosis, but not in neurotypical adults. This analysis revealed that persons with multiple sclerosis exhibit poorer transcallosal microstructural integrity than neurotypical peers. Furthermore, these structural deficits were correlated to poorer consistency and accuracy of gait in those with multiple sclerosis. Together, these results, emphasize the importance of transcallosal communication for gait coordination in those with multiple sclerosis.

PIMD: 35083815

Automatic deep learning multicontrast corpus callosum segmentation in multiple sclerosis.

Corpus callosum (CC) atrophy is predictive of future disability in multiple sclerosis (MS). However, current segmentation methods are either labor- or computationally intensive. We therefore developed an automated deep learning-based CC segmentation tool and hypothesized that its output would correlate with disability.A cohort of 631 MS patients (449 females, baseline age 41 ± 11 years) with both 3-dimensional T1-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI was used for the development. Data from 204 patients were manually segmented to train convolutional neural networks in extracting the midsagittal intracranial and CC areas. Remaining data were used to compare segmentations with FreeSurfer and benchmark the outputs with regard to clinical correlations. A 1.5 and 3 Tesla reproducibility cohort of 9 MS patients evaluated the segmentation robustness.The deep learning-based tool was accurate in selecting the appropriate slice for segmentation (98% accuracy within 3 mm of the manual ground truth) and segmenting the CC (Dice coefficient .88-.91) and intracranial areas (.97-.98). The accuracy was lower with higher atrophy. Reproducibility was excellent (intraclass correlation coefficient > .90) for T1-weighted scans and moderate-good for FLAIR (.74-.75). Segmentations were associated with baseline and future (average follow-up time 6-7 years) Expanded Disability Status Scale (ρ = -.13 to -.24) and Symbol Digit Modalities Test (r = .18-.29) scores.We present a fully automatic deep learning-based CC segmentation tool optimized to modern imaging in MS with clinical correlations on par with computationally expensive alternatives.

PIMD: 35082605

Smoothened/AMP-Activated Protein Kinase Signaling in Oligodendroglial Cell Maturation.

The regeneration of myelin is known to restore axonal conduction velocity after a demyelinating event. Remyelination failure in the central nervous system contributes to the severity and progression of demyelinating diseases such as multiple sclerosis. Remyelination is controlled by many signaling pathways, such as the Sonic hedgehog (Shh) pathway, as shown by the canonical activation of its key effector Smoothened (Smo), which increases the proliferation of oligodendrocyte precursor cells the upregulation of the transcription factor Gli1. On the other hand, the inhibition of Gli1 was also found to promote the recruitment of a subset of adult neural stem cells and their subsequent differentiation into oligodendrocytes. Since Smo is also able to transduce Shh signals various non-canonical pathways such as the blockade of Gli1, we addressed the potential of non-canonical Smo signaling to contribute to oligodendroglial cell maturation in myelinating cells using the non-canonical Smo agonist GSA-10, which downregulates Gli1. Using the Oli-neuM cell line, we show that GSA-10 promotes Gli2 upregulation, MBP and MAL/OPALIN expression Smo/AMP-activated Protein Kinase (AMPK) signaling, and efficiently increases the number of axonal contact/ensheathment for each oligodendroglial cell. Moreover, GSA-10 promotes the recruitment and differentiation of oligodendroglial progenitors into the demyelinated corpus callosum . Altogether, our data indicate that non-canonical signaling involving Smo/AMPK modulation and Gli1 downregulation promotes oligodendroglia maturation until axon engagement. Thus, GSA-10, by activation of this signaling pathway, represents a novel potential remyelinating agent.

PIMD: 35078126

Two-dimensional measurements with cut-off values are useful for assessing brain volume, physical disability, and processing speed in multiple sclerosis.

Two-dimensional (2D) measures have been proposed as potential proxy measures for whole-brain volume in multiple sclerosis (MS); however, cut-off values that determine the degree of brain volume loss (BVL) have not been established. Since we had previously developed a system to categorize MS patients into clusters with significantly different degrees of BVL, we tried to identify cut-off values for 2D measurements that can discriminate MS patients on the basis of disease severity associated with brain atrophy.In this cross-sectional analysis, ninety-one consecutive Japanese MS patients-clinically isolated syndrome (5%), relapsing-remitting MS (78%) and progressive MS (17%)-were categorized into two clusters (CL1 and CL2) with a significantly different degree of BVL using the method described in our previous study. MS patients were also evaluated for 2D measurements, namely, third ventricle width, lateral ventricle width (LVW), bicaudate ratio (BCR), and corpus callosum index (CCI). Thereafter, we performed receiver operating characteristic analysis to determine the cut-off values of the 2D measurements for categorizing the MS patients into two clusters.We identified optimal cut-off values for each 2D measure with high specificity and sensitivity. The cut-off values for LVW, BCR, and CCI divided the MS patients into two subgroups, in which whole-brain and grey matter volume, EDSS, and processing speed were significantly different.LVW, BCR, and CCI with particular cut-off values are useful to discriminate MS patients with decreased brain volume, physical disability, and processing speed.

PIMD: 35048999

Corpus callosum volumetrics and clinical progression in early multiple sclerosis.

Corpus callosum (CC) is commonly affected in multiple sclerosis (MS), with known association between CC atrophy and MS clinical activity. In this study, we assessed the association of callosal atrophy, lesions volume and residual CC volume with the clinical disability of early MS patients.Thirteen MS subjects (9 female, mean age 36.9 years), studied with magnetic resonance imaging (MRI) were selected. MRI scans were performed at baseline (T0), at 6 (T1), 12 (T2), and 24 months (T3) from baseline. CC was segmented into three sections (genu, body, and splenium); callosal boundaries were outlined and all CC lesions were manually traced. Normal CC and CC lesion volumes were measured using a semiautomatic software.From January 2014 to December 2016, all selected patients had confluent lesions on MRI at T3 with a significant increase in the size of confluent lesions compared to baseline (p=0.0007). At T1, a significant increase in the size of confluent (p=0.02) and single lesions located in the callosal body (p=0.04) was detected in patients with EDSS ≥1.5. Also, CC residual volume (CCR) rather than the whole CC volume (CCV) significantly correlated (p=0.03) with the clinical progression of MS in the whole cohort.In early MS patients with higher EDSS at baseline, a significant increase in confluent CC lesions size is evident, particularly in the callosal body. Also, median CCR is significantly associated with MS progression in the whole MS group, regardless of initial EDSS. Given their significant association with disability, we encourage measuring CC body lesions and residual CC size for therapeutic decisions and prognostic planning in early MS.

PIMD: 35024162

Usefulness of two-dimensional measurements for the evaluation of brain volume and disability in multiple sclerosis.

Two-dimensional (2D) measures have been proposed as potential proxies for whole-brain volume in multiple sclerosis (MS).To verify whether 2D measurements by routine MRI are useful in predicting brain volume or disability in MS.In this cross-sectional analysis, eighty-five consecutive Japanese MS patients-relapsing-remitting MS (81%) and progressive MS (19%)-underwent 1.5 Tesla T1-weighted 3D MRI examinations to measure whole-brain and grey matter volume. 2D measurements, namely, third ventricle width, lateral ventricle width (LVW), brain width, bicaudate ratio, and corpus callosum index (CCI), were obtained from each scan. Correlations between 2D measurements and 3D measurements, the Expanded Disability Status Scale (EDSS), or processing speed were analysed.The third and lateral ventricle widths were well-correlated with the whole-brain volume (< 0.0001), grey matter volume (< 0.0001), and EDSS scores (= 0.0001, = .0004, respectively).The least squares regression model revealed that 78% of the variation in whole-brain volume could be explained using five explanatory variables, namely, LVW, CCI, age, sex, and disease duration. By contrast, the partial correlation coefficient excluding the effect of age showed that the CCI was significantly correlated with the EDSS and processing speed (< 0.0001).Ventricle width correlated well with brain volumes, while the CCI correlated well with age-independent (i.e. disease-induced) disability.

PIMD: 34987466

The Salvinorin Analogue, Ethoxymethyl Ether Salvinorin B, Promotes Remyelination in Preclinical Models of Multiple Sclerosis.

Multiple sclerosis is a neurodegenerative disease associated with demyelination and neuroinflammation in the central nervous system. There is an urgent need to develop remyelinating therapies to better treat multiple sclerosis and other demyelinating diseases. The kappa opioid receptor (KOR) has been identified as a potential target for the development of remyelinating therapies; however, prototypical KOR agonists, such as U50,488 have side effects, which limit clinical use. In the current study, we investigated a Salvinorin A analog, ethoxymethyl ether Salvinorin B (EOM SalB) in two preclinical models of demyelination in C57BL/6J mice. We showed that in cellular assays EOM SalB was G-protein biased, an effect often correlated with fewer KOR-mediated side effects. In the experimental autoimmune encephalomyelitis model, we found that EOM SalB (0.1-0.3 mg/kg) effectively decreased disease severity in a KOR-dependent manner and led to a greater number of animals in recovery compared to U50,488 treatment. Furthermore, EOM SalB treatment decreased immune cell infiltration and increased myelin levels in the central nervous system. In the cuprizone-induced demyelination model, we showed that EOM SalB (0.3 mg/kg) administration led to an increase in the number of mature oligodendrocytes, the number of myelinated axons and the myelin thickness in the corpus callosum. Overall, EOM SalB was effective in two preclinical models of multiple sclerosis and demyelination, adding further evidence to show KOR agonists are a promising target for remyelinating therapies.

PIMD: 34986275

{'sub': '1', '#text': 'Ponesimod inhibits astrocyte-mediated neuroinflammation and protects against cingulum demyelination via S1P -selective modulation.'}

Ponesimod is a sphingosine 1-phosphate (S1P) receptor (S1PR) modulator that was recently approved for treating relapsing forms of multiple sclerosis (MS). Three other FDA-approved S1PR modulators for MS-fingolimod, siponimod, and ozanimod-share peripheral immunological effects via common S1P interactions, yet ponesimod may access distinct central nervous system (CNS) mechanisms through its selectivity for the S1P receptor. Here, ponesimod was examined for S1PR internalization and binding, human astrocyte signaling and single-cell RNA-seq (scRNA-seq) gene expression, and in vivo using murine cuprizone-mediated demyelination. Studies confirmed ponesimod's selectivity for S1P without comparable engagement to the other S1PR subtypes (S1P). Ponesimod showed pharmacological properties of acute agonism followed by chronic functional antagonism of S1P . A major locus of S1P expression in the CNS is on astrocytes, and scRNA-seq of primary human astrocytes exposed to ponesimod identified a gene ontology relationship of reduced neuroinflammation and reduction in known astrocyte disease-related genes including those of immediate early astrocytes that have been strongly associated with disease progression in MS animal models. Remarkably, ponesimod prevented cuprizone-induced demyelination selectively in the cingulum, but not in the corpus callosum. These data support the CNS activities of ponesimod through S1P , including protective, and likely selective, effects against demyelination in a major connection pathway of the brain, the limbic fibers of the cingulum, lesions of which have been associated with several neurologic impairments including MS fatigue.

PIMD: 34935529

Effect of fluoxetine treatment on neurotoxicity induced by lysolecithin in male rats.

Demyelination disorder is an unusual pathologic event, which occurs in the central nervous system (CNS). Multiple sclerosis (MS) is an inflammatory demyelinating disease that affects the CNS, and it is the leading cause of disability in young adults. Lysolecithin (LPC) is one of the best toxin-induced demyelination models. In this study, a suitable model is created, and the effect of fluoxetine treatment is examined on this model. In this case, it was assumed that daily fluoxetine treatment had increased the endogenous remyelination in the LPC model. This study was focused on investigating the influence of the fluoxetine dose of 5 or 10 mg/kg per day for 1 and 4 weeks on LPC-induced neurotoxicity in the corpus callosum region. It was performed as a demyelinating model in male Wistar rats. After 3 days, fluoxetine was injected intraperitoneally (5 or 10 mg/kg per day) for 1 and 4 weeks in each group. After completing the treatment course, the corpus callosum was removed to examine the gene expression and histological analysis was performed. The results of the histopathological study of hematoxylin and eosin staining of the corpus callosum showed that in 1 and 4-week treatment groups, fluoxetine has reduced the level of inflammation at the LPC injection site (5 and 10 mg/kg per day). Fluoxetine treatment in the luxol fast blue (LFB) staining of the corpus callosum has been led to an increase in myelination capacity in all doses and times. The results of the genetic study showed that the fluoxetine has significantly reduced the expression level of tumor necrosis factor-α, nuclear factor κβ, and induced nitric oxide synthase in comparison with the untreated LPC group. Also, the fluoxetine treatment has enhanced the expression level of the forkhead box P3 () gene in comparison with the untreated group. Fluoxetine has increased the expression level of myelination and neurotrophic genes such as myelin basic protein (), oligodendrocyte transcription factor 2 (), and brain-derived neurotrophic factor (). The outcomes demonstrated that fluoxetine reduces inflammation and strengthens the endogenous myelination in the LPC-induced demyelination model; however, supplementary studies are required for specifying the details of its mechanisms.

PIMD: 34902359

C1q inhibits differentiation of oligodendrocyte progenitor cells via Wnt/β-catenin signaling activation in a cuprizone-induced mouse model of multiple sclerosis.

Multiple sclerosis (MS) is a chronic central nervous system demyelinating disease of autoimmune originate. Complement C1q, a complex glycoprotein, mediates a variety of immunoregulatory functions considered important in the prevention of autoimmunity. Although we found that the increased serum C1q level was highly associated with the Fazekas scores and T2 lesion volume of MS patients, the effect and mechanism of C1q on demyelination remains unclear. Cluster analysis and protein array results showed that serum Wnt receptors Frizzled-6 and LRP-6 levels in MS patients were both increased, we proposed that C1q may be involved in demyelination via Wnt signaling. The increased C1q protein levels in the serum and brain tissue were confirmed in a cuprizone (CPZ)-induced demyelination mice model. Moreover, CPZ treatment induced significant increase of LRP-6 and Frizzled-6 protein in mice corpus callosum. LRP-6 extra-cellular domain (LRP-6-ECD) level in the serum and cerebrospinal fluid (CSF) of CPZ mice also significantly increased. Knockdown of the subunit C1s of C1 not only substantially attenuated demyelination, promoted M2 microglia polarization and improved neurological function, but inhibited β-catenin expression and its nuclear translocation in oligodendrocyte progenitor cells (OPCs). In vitro, C1s silence reversed the increased level of LRP-6-ECD in the medium and β-catenin expression in OPCs induced by C1q treatment. Meanwhile, inhibition of C1s also markedly lowered the number of EDU positive OPCs, but enhanced the number of CNPase positive oligodendrocyte and the protein of MBP. The present study indicated that C1q was involved in demyelination in response to CPZ in mice by preventing OPC from differentiating into mature oligodendrocyte via Wnt/β-catenin signaling activation.

PIMD: 34884611

Differential Role of p53 in Oligodendrocyte Survival in Response to Various Stresses: Experimental Autoimmune Encephalomyelitis, Cuprizone Intoxication or White Matter Stroke.

Promoting oligodendrocyte viability has been proposed as a therapeutic strategy for alleviating many neuronal diseases, such as multiple sclerosis and stroke. However, molecular pathways critical for oligodendrocyte survival under various stresses are still not well known. p53 is a strong tumor suppressor and regulates cell cycle, DNA repair and cell death. Our previous studies have shown that p53 plays an important role in promoting neuronal survival after insults, but its specific role in oligodendrocyte survival is not known. Here, we constructed the mice with oligodendrocyte-specific p53 loss by crossing TRP53 mice and CNP-cre mice, and found that p53 was dispensable for oligodendrocyte differentiation and myelin formation under physiological condition. In the experimental autoimmune encephalomyelitis (EAE) model, p53 loss of function, specifically in oligodendrocytes, did not affect the EAE disease severity and had no effect on demyelination in the spinal cord of the mice. Interestingly, p53 deficiency in oligodendrocytes significantly attenuated the demyelination of corpus callosum and alleviated the functional impairment of motor coordination and spatial memory in the cuprizone demyelination model. Moreover, the oligodendrocyte-specific loss of p53 provided protection against subcortical white matter damage and mitigated recognition memory impairment in mice in the white matter stroke model. These results suggest that p53 plays different roles in the brain and spinal cord or in response to various stresses. Thus, p53 may be a therapeutic target for oligodendrocyte prevention in specific brain injuries, such as white matter stroke and multiple sclerosis.

PIMD: 34824899

Medroxyprogesterone acetate attenuates demyelination, modulating microglia activation, in a cuprizone neurotoxic demyelinating mouse model.

Clinical data reported a reduction of Multiple sclerosis (MS) symptoms during pregnancy when progesterone levels are high. Medroxyprogesterone acetate (MPA) is a synthetic progestin contraceptive with unknown neuroprotective effects. This study investigated the effect of a contraceptive dose of MPA on microglia polarization and neuroinflammation in the neurotoxic cuprizone (CPZ)-induced demyelinating mouse model of MS. Mice received 1 mg of MPA weekly, achieving similar serum concentrations in human contraceptive users. Results revealed that MPA therapy significantly reduced the demyelination in the corpus callosum. In addition, MPA treatment induced a significant reduction in microglia M1-markers (iNOS, IL-1β and TNF-α) while M2-markers (Arg-1, IL-10 and TGF-β) were significantly increased. Moreover, MPA resulted in a significant decrease in the number of iNOS positive cells (M1), whereas TREM-2 positive cells (M2) significantly increased. Furthermore, MPA decreased the protein expression levels of NF-κB and NLRP3 inflammasome as well as mRNA expression levels of the downstream product IL-18. In summary, MPA reduces the level of demyelination and has an anti-inflammatory role in CNS demyelination by inducing M2 microglia polarization and suppressing the M1 phenotype through the inhibition of NF-κB and NLRP3 inflammasome. Our results suggest that MPA should be a suitable contraceptive pharmacological agent in demyelinating diseases.

PIMD: 34803461

Investigation of neuro-inflammatory parameters in a cuprizone induced mouse model of multiple sclerosis.

Cuprizone, copper chelator, treatment of mouse is a toxic model of multiple sclerosis (MS) in which oligodendrocyte death, demyelination and remyelination can be observed. Understanding T and B cell subset as well as their cytokines involved in MS pathogenesis still requires further scrutiny to better understand immune component of MS. The study presented here, aimed to evaluate relevant cytokines, lymphocytes, and gene expressions profiles during demyelination and remyelination in the cuprizone mouse model of MS. Eighty male C57BL/6J mice fed with 0.2% cuprizone for eight weeks. Cuprizone has been removed from the diet in the following eight weeks. Cuprizone treated and control mice sacrificed biweekly, and corpus callosum of the brain was investigated by staining. Lymphocyte cells of mice analyzed by flow cytometry with CD3e, CD11b, CD19, CD80, CD86, CD4, CD25 and FOXP3 antibodies. IFN-gamma, IL-1alpha, IL-2, IL-5, IL-6, IL-10, IL-17, TNF-alpha cytokines were analyzed in plasma samples. Neuregulin 1 (Nrg1), ciliary neurotrophic factor (Cntf) and C-X-C chemokine receptor type 4 (Cxcr4) gene expressions in corpus callosum sections of the mice brain were quantified. Histochemistry analysis showed that demyelination began at the fourth week of cuprizone administration and total demyelination occurred at the twelfth week in chronic model. Remyelination occurred at the fourth week of following withdrawal of cuprizone from diet. The level of mature and activated T cells, regulatory T cells, T helper cells and mature B cells increased during demyelination and decreased when cuprizone removed from diet. Further, both type 1 and type 2 cytokines together with the proinflammatory cytokines increased. The level of oligodendrocyte maturation and survival genes showed differential gene expression in parallel to that of demyelination and remyelination. In conclusion, for the first-time, involvement of both cellular immune response and antibody response as well as oligodendrocyte maturation and survival factors having role in demyelination and remyelination of cuprizone mouse model of MS have been shown.

PIMD: 34799851

Multiple sclerosis impairment scale and brain MRI in secondary progressive multiple sclerosis.

To examine the Multiple Sclerosis Impairment Scale (MSIS) in secondary progressive MS (SPMS) in relation to the Expanded Disability Status Scale (EDSS), magnetic resonance imaging (MRI) outcomes, and mobility.In this observational single-center study, 68 secondary progressive multiple sclerosis (SPMS) patients were examined by MSIS, EDSS, functional mobility tests of upper/lower extremities, and multimodal MRI. Participants had EDSS ≥3.5, a decline in daily activities over the last year unrelated to relapses, and/or 6-month confirmed disability progression.Mean disease duration was 23.1 ± 8.3 years and mean age 54.4 ± 8.1 years. MSIS, EDSS, and their corresponding motor, cerebellar, and sensory subscores correlated ($p < .0001$). Motor subscores of MSIS correlated stronger with Timed-25-Foot-Walk (T25FW) than pyramidal functional system score (FSS) ($p = .03$), but EDSS had a stronger correlation to T25FW than the total MSIS score ($p = .01$). MSIS cerebellar subscore correlated stronger with 9-Hole Peg Test (9-HPT) than cerebellar FSS ($p = .04$). The sensory MSIS subscore also showed correlation with 9-HPT in contrast to sensory FSS ($p = .006$). MSIS subscores had stronger correlations with MRI volumetry measures than FSS scores (lesion volume and putamen, thalamus, corpus callosum volumetry, $p = .0001$-0.0017).In patients with SPMS, MSIS correlated with functional motor tests. MSIS showed stronger correlations with atrophy of central nervous system areas, and may be more sensitive to scale cerebellar and sensory function than EDSS.

PIMD: 34799634

Cuprizone feed formulation influences the extent of demyelinating disease pathology.

Cuprizone is a copper-chelating agent that induces pathology similar to that within some multiple sclerosis (MS) lesions. The reliability and reproducibility of cuprizone for inducing demyelinating disease pathology depends on the animals ingesting consistent doses of cuprizone. Cuprizone-containing pelleted feed is a convenient way of delivering cuprizone, but the efficacy of these pellets at inducing demyelination has been questioned. This study compared the degree of demyelinating disease pathology between mice fed cuprizone delivered in pellets to mice fed a powdered cuprizone formulation at an early 3 week demyelinating timepoint. Within rostral corpus callosum, cuprizone pellets were more effective than cuprizone powder at increasing astrogliosis, microglial activation, DNA damage, and decreasing the density of mature oligodendrocytes. However, cuprizone powder demonstrated greater protein nitration relative to controls. Furthermore, mice fed control powder had significantly fewer mature oligodendrocytes than those fed control pellets. In caudal corpus callosum, cuprizone pellets performed better than cuprizone powder relative to controls at increasing astrogliosis, microglial activation, protein nitration, DNA damage, tissue swelling, and reducing the density of mature oligodendrocytes. Importantly, only cuprizone pellets induced detectable demyelination compared to controls. The two feeds had similar effects on oligodendrocyte precursor cell (OPC) dynamics. Taken together, these data suggest that demyelinating disease pathology is modelled more effectively with cuprizone pellets than powder at 3 weeks. Combined with the added convenience, cuprizone pellets are a suitable choice for inducing early demyelinating disease pathology.

PIMD: 34755279

Adult-onset vanishing white matter in a patient with EIF2B3 variants misdiagnosed as multiple sclerosis.

Vanishing white matter (VWM) is an autosomal recessive disorder characterized by childhood ataxia with central hypomyelination. Adult-onset VWM should be considered as a differential diagnosis for suspected cases of multiple sclerosis (MS).Targeted region sequencing (TRS) and Sanger sequencing validation were performed to identify and validate the likely pathogenic mutations in a family with VWM.The main clinical manifestations of the proband included decreased vision and sleepiness accompanied by atrophy of the corpus callosum, affected inner rim of the corpus callosum, decreased apparent diffusion coefficient value or persistent hyperintensity-diffusion-weighted imaging, atrophied optic nerve, and no recordable visual evoked potentials. Due to the slow development and atypical VWM image features, MS was initially suspected. After prednisone was administered, the patient's condition did not improve significantly, and other diseases were considered. The TRS and Sanger sequencing identified compound heterozygous mutations of EIF2B3 in the proband; c.965C > G /p.Ala322Gly in exon 8 and c.130G > A/p.Glu44Lys in exon 2 were missense mutations inherited from the mother and father, respectively. The proband's oldest brother had the same compound heterozygous mutations but showed no symptoms.This is the first report of adult-onset VWM in a Chinese family. Initially, MS was suspected, and genetic testing confirmed the diagnosis of VWM. This study may further broaden the clinical spectrum of EIF2B3, thus providing a foundation for further research on the pathogenesis and genetic therapy for VWM.

PIMD: 34725188

Sustained ErbB Activation Causes Demyelination and Hypomyelination by Driving Necroptosis of Mature Oligodendrocytes and Apoptosis of Oligodendrocyte Precursor Cells.

Oligodendrocytes are vulnerable to genetic and environmental insults and its injury leads to demyelinating diseases. The roles of ErbB receptors in maintaining the CNS myelin integrity are largely unknown. Here, we overactivate ErbB receptors that mediate signaling of either neuregulin (NRG) or epidermal growth factor (EGF) family growth factors and found their synergistic activation caused deleterious outcomes in white matter. Sustained ErbB activation induced by the tetracycline-dependent mouse tool -tTA resulted in demyelination, axonal degeneration, oligodendrocyte precursor cell (OPC) proliferation, astrogliosis, and microgliosis in white matter. Moreover, there was hypermyelination before these inflammatory pathologic events. In contrast, sustained ErbB activation induced by another tetracycline-dependent mouse tool caused hypomyelination in the corpus callosum and optic nerve, which appeared to be a developmental deficit and did not associate with OPC regeneration, astrogliosis, or microgliosis. By tracing the differentiation states of cells expressing tetracycline-controlled transcriptional activator (tTA)/reverse tTA (rtTA)-dependent transgene or pulse-labeled reporter proteins and , we found that -tTA targeted mainly mature oligodendrocytes (MOs), whereas targeted OPCs and newly-formed oligodendrocytes (NFOs). The distinct phenotypes of mice with ErbB overactivation induced by -tTA and consolidated their nonoverlapping targeting preferences in the oligodendrocyte lineage, and enabled us to demonstrate that ErbB overactivation in MOs induced necroptosis that caused inflammatory demyelination, whereas in OPCs induced apoptosis that caused noninflammatory hypomyelination. Early interference with aberrant ErbB activation ceased oligodendrocyte deaths and restored myelin development in both mice. This study suggests that aberrant ErbB activation is an upstream pathogenetic mechanism of demyelinating diseases, providing a potential therapeutic target. Primary oligodendropathy is one of the etiologic mechanisms for multiple sclerosis, and oligodendrocyte necroptosis is a pathologic hallmark in the disease. Moreover, the demyelinating disease is now a broad concept that embraces schizophrenia, in which white matter lesions are an emerging feature. ErbB overactivation has been implicated in schizophrenia by genetic analysis and postmortem studies. This study suggests the etiologic implications of ErbB overactivation in myelin pathogenesis and elucidates the pathogenetic mechanisms.

PIMD: 34717909

A biocompatible and injectable hydrogel to boost the efficacy of stem cells in neurodegenerative diseases treatment.

Stem cell therapies emerged as treatment modalities with potential to cure neurodegenerative diseases (NDs). However, despite high expectations, their clinical use is still limited. Critical issues in treatment outcomes may be related to stem cells formulation and administration route. We develop a hydrogel as a cell carrier, consisting of compounds (phospholipids and hyaluronic acid-HA) naturally present in the central nervous system (CNS). The HA-based hydrogel physically crosslinked with liposomes is designed for direct injection into the CNS to significantly increase the bone marrow mesenchymal stem cells (BMSCs) bioavailability.Hydrogel compatibility is confirmed in vitro with BMSCs and in vivo through its intracerebroventricular injection in rats. To assess its efficacy, the main cause of chronic neurologic disability in young adults is selected, namely multiple sclerosis (MS). The efficacy of the developed formulation containing a lower number of cells than previously reported is demonstrated using an experimental autoimmune encephalomyelitis (EAE) rat model.The distribution of the engineered hydrogel into corpus callosum can be ideal for NDs treatment, since damage of this white matter structure is responsible for important neuronal deficits. Moreover, the BMSCs-laden hydrogel significantly decreases disease severity and maximum clinical score and eliminated the relapse.The engineering of advanced therapies using this natural carrier can result in efficacious treatments for MS and related debilitating conditions.

PIMD: 34712419

Anti-LINGO-1 improved remyelination and neurobehavioral deficit in cuprizone-induced demyelination.

Central nervous system demyelination is the main feature of multiple sclerosis (MS). The most important unmet need in MS is use of treatments that delay the progression of the disease. Leucine-rich repeat and Immunoglobulin-like domain containing NOGO receptor-interacting protein 1(LINGO-1) have been known as inhibitors of oligodendrocyte differentiation and myelination.We investigated LINGO-1 antibody effects on remyelination and neurobehavioral deficit using cuprizone-induced demyelination. Animals were randomly divided into three groups (n = 10): (1) Control group; received the regular diet, (2) CPZ group; normal saline was injected intraperitoneally, and (3) Treatment group; LINGO-1 antibody (10 mg/kg) was injected IP once every six days for 3 weeks. We assessed the level of myelin basic protein (MBP), neurofilament heavy chain (NF200), and Brain-derived neuroprotective factor (BDNF) in the corpus callosum (CC) by immunostaining against MBP, NF200, and BDNF.We found decreased levels of MBP, NF200, and BDNF in demyelinated CC, and anti-LINGO-1 treatment improved demyelinated structures. Furthermore, motor impairment was measured by Open-field (OFT) and Balance beam tests. In the treatment group, motor impairment was significantly improved.These results provide evidence that LINGO-1 antibody can improve remyelination and neurobehavioral deficit.

PIMD: 34687571

N-myc downstream regulated family member 1 (NDRG1) is enriched in myelinating oligodendrocytes and impacts myelin degradation in response to demyelination.

The N-myc downstream regulated gene family member 1 (NDRG1) is a gene whose mutation results in peripheral neuropathy with central manifestations. While most of previous studies characterized NDRG1 role in Schwann cells, the detection of central nervous system symptoms and the identification of NDRG1 as a gene silenced in the white matter of multiple sclerosis brains raise the question regarding its role in oligodendrocytes. Here, we show that NDRG1 is enriched in oligodendrocytes and myelin preparations, and we characterize its expression using a novel reporter mouse (TgNdrg1-EGFP). We report NDRG1 expression during developmental myelination and during remyelination after cuprizone-induced demyelination of the adult corpus callosum. The transcriptome of Ndrg1-EGFP+ cells further supports the identification of late myelinating oligodendrocytes, characterized by expression of genes regulating lipid metabolism and bioenergetics. We also generate a lineage specific conditional knockout (Olig1 ;Ndrg1) line to study its function. Null mice develop normally, and despite similar numbers of progenitor cells as wild type, they have fewer mature oligodendrocytes and lower levels of myelin proteins than controls, thereby suggesting NDRG1 as important for the maintenance of late myelinating oligodendrocytes. In addition, when control and Ndrg1 null mice are subject to cuprizone-induced demyelination, we observe a higher degree of demyelination in the mutants. Together these data identify NDRG1 as an important molecule for adult myelinating oligodendrocytes, whose decreased levels in the normal appearing white matter of human MS brains may result in greater susceptibility of myelin to damage.

PIMD: 34679335

Thalamus Atrophy in the Peri-Pregnancy Period in Clinically Stable Multiple Sclerosis Patients: Preliminary Results.

Radiological activity in the post-partum period in MS patients is a well-known phenomenon, but there is no data concerning the influence of pregnancy on regional brain atrophy. The aim of this article was to investigate local brain atrophy in the peri-pregnancy period (PPP) in patients with MS. Thalamic volume (TV); corpus callosum volume (CCV) and classical MRI activity (new gadolinium enhancing lesions (Gd+), new T2 lesions, T1 lesions volume (T1LV) and T2 lesions volume (T2LV)) were analyzed in 12 clinically stable women with relapsing-remitting MS and with MRI performed in the PPP. We showed that there was a significant decrease in TV (= 0.021) in the PPP. We also observed a significant increase in the T1 lesion volume (= 0.028), new gadolinium-enhanced and new T2 lesions (in 46% and 77% of the scans, respectively) in the post-partum period. Our results suggest that the PPP in MS may be associated not only with classical MRI activity but, also, with regional brain atrophy.

PIMD: 34634393

Enhanced re-myelination in transthyretin null mice following cuprizone mediated demyelination.

Thyroid hormones (THs) impact nearly every tissue in the body, including the adult and developing central nervous system. The distribution of THs around the body is facilitated by specific TH distributor proteins including transthyretin (TTR). In addition to being produced in the liver, TTR is synthesized in the choroid plexus of the brain. The synthesis of TTR by choroid plexus epithelial cells allows transport of THs from the blood into the brain. Adequate supply of THs to the brain is required for developmental myelination of axons and the maintenance of mature myelin throughout adult life, essential for the proper conduction of nerve impulses. Insufficient THs in developing mice results in hypo-myelination (thinner myelin around axons). However, confounding evidence demonstrated that in developing brain of TTR null mice, hyper-myelination of axons was observed in the corpus callosum. This raised the question whether increased myelination occurs during re-myelination in the adult brain following targeted demyelination. To investigate the effect of TTR during re-myelination, cuprizone induced depletion of myelin in the corpus callosum of adult mice was initiated, followed by a period of myelin repair. Myelin thickness was measured to assess re-myelination rates for 6 weeks. TTR null mice displayed expedited rates of early re-myelination, preferentially re-myelinating smaller axons compared to those of wild type mice. Furthermore, TTR null mice produced thicker myelin than wild type mice during re-myelination. These results may have broader implications in understanding mechanisms governing re-myelination, particularly in potential therapeutic contexts for acquired demyelinating diseases such as multiple sclerosis.

PIMD: 34634288

Sex-specific disruption in corticospinal excitability and hemispheric (a)symmetry in multiple sclerosis.

Multiple Sclerosis (MS) is a neurodegenerative disease in which pathophysiology and symptom progression presents differently between the sexes. In a cohort of people with MS (n = 110), we used transcranial magnetic stimulation (TMS) to investigate sex differences in corticospinal excitability (CSE) and sex-specific relationships between CSE and cognitive function. Although demographics and disease characteristics did not differ between sexes, males were more likely to have cognitive impairment as measured by the Montreal Cognitive Assessment (MoCA); 53.3% compared to females at 26.3%. Greater CSE asymmetry was noted in females compared to males. Females demonstrated higher active motor thresholds and longer silent periods in the hemisphere corresponding to the weaker hand which was more typical of hand dominance patterns in healthy individuals. Males, but not females, exhibited asymmetry of nerve conduction latency (delayed MEP latency in the hemisphere corresponding to the weaker hand). In males, there was also a relationship between delayed onset of ipsilateral silent period (measured in the hemisphere corresponding to the weaker hand) and MoCA, suggestive of cross-callosal disruption. Our findings support that a sex-specific disruption in CSE exists in MS, pointing to interhemispheric disruption as a potential biomarker of cognitive impairment and target for neuromodulating therapies.

PIMD: 34607229

Antagonizing astrocytic platelet activating factor receptor-neuroinflammation for total flavone of epimedium in response to cuprizone demyelination.

Demyelinating diseases of the central nervous system are characterized by recurrent demyelination and progressive neurodegeneration, but there are no clinical drugs targeting myelin regeneration or improving functional disability in the treatment of multiple sclerosis. Total flavone of Epimedium (TFE) is the main active components of Epimedium, which exhibits the beneficial biological activities in the treatment of diseases, but there is no report in the treatment of demyelinating disorder. The purpose of this study was to explore the therapeutic potential and possible mechanism of TFE in the treatment of demyelination. The results showed that TFE efficiently improved the behavioural performance and histological demyelination in cuprizone (CPZ)-induced demyelinating model. In terms of action, TFE increased astrocytes enrichment in corpus callosum, striatum and cortex, and promoted astrocytes to express neurotrophic factors. Furthermore, the expression of platelet-activating factor receptor (PAFR) in astrocytes was induced by CPZ feeding and LPS stimulation, accompanied by the increase of inflammatory cytokines TNF-α,IL-6 and IL-1β. TFE declined the expression of PAFR, and inhibited inflammatory response. At the same time, TFE also antagonized PAFR activation and inflammatory response triggered by PAF, which further confirmed that TFE, as a new PAFR antagonist, inhibited the astrocyte-derived inflammatory response by antagonizing PAFR-neuroinflammation axis, thus contributing to myelin protection and regeneration.

PIMD: 34570348

Metformin Therapy Attenuates Pro-inflammatory Microglia by Inhibiting NF-κB in Cuprizone Demyelinating Mouse Model of Multiple Sclerosis.

Multiple sclerosis (MS) is a chronic disorder characterized by reactive gliosis, inflammation, and demyelination. Microglia plays a crucial role in the pathogenesis of MS and has the dynamic plasticity to polarize between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. Metformin, a glucose-lowering drug, attenuates inflammatory responses by activating adenosine monophosphate protein kinase (AMPK) which suppresses nuclear factor kappa B (NF-κB). In this study, we indirectly investigated whether metformin therapy would regulate microglia activity in the cuprizone (CPZ)-induced demyelination mouse model of MS via measuring the markers associated with pro- and anti-inflammatory microglia. Evaluation of myelin by luxol fast blue staining revealed that metformin treatment (CPZ + Met) diminished demyelination, in comparison to CPZ mice. In addition, metformin therapy significantly alleviated reactive microgliosis and astrogliosis in the corpus callosum, as measured by Iba-1 and GFAP staining. Moreover, metformin treatment significantly downregulated the expression of pro-inflammatory associated genes (iNOS, H2-Aa, and TNF-α) in the corpus callosum, whereas expression of anti-inflammatory markers (Arg1, Mrc1, and IL10) was not promoted, compared to CPZ mice. Furthermore, protein levels of iNOS (pro-inflammatory marker) were significantly decreased in the metformin group, while those of Trem2 (anti-inflammatory marker) were increased. In addition, metformin significantly increased AMPK activation in CPZ mice. Finally, metformin administration significantly reduced the activation level of NF-κB in CPZ mice. In summary, our data revealed that metformin attenuated pro-inflammatory microglia markers through suppressing NF-κB activity. The positive effects of metformin on microglia and remyelination suggest that it could be used as a promising candidate to lessen the incidence of inflammatory neurodegenerative diseases such as MS.

PIMD: 34567412

Untargeted Metabolomic Profiling of Cuprizone-Induced Demyelination in Mouse Corpus Callosum by UPLC-Orbitrap/MS Reveals Potential Metabolic Biomarkers of CNS Demyelination Disorders.

Multiple sclerosis (MS) is a neurodegenerative disorder characterized by periodic neuronal demyelination, which leads to a range of symptoms and eventually to disability. The goal of this research was to use UPLC-Orbitrap/MS to identify validated biomarkers and explore the metabolic mechanisms of MS in mice. Thirty-two C57BL/6 male mice were randomized into two groups that were fed either normal food or 0.2% CPZ for 11 weeks. The mouse demyelination model was assessed by LFB and the expression of MBP by immunofluorescence and immunohistochemistry. The metabolites of the corpus callosum were quantified using UPLC-Orbitrap/MS. The mouse pole climbing experiment was used to assess coordination ability. Multivariate statistical analysis was adopted for screening differential metabolites, and the ingenuity pathway analysis (IPA) was used to reveal the metabolite interaction network. We successfully established the demyelination model. The CPZ group slowly lost weight and showed an increased pole climbing time during feeding compared to the CON group. A total of 81 metabolites (VIP > 1 and < 0.05) were determined to be enriched in 24 metabolic pathways; 41 metabolites were markedly increased, while 40 metabolites were markedly decreased in the CPZ group. The IPA results revealed that these 81 biomarker metabolites were associated with neuregulin signaling, PI3K-AKT signaling, mTOR signaling, and ERK/MAPK signaling. KEGG pathway analysis showed that two significantly different metabolic pathways were enriched, namely, the glycerophospholipid and sphingolipid metabolic pathways, comprising a total of nine biomarkers. Receiver operating characteristic analysis showed that the metabolites (e.g., PE (16 : 0/22 : 6(4Z, 7Z, 10Z, 13Z, 16Z, 19Z)), PC (18 : 0/22 : 4(7Z, 10Z, 13Z, 16Z)), cytidine 5'-diphosphocholine, PS (18 : 0/22 : 6(4Z, 7Z, 10Z, 13Z, 16Z, 19Z)), glycerol 3-phosphate, SM (d18 : 0/16 : 1(9Z)), Cer (d18:1/18 : 0), galabiosylceramide (d18:1/18 : 0), and GlcCer (d18:1/18 : 0)) have good discrimination ability for the CPZ group. In conclusion, the differential metabolites have great potential to serve as biomarkers of demyelinating diseases. In addition, we identified metabolic pathways associated with CPZ-induced demyelination pathogenesis, which provided a new perspective for understanding the relationship between metabolites and CNS demyelination pathogenesis.

PIMD: 34566866

MRI Patterns Distinguish AQP4 Antibody Positive Neuromyelitis Optica Spectrum Disorder From Multiple Sclerosis.

Neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS) are inflammatory diseases of the CNS. Overlap in the clinical and MRI features of NMOSD and MS means that distinguishing these conditions can be difficult. With the aim of evaluating the diagnostic utility of MRI features in distinguishing NMOSD from MS, we have conducted a cross-sectional analysis of imaging data and developed predictive models to distinguish the two conditions. NMOSD and MS MRI lesions were identified and defined through a literature search. Aquaporin-4 (AQP4) antibody positive NMOSD cases and age- and sex-matched MS cases were collected. MRI of orbits, brain and spine were reported by at least two blinded reviewers. MRI brain or spine was available for 166/168 (99%) of cases. Longitudinally extensive (OR = 203), "bright spotty" (OR = 93.8), whole (axial; OR = 57.8) or gadolinium (Gd) enhancing (OR = 28.6) spinal cord lesions, bilateral (OR = 31.3) or Gd-enhancing (OR = 15.4) optic nerve lesions, and nucleus tractus solitarius (OR = 19.2), periaqueductal (OR = 16.8) or hypothalamic (OR = 7.2) brain lesions were associated with NMOSD. Ovoid (OR = 0.029), Dawson's fingers (OR = 0.031), pyramidal corpus callosum (OR = 0.058), periventricular (OR = 0.136), temporal lobe (OR = 0.137) and T1 black holes (OR = 0.154) brain lesions were associated with MS. A score-based algorithm and a decision tree determined by machine learning accurately predicted more than 85% of both diagnoses using first available imaging alone. We have confirmed NMOSD and MS specific MRI features and combined these in predictive models that can accurately identify more than 85% of cases as either AQP4 seropositive NMOSD or MS.

PIMD: 34563964

{'sup': '18', '#text': 'Development of [F]MIPS15692, a radiotracer with in\xa0vitro proof-of-concept for the imaging of MER tyrosine kinase (MERTK) in neuroinflammatory disease.'}

MER tyrosine kinase (MERTK) upregulation is associated with M2 polarization of microglia, which plays a vital role in neuroregeneration following damage induced by neuroinflammatory diseases such as multiple sclerosis (MS). Therefore, a radiotracer specific for MERTK could be of great utility in the clinical management of MS, for the detection and differentiation of neuroregenerative and neurodegenerative processes. This study aimed to develop an [F] ligand with high affinity and selectivity for MERTK as a potential positron emission tomography (PET) radiotracer. MIPS15691 and MIPS15692 were synthesized and kinase assays were utilized to determine potency and selectivity for MERTK. Both compounds were shown to be potent against MERTK, with respective IC values of 4.6 nM and 4.0 nM, and were also MERTK-selective. Plasma and brain pharmacokinetics were measured in mice and led to selection of MIPS15692 over MIPS15691. X-ray crystallography was used to visualize how MIPS15692 is recognized by the enzyme. [F]MIPS15692 was synthesized using an automated iPHASE FlexLab module, with a molar activity (A) of 49 ± 26 GBq/μmol. The radiochemical purity of [F]MIPS15692 was >99% and the decay-corrected radiochemical yields (RCYs) were determined as 2.45 ± 0.85%. Brain MERTK protein density was measured by a saturation binding assay in the brain slices of a cuprizone mouse model of MS. High levels of specific binding of [F]MIPS15692 to MERTK were found, especially in the corpus callosum/hippocampus (CC/HC). The in vivo PET imaging study of [F]MIPS15692 suggested that its neuroPK is sub-optimal for clinical use. Current efforts are underway to optimize the neuroPK of our next generation PET radiotracers for maximal in vivo utility.

PIMD: 34511865

Cognitive impairment and depression in patients with relapsing-remitting multiple sclerosis depending on age and neuroimaging findings.

Multiple sclerosis is an insidious, disabling, both physically and mentally, demyelinating disease of the central nervous system. This work aims to evaluate relationships between cognitive impairment in separate domains, depression and their correspondence with MRI-findings, as well as the influence on each other's manifestations, in patients with relapsing-remitting multiple sclerosis.Visual-spatial/executive functions and memory domains suffered more frequently than others in the study subjects under 40 years; in patients over 40 years old memory, visual-spatial/executive functions and abstract thinking impairment prevailed the most. Such cognitive domains as memory, language, abstract thinking, visual-spatial and executive functions were impacted in both groups of patients even without the apparent cognitive decline according to MoCA scale. Presence of depression impacted language and attention more prominently than the rest of the domains only in participants younger 40 years. According to the MRI, frontal lobe, corpus callosum and periventricular area were affected more often compared to other brain regions in case of cognitive impairment; meanwhile, combined lesions of frontal lobe and corpus callosum, fronto-temporal region were associated with depression.Cognitive impairment and depression are one of the common, yet disabling and socially disrupting manifestations of MS. Quite frequently such complaints are neglected or considered as parts of comorbidities. At the same time cognitive impairment can be amplified by depression, especially in patients under 40 years.

PIMD: 34437581

A higher proportion of ermin-immunopositive oligodendrocytes in areas of remyelination.

Incomplete remyelination is frequent in multiple sclerosis (MS)-lesions, but there is no established marker for recent remyelination. We investigated the role of the oligodendrocyte/myelin protein ermin in de- and remyelination in the cuprizone (CPZ) mouse model, and in MS. The density of ermin+ oligodendrocytes in the brain was significantly decreased after one week of CPZ exposure ($p < 0.02$). The relative proportion of ermin+ cells compared to cells positive for the late-stage oligodendrocyte marker Nogo-A increased at the onset of remyelination in the corpus callosum ($p < 0.02$). The density of ermin-positive cells increased in the corpus callosum during the CPZ-phase of extensive remyelination ($p < 0.0001$). In MS, the density of ermin+ cells was higher in remyelinated lesion areas compared to non-remyelinated areas both in white- ($p < 0.0001$) and grey matter ($p < 0.0001$) and compared to normal-appearing white matter ($p < 0.001$). Ermin immunopositive cells in MS-lesions were not immunopositive for the early-stage oligodendrocyte markers O4 and O1, but a subpopulation was immunopositive for Nogo-A. The data suggest a relatively higher proportion of ermin immunopositivity in oligodendrocytes compared to Nogo-A indicates recent or ongoing remyelination.

PIMD: 34417330

mTOR Signaling Regulates Metabolic Function in Oligodendrocyte Precursor Cells and Promotes Efficient Brain Remyelination in the Cuprizone Model.

In demyelinating diseases, such as multiple sclerosis, primary loss of myelin and subsequent neuronal degeneration throughout the CNS impair patient functionality. While the importance of mechanistic target of rapamycin (mTOR) signaling during developmental myelination is known, no studies have yet directly examined the function of mTOR signaling specifically in the oligodendrocyte (OL) lineage during remyelination. Here, we conditionally deleted from adult oligodendrocyte precursor cells (OPCs) using in male adult mice to test its function in new OLs responsible for remyelination. During early remyelination after cuprizone-induced demyelination, mice lacking mTOR in adult OPCs had unchanged OL numbers but thinner myelin. Myelin thickness recovered by late-stage repair, suggesting a delay in myelin production when is deleted from adult OPCs. Surprisingly, loss of mTOR in OPCs had no effect on efficiency of remyelination after lysophosphatidylcholine lesions in either the spinal cord or corpus callosum, suggesting that mTOR signaling functions specifically in a pathway dysregulated by cuprizone to promote remyelination efficiency. We further determined that cuprizone and inhibition of mTOR cooperatively compromise metabolic function in primary rat OLs undergoing differentiation. Together, our results support the conclusion that mTOR signaling in OPCs is required to overcome the metabolic dysfunction in the cuprizone-demyelinated adult brain. Impaired remyelination by oligodendrocytes contributes to the progressive pathology in multiple sclerosis, so it is critical to identify mechanisms of improving remyelination. The goal of this study was to examine mechanistic target of rapamycin (mTOR) signaling in remyelination. Here, we provide evidence that mTOR signaling promotes efficient remyelination of the brain after cuprizone-mediated demyelination but has no effect on remyelination after lysophosphatidylcholine demyelination in the spinal cord or brain. We also present novel data revealing that mTOR inhibition and cuprizone treatment additively affect the metabolic profile of differentiating oligodendrocytes, supporting a mechanism for the observed remyelination delay. These data suggest that altered metabolic function may underlie failure of remyelination in multiple sclerosis lesions and that mTOR signaling may be of therapeutic potential for promoting remyelination.

PIMD: 34399014

Sphingosine kinase 2 is essential for remyelination following cuprizone intoxication.

Therapeutics that promote oligodendrocyte survival and remyelination are needed to restore neurological function in demyelinating diseases. Sphingosine 1-phosphate (S1P) is an essential lipid metabolite that signals through five G-protein coupled receptors. S1P receptor agonists such as Fingolimod are valuable immunosuppressants used to treat multiple sclerosis, and promote oligodendrocyte survival. However, the role for endogenous S1P, synthesized by the enzyme sphingosine kinase 2 (SphK2), in oligodendrocyte survival and myelination has not been established. This study investigated the requirement for SphK2 in oligodendrocyte survival and remyelination using the cuprizone mouse model of acute demyelination, followed by spontaneous remyelination. Oligodendrocyte density did not differ between untreated wild-type (WT) and SphK2 knockout (SphK2) mice. However, cuprizone treatment caused significantly greater loss of mature oligodendrocytes in SphK2 compared to WT mice. Following cuprizone withdrawal, spontaneous remyelination occurred in WT but not SphK2 mice, even though progenitor and mature oligodendrocyte density increased in both genotypes. Levels of cytotoxic sphingosine and ceramide were higher in the corpus callosum of SphK2 mice, and in contrast to WT mice, did not decline following cuprizone withdrawal in SphK2 mice. We also observed a significant reduction in myelin thickness with aging in SphK2 compared to WT mice. These results provide the first evidence that SphK2, the dominant enzyme catalyzing S1P synthesis in the adult brain, is essential for remyelination following a demyelinating insult and myelin maintenance with aging. We propose that persistently high levels of sphingosine and ceramide, a direct consequence of SphK2 deficiency, may block remyelination.

PIMD: 34392392

The clinical and paraclinical correlates of employment status in multiple sclerosis.

To identify the clinical and paraclinical markers of employment status in multiple sclerosis (MS).This was a cross-sectional sub-study investigating 1226 MS patients. To minimalized confounding effect, two groups of patients, matched by sex, age, and education, were selected: 307 patients with full time employment and 153 unemployed patients receiving disability pension. We explored associations between employment status and Expanded Disability Status Scale (EDSS), 25 Foot Walk Test (25FWT), Nine Hole Peg Test (9HPT), Brief International Cognitive Assessment for MS (BICAMS), Paced Auditory Serial Addition Test (PASAT), Beck Depression Inventory (BDI), SLOAN charts (SLOAN), and brain volumetric MRI measures.Both groups differed significantly on all variables of interest ($p < 0.001$). In the univariate analyses, EDSS, SDMT (Symbol Digit Modalities Test) adjusted for BDI, 25FWT, and 9HPT best explained variability in vocational status. In multivariate analyses, the combination of EDSS, 25FWT, SDMT, BDI, and corpus callosum fraction (CCF) explained the greatest variability. As a next step, after patients were matched by EDSS, differences in SDMT, 25FWT (both $p < 0.001$), 9HPT, CCF, and T2 lesion volume were still present (all $p < 0.005$) between both groups. The best multivariate model consisted of SDMT, BDI, and T2 lesion volume.EDSS, walking ability, cognitive performance, and MRI volumetric parameters are independently associated with employment status.

PIMD: 34387534

Functional and structural MRI correlates of executive functions in multiple sclerosis.

Executive dysfunctions, including difficulties in attention, working memory, planning, and inhibition affect 15%-28% of multiple sclerosis (MS) patients.To investigate structural and functional magnetic resonance imaging (MRI) abnormalities underlying executive function (EF) in MS patients.A total 116 MS patients and 65 controls underwent resting-state (RS) and diffusion-weighted sequences and neuropsychological examination, including Wisconsin Card Sorting Test (WCST) to test EF. Brain RS cognitive networks and fractional anisotropy (FA) from a priori selected white matter tracts were derived. Associations of WCST scores with RS functional connectivity (FC) and FA abnormalities were investigated.In MS patients, predictors of working memory/updating were: lower corpus callosum (CC) FA, lower left working-memory network (WMN), right WMN RS FC for worse performance; lower executive control network (ECN), higher default-mode network (DMN), and salience network (SN) RS FC for better performance (= 0.35). Predictors of attention were lower CC genu FA, lower left WMN, and DMN RS FC for worse performance; higher left WMN and ECN RS FC for better performance (= 0.24). Predictors of worse shifting/inhibition were lower CC genu and superior cerebellar peduncle (SCP) FA, lower left WMN RS FC for worse performance; and higher ECN RS FC for better performance (= 0.24).CC and SCP microstructural damage and RS FC abnormalities in cognitive networks underlie EF frailty in MS.

PIMD: 34379023

White matter microstructural differences in children and genetic risk for multiple sclerosis: A population-based study.

MS patients show abnormalities in white matter (WM) on brain imaging, with heterogeneity in the location of WM lesions. The "pothole" method can be applied to diffusion-weighted images to identify spatially distinct clusters of divergent brain WM microstructure.To investigate the association between genetic risk for MS and spatially independent clusters of decreased or increased fractional anisotropy (FA) in the brain. In addition, we studied sex- and age-related differences.3 Tesla diffusion tensor imaging (DTI) data were collected in 8- to 12-year-old children from a population-based study. Global and tract-based potholes (lower FA clusters) and molehills (higher FA clusters) were quantified in 3047 participants with usable DTI data. A polygenic risk score (PRS) for MS was calculated in genotyped individuals (= 1087) and linear regression analyses assessed the relationship between the PRS and the number of potholes and molehills, correcting for multiple testing using the False Discovery Rate.The number of molehills increased with age, potholes decreased with age, and fewer potholes were observed in girls during typical development. The MS-PRS was positively associated with the number of molehills (β = 0.9, SE = 0.29, = 0.002). Molehills were found more often in the corpus callosum (β = 0.3, SE = 0.09, = 0.0003).Genetic risk for MS is associated with spatially distinct clusters of increased FA during childhood brain development.

PIMD: 34357453

An in vivo implementation of the MEX MRI for myelin fraction of mice brain.

Magnetization EXchange (MEX) sequence measures a signal linearly dependent on the myelin proton fraction by selective suppression of water magnetization and a recovery period. Varying the recovery period enables extraction of the percentile fraction of myelin bound protons. We aim to demonstrate the MEX sequence sensitivity to the fraction of protons associated with myelin in mice brain, in vivo.The cuprizone mouse model was used to manipulate the myelin content. Mice fed cuprizone (n = 15) and normal chow (n = 8) were imaged in vivo using MEX sequence. MR images were segmented into corpus callosum and internal capsule (white matter) and cortical gray matter, and fitted to the recovery equation. Results were analyzed with correlation to MWF and histopathology.The extracted parameters show significant differences in the corpus callosum between the cuprizone and control groups. The cuprizone group exhibited reduced myelin fraction 26.5% ($P < 0.01$). The gray matter values were less affected, with 13.5% reduction ($P < 0.05$); no changes were detected in the internal capsule. Results were validated by MWF scans and good correlation to the histology analysis ($R = 0.685$).The results of this first in vivo implementation of the MEX sequence provide a quantitative measure of demyelination in brain white matter.

PIMD: 34342813

Analysis of platelet-derived growth factor receptor A and oligodendrocyte transcription factor 2 markers following Hydroxychloroquine administration in animal induced multiple sclerosis model.

It has been shown that following demyelination, Oligodendrocyte Progenitor Cells (OPCs) migrate to the lesion site and begin to proliferate, and differentiate. This study aimed to investigate the effects of Hydroxychloroquine (HCQ) on the expression of OLIG-2 and PDGFR-α markers during the myelination process. C57BL/6 mice were fed cuprizone pellets for 5 weeks to induce demyelination and return to a normal diet for 1 week to stimulate remyelination. During the Phase I all of the animals except CPZ and Vehicle groups were exposed to HCQ (2.5, 10, and 100 mg/kg) via drinking water. At the end of the study, animals were euthanized, perfused and the brain samples were assessed for myelination and immunohistochemistry evaluation. What is remarkable is the high rate of Olig2 + cells in the groups treated with 10 and 100 mg/kg HCQ in the demyelination phase and its decreasing trend in the remyelination phase. However, there was no significant difference between groups during phase I and Phase II based on the percentage of olig-2+/total cells in the corpus callosum region. The number of PDGFR-α+ cells in the group treated with 10 mg/kg HCQ was significant in the first phase (p value < 0.05). Considering that the 100 mg/kg HCQ group had the highest level of PDGFR-α as well as the highest level of myelin repair in LFB staining, it could be inferred that it was the most effective dose in inducing proliferation and migration of OPCs.

PIMD: 34335450

Sodium Intensity Changes Differ Between Relaxation- and Density-Weighted MRI in Multiple Sclerosis.

The source of Tissue Sodium Concentration (TSC) increase in Multiple Sclerosis (MS) remains unclear, and could be attributed to altered intracellular sodium concentration or tissue microstructure. This paper investigates sodium in MS using three new MRI sequences. Three sodium scans were acquired at 4.7 T from 30 patients (11 relapsing-remitting, 10 secondary-progressive, 9 primary-progressive) and 9 healthy controls including: Density-Weighted (NaDW), with very short 30° excitation for more accurate TSC measurement; Projection Acquisition with Coherent MAgNetization (NaPACMAN), designed for enhanced relaxation-based contrast; and Soft Inversion Recovery FLuid Attenuation (NaSIRFLA), developed to reduce fluid space contribution. Signal was measured in both lesions (= 397) and normal appearing white matter (NAWM) relative to controls in the splenium of corpus callosum and the anterior and posterior limbs of internal capsule. Correlations with clinical and cognitive evaluations were tested over all MS patients. Sodium intensity in MS lesions was elevated over control WM by a greater amount for NaPACMAN (75%) than NaDW (35%), the latter representing TSC. In contrast, NaSIRFLA exhibited lower intensity, but only for region specific analysis in the SCC (-7%). Sodium intensity in average MS NAWM was not significantly different than control WM for either of the three scans. NaSIRFLA in the average NAWM and specifically the posterior limb of internal capsules positively correlated with the Paced Auditory Serial Addition Test (PASAT). Lower NaSIRFLA signal in lesions and ~2× greater NaPACMAN signal elevation over control WM than NaDW can be explained with a demyelination model that also includes edema. A NAWM demyelination model that includes tissue atrophy suggests no signal change for NaSIRFLA, and only slightly greater NAWM signal than control WM for both NaDW and NaPACMAN, reflecting experimental results. Models were derived from previous total and myelin water fraction study in MS with T2-relaxometry, and for the first time include sodium within the myelin water space. Reduced auditory processing association with lower signal on NaSIRFLA cannot be explained by greater demyelination and its modeled impact on the three sodium MRI sequences. Alternative explanations include intra- or extracellular sodium concentration change. Relaxation-weighted sodium MRI in combination with sodium-density MRI may help elucidate microstructural and metabolic changes in MS.

PIMD: 34269618

Ensemble Learning for Multiple Sclerosis Disability Estimation Using Brain Structural Connectivity.

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system characterized by demyelination and neurodegeneration processes. It leads to different clinical courses and degrees of disability that need to be anticipated by the neurologist for personalized therapy. Recently, machine learning (ML) techniques have reached a high level of performance in brain disease diagnosis and/or prognosis, but the decision process of a trained ML system is typically nontransparent. Using brain structural connectivity data, a fully automatic ensemble learning model, augmented with an interpretable model, is proposed for the estimation of MS patients' disability, measured by the Expanded Disability Status Scale (EDSS). An ensemble of four boosting-based models (GBM, XGBoost, CatBoost, and LightBoost) organized following a stacking generalization scheme was developed using diffusion tensor imaging (DTI)-based structural connectivity data. In addition, an interpretable model based on conditional logistic regression was developed to explain the best performances in terms of white matter (WM) links for three classes of EDSS (low, medium, and high). The ensemble model reached excellent level of performance (root mean squared error of 0.92 ± 0.28) compared with single-based models and provided a better EDSS estimation using DTI-based structural connectivity data compared with conventional magnetic resonance imaging measures associated with patient data (age, gender, and disease duration). Used for interpretation of the estimation process, the counterfactual method showed the importance of certain brain networks, corresponding mainly to left hemisphere WM links, connecting the left superior temporal with the left posterior cingulate and the right precuneus gray matter regions, and the interhemispheric WM links constituting the corpus callosum. Also, a better accuracy estimation was found for the high disability class.

The combination of advanced ML models and sensitive techniques such as DTI-based structural connectivity demonstrated to be useful for the estimation of MS patients' disability and to point out the most important brain WM networks involved in disability. Impact statement An ensemble of "boosting" machine learning (ML) models was more performant than single models to estimate disability in multiple sclerosis. Diffusion tensor imaging (DTI)-based structural connectivity led to better performance than conventional magnetic resonance imaging. An interpretable model, based on counterfactual perturbation, highlighted the most relevant white matter fiber links for disability estimation. These findings demonstrated the clinical interest of combining DTI, graph modeling, and ML techniques.

PIMD: 34255918

Unraveling the substrates of cognitive impairment in multiple sclerosis: A multiparametric structural and functional magnetic resonance imaging study.

Cognitive impairment frequently affects multiple sclerosis (MS) patients. However, its neuroanatomical correlates still need to be fully explored. We investigated the contribution of structural and functional magnetic resonance imaging (MRI) abnormalities in explaining cognitive impairment in MS.Brain dual-echo, diffusion tensor, 3D T1-weighted and resting-state (RS) MRI sequences were acquired from 276 MS patients and 102 healthy controls. Using random forest analysis, the contribution of regional white matter (WM) lesions, WM fractional anisotropy (FA) abnormalities, gray matter (GM) atrophy and RS functional connectivity (FC) alterations to cognitive impairment in MS patients was investigated.Eighty-four MS patients (30.4%) were cognitively impaired. The best MRI predictors of cognitive impairment (relative importance [%]) (out-of-bag area under the curve [AUC] = 0.795) were (a) WM lesions in the right superior longitudinal fasciculus (100%), left anterior thalamic radiation (93.4%), left posterior corona radiata (78.5%), left medial lemniscus (74.2%), left inferior longitudinal fasciculus (70.4%), left optic radiation (68.7%), right middle cerebellar peduncle (60.6%) and right optic radiation (53.5%); (b) decreased FA in the splenium of the corpus callosum (64.3%), left optic radiation (61.0%), body of the corpus callosum (51.9%) and fornix (50.9%); and (c) atrophy of the left precuneus (91.4%), right cerebellum crus I (84.4%), right caudate nucleus (78.6%), left thalamus (76.2%) and left supplementary motor area (59.8%). The relevance of these MRI measures in explaining cognitive impairment was confirmed in a cross-validation analysis (AUC =0.765).Structural damage in strategic WM and GM regions explains cognitive impairment in MS patients more than RS FC abnormalities.

PIMD: 34240251

Neuroprotective effect of newly synthesized 4-aminopyridine derivatives on cuprizone-induced demyelination in mice-a behavioral and immunohistochemical study.

The aim of this study was to assess the effect of newly synthesized derivatives of 4-aminopyridine (4-AP) on cuprizone-induced model of brain demyelination in mice. 4-AP is already approved for the treatment of walking difficulties in patients with multiple sclerosis. The model of demyelination was carried out by the administration of cuprizone to the drinking water of the experimental mice. Besides cuprizone, 4-AP derivatives and 4-AP were administered to the groups in order to assess their protective effect on the demyelination. We used immunohistochemistry for visualization of changes in corpus callosum. Memory storage processes were also assessed with the passive avoidance test on the last two days of the experiment. The experimental mice treated with compounds 4b and 4c increased significantly their latency time on the second day in comparison to the control group which indicated an improved memory process. The number of mature oligodendrocytes in the groups treated with compounds 4b, 4c and 4-AP is closer to those in the control group. The results of our studies showed that the newly synthesized compounds 4b and 4c reverse the effect of cuprizone. These groups also showed increased latency time in the passive avoidance test in comparison to the control group.

PIMD: 34239419

{'sup': '+', '#text': 'IL-17 Inhibits Oligodendrocyte Progenitor Cell Proliferation and Differentiation by Increasing K Channel Kv1.3.'}

Interleukin 17 (IL-17) is a signature cytokine of Th17 cells. IL-17 level is significantly increased in inflammatory conditions of the CNS, including but not limited to post-stroke and multiple sclerosis. IL-17 has been detected direct toxicity on oligodendrocyte (Ol) lineage cells and inhibition on oligodendrocyte progenitor cell (OPC) differentiation, and thus promotes myelin damage. The cellular mechanism of IL-17 in CNS inflammatory diseases remains obscure. Voltage-gated K (Kv) channel 1.3 is the predominant Kv channel in Ol and potentially involved in Ol function and cell cycle regulation. Kv1.3 of T cells involves in immunomodulation of inflammatory progression, but the role of Ol Kv1.3 in inflammation-related pathogenesis has not been fully investigated. We hypothesized that IL-17 induces myelin injury through Kv1.3 activation. To test the hypothesis, we studied the involvement of OPC/Ol Kv1.3 in IL-17-induced Ol/myelin injury in vitro and in vivo. Kv1.3 currents and channel expression gradually decreased during the OPC development. Application of IL-17 to OPC culture increased Kv1.3 expression, leading to a decrease of AKT activation, inhibition of proliferation and myelin basic protein reduction, which were prevented by a specific Kv1.3 blocker 5-(4-phenoxybutoxy) psoralen. IL-17-caused myelin injury was validated in LPC-induced demyelination mouse model, particularly in corpus callosum, which was also mitigated by aforementioned Kv1.3 antagonist. IL-17 altered Kv1.3 expression and resultant inhibitory effects on OPC proliferation and differentiation may by interrupting AKT phosphorylating activation. Taken together, our results suggested that IL-17 impairs remyelination and promotes myelin damage by Kv1.3-mediated Ol/myelin injury. Thus, blockade of Kv1.3 as a potential therapeutic strategy for inflammatory CNS disease may partially attribute to the direct protection on OPC proliferation and differentiation other than immunomodulation.

PIMD: 34159538

Specific Blockade of Bone Morphogenetic Protein-2/4 Induces Oligodendrogenesis and Remyelination in Demyelinating Disorders.

Oligodendrocyte precursor cells (OPCs) are present in demyelinated lesions of multiple sclerosis (MS) patients. However, their differentiation into functional oligodendrocytes is insufficient, and most lesions evolve into nonfunctional astroglial scars. Blockade of bone morphogenetic protein (BMP) signaling induces differentiation of OPCs into myelin-producing oligodendrocytes. We studied the effect of specific blockade of BMP-2/4 signaling, by intravenous (IV) treatment with anti-BMP-2/4 neutralizing mAb in both the inflammatory model of relapsing experimental autoimmune encephalomyelitis (R-EAE) and the cuprizone-toxic model of demyelination in mice. Administration of anti-BMP-2/4 to R-EAE-induced mice, on day 9 post-immunization (p.i.), ameliorated R-EAE signs, diminished the expression of phospho-SMAD1/5/8, primarily within the astrocytic lineage, increased the numbers of de novo immature and mature oligodendrocytes, and reduced the numbers of newly generated astrocytes within the spinal cord as early as day 18 p.i. This effect was accompanied with elevated remyelination, manifested by increased density of remyelinating axons ($0.8 < \text{g-ratios} < 1$), and reduced fully demyelinated and demyelinating axons, in the anti-BMP-2/4-treated R-EAE mice, studied by electron microscopy. No significant immunosuppressive effect was observed in the CNS and in the periphery, during the peak of the first attack, or at the end of the experiment. Moreover, IV treatment with anti-BMP-2/4 mAb in the cuprizone-challenged mice augmented the numbers of mature oligodendrocytes and remyelination in the corpus callosum during the recovery phase of the disease. Based on our findings, the specific blockade of BMP-2/4 has a therapeutic potential in demyelinating disorders such as MS, by inducing early oligodendrogenesis-mediated remyelination in the affected tissue.

PIMD: 34149350

Innate Signaling in the CNS Prevents Demyelination in a Focal EAE Model.

The pathological hallmark of multiple sclerosis (MS) is the formation of multifocal demyelinating lesions in the central nervous system (CNS). Stimulation of innate receptors has been shown to suppress experimental autoimmune encephalomyelitis (EAE), an MS-like disease in mice. Specifically, targeting Toll-like receptor 9 (TLR9) and NOD-like receptor 2 (NOD2) significantly reduced disease severity. In the present work we have developed a novel focal EAE model to further study the effect of innate signaling on demyelinating pathology. Focal lesions were induced by stereotactic needle insertion into the corpus callosum (CC) of mice previously immunized for EAE. This resulted in focal pathology characterized by infiltration and demyelination in the CC. We find that intrathecal delivery of MIS416, a TLR9 and NOD2 bispecific innate ligand, into the cerebrospinal fluid reduced focal lesions in the CC. This was associated with upregulation of type I and II interferons, interleukin-10, arginase-1, CCL-2 and CXCL-10. Analysis of draining cervical lymph nodes showed upregulation of type II interferons and interleukin 10. Moreover, intrathecal MIS416 altered the composition of early CNS infiltrates, increasing proportions of myeloid and NK cells and reducing T cells at the lesion site. This study contributes to an increased understanding of how innate immune responses can play a protective role, which in turn may lead to additional therapeutic strategies for the prevention and treatment of demyelinating pathologies.

PIMD: 34132126

Characterization of multiple sclerosis neuroinflammation and neurodegeneration with relaxation and diffusion basis spectrum imaging.

Advanced magnetic resonance imaging (MRI) methods can provide more specific information about various microstructural tissue changes in multiple sclerosis (MS) brain. Quantitative measurement of T and T relaxation, and diffusion basis spectrum imaging (DBSI) yield metrics related to the pathology of neuroinflammation and neurodegeneration that occurs across the spectrum of MS.To use relaxation and DBSI MRI metrics to describe measures of neuroinflammation, myelin and axons in different MS subtypes.103 participants (20 clinically isolated syndrome (CIS), 33 relapsing-remitting MS (RRMS), 30 secondary progressive MS and 20 primary progressive MS) underwent quantitative T, T, DBSI and conventional 3T MRI. Whole brain, normal-appearing white matter, lesion and corpus callosum MRI metrics were compared across MS subtypes.A gradation of MRI metric values was seen from CIS to RRMS to progressive MS. RRMS demonstrated large oedema-related differences, while progressive MS had the most extensive abnormalities in myelin and axonal measures.Relaxation and DBSI-derived MRI measures show differences between MS subtypes related to the severity and composition of underlying tissue damage. RRMS showed oedema, demyelination and axonal loss compared with CIS. Progressive MS had even more evidence of increased oedema, demyelination and axonal loss compared with CIS and RRMS.

PIMD: 34095120

{'i': 'in vivo', '#text': 'A Novel Lysolecithin Model for Visualizing Damage in the Larval Zebrafish Spinal Cord.'}

Lysolecithin is commonly used to induce demyelinating lesions in the spinal cord and corpus callosum of mammalian models. Although these models and clinical patient samples are used to study neurodegenerative diseases, such as multiple sclerosis (MS), they do not allow for direct visualization of disease-related damage . To overcome this limitation, we created and characterized a focal lysolecithin injection model in zebrafish that allows us to investigate the temporal dynamics underlying lysolecithin-induced damage . We injected lysolecithin into 4-6 days post-fertilization (dpf) zebrafish larval spinal cords and, coupled with , time-lapse imaging, observed hallmarks consistent with mammalian models of lysolecithin-induced demyelination, including myelinating glial cell loss, myelin perturbations, axonal sparing, and debris clearance. We have developed and characterized a lysolecithin injection model in zebrafish that allows us to investigate myelin damage in a living, vertebrate organism. This model may be a useful pre-clinical screening tool for investigating the safety and efficacy of novel therapeutic compounds that reduce damage and/or promote repair in neurodegenerative disorders, such as MS.

PIMD: 34084605

Co-existence of multiple sclerosis and germinoma in an adult male: Case report.

Concurrent diagnosis of multiple sclerosis (MS) and the central nervous system (CNS) germinoma is rare. The diagnostic criteria for MS rely primarily on clinical presentation, and CNS germinoma can present as an MS mimic. These factors contribute to the rarity of dual diagnosis.A 28-year-old man presented initially with bilateral optic neuritis, manifesting as persistently worsening vision for 2 years, and demyelinating plaques identified within the corpus callosum on magnetic resonance imaging. Initial work-up, in addition to clinical presentation, led to diagnosis of MS. Three months following the diagnosis of MS, the patient then presented with obstructive hydrocephalus due to a newly diagnosed intraventricular mass. The patient underwent an endoscopic third ventriculostomy and biopsy which confirmed diagnosis of CNS germinoma.To the best of our knowledge, dual presentation of both MS and CNS germinoma has never been reported in the literature. The clinical presentation of bilateral optic neuritis (persisting for roughly 2 years before initial MS diagnosis), demyelinating plaques, and intrathecal oligoclonal bands before the development of an intraventricular mass indicates that both MS and CNS germinoma presented simultaneously in this patient. The treatment plan for this patient included carboplatin + etoposide, followed by adjuvant radiation and subsequent IVIG therapy.

PIMD: 34080180

Magnetic resonance imaging in neuromyelitis optica spectrum disorder.

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease of the central nervous system (CNS) associated with antibodies to aquaporin-4 (AQP4), which has distinct clinical, radiological and pathological features, but also has some overlap with multiple sclerosis and myelin oligodendrocyte glycoprotein (MOG) antibody associated disease. Early recognition of NMOSD is important because of differing responses to both acute and preventive therapy. Magnetic resonance (MR) imaging has proved essential in this process. Key MR imaging clues to the diagnosis of NMOSD are longitudinally extensive lesions of the optic nerve (more than half the length) and spinal cord (three or more vertebral segments), bilateral optic nerve lesions and lesions of the optic chiasm, area postrema, floor of the IV ventricle, periaqueductal grey matter, hypothalamus and walls of the III ventricle. Other NMOSD-specific lesions are denoted by their unique morphology: heterogeneous lesions of the corpus callosum, 'cloud-like' gadolinium (Gd)-enhancing white matter lesions and 'bright spotty' lesions of the spinal cord. Other lesions described in NMOSD, including linear periventricular peri-ependymal lesions and patch subcortical white matter lesions, may be less specific. The use of advanced MR imaging techniques is yielding further useful information regarding focal degeneration of the thalamus and optic radiation in NMOSD and suggests that paramagnetic rim patterns and changes in normal appearing white matter are specific to MS. MR imaging is crucial in the early recognition of NMOSD and in directing testing for AQP4 antibodies and guiding immediate acute treatment decisions. Increasingly, MR imaging is playing a role in diagnosing seronegative cases of NMOSD.

PIMD: 34040141

Demyelination and remyelination detected in an alternative cuprizone mouse model of multiple sclerosis with 7.0 T multiparameter magnetic resonance imaging.

The aim of this study was to investigate the mechanisms underlying demyelination and remyelination with 7.0 T multiparameter magnetic resonance imaging (MRI) in an alternative cuprizone (CPZ) mouse model of multiple sclerosis (MS). Sixty mice were divided into six groups (n = 10, each), and these groups were imaged with 7.0 T multiparameter MRI and treated with an alternative CPZ administration schedule. T-weighted imaging (TWI), susceptibility-weighted imaging (SWI), and diffusion tensor imaging (DTI) were used to compare the splenium of the corpus callosum (sCC) among the groups. Prussian blue and Luxol fast blue staining were performed to assess pathology. The correlations of the mean grayscale value (mGSV) of the pathology results and the MRI metrics were analyzed to evaluate the multiparameter MRI results. One-way ANOVA and post hoc comparison showed that the normalized TWI (T-nor), fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) values were significantly different among the six groups, while the mean phase (Φ) value of SWI was not significantly different among the groups. Correlation analysis showed that the correlation between the T-nor and mGSV was higher than that among the other values. The correlations among the FA, RD, MD, and mGSV remained instructive. In conclusion, ultrahigh-field multiparameter MRI can reflect the pathological changes associated with and the underlying mechanisms of demyelination and remyelination in MS after the successful establishment of an acute CPZ-induced model.

PIMD: 34015640

Positivity of oligoclonal bands in the cerebrospinal fluid predisposed to metabolic changes and rearrangement of inhibitory/excitatory neurotransmitters in subcortical brain structures in multiple sclerosis.

The latest diagnostic criteria for multiple sclerosis (MS) have revitalized the role of oligoclonal bands synthesis in the cerebrospinal fluid (CSF-OCB). This study identifies predictors of CSF-OCB-positivity among in vivo metabolic markers in the subcortical gray/white matter in MS patients after their first episode (CIS) and in patients with relapsing-remitting course (RRMS).The study enrolled 13 CIS and 23 RRMS patients. Metabolism was evaluated using Mescher-Garwood-edited proton-magnetic resonance spectroscopy on a 3T MR scanner. In addition to N-acetyl-aspartate (tNAA), myoinositol (mIns), and choline- and creatine compounds (tCho, tCr) were also evaluated γ-aminobutyric acid (GABA) and glutamate-glutamine (Glx) ratios.CSF-OCB-positivity was found in 76.9% of CIS and 78.2% of RRMS patients. GABA and Glx ratios in putamen and corpus callosum strongly determined CSF-OCB-positive CIS patients. Other essential predictors of CSF-OCB-positive CIS were mIns and Glx ratios in the putamen, and tCho/tNAA in the corpus callosum. In RRMS, GABA ratios in the right thalamus and Glx ratios in the left hippocampus strongly predicted CSF-OCB-positive patients. tCho/tNAA and tNAA/tCr in the left hippocampus were also identified as essential predictors of CSF-OCB-positive RRMS patients.This is the first in vivo evidence of GABA-Glx rearrangement in CSF-OCB-positive patients since its early stages of MS.

PIMD: 33965566

ADAM10 suppresses demyelination and reduces seizure susceptibility in cuprizone-induced demyelination model.

The metalloproteinase ADAM10 is the most important amyloid precursor protein (APP) α-secretase, preventing the deposit of neurotoxic amyloid β (Aβ) peptide and generating a soluble APP fragment (sAPP) with neurotrophic functions. Recent studies have suggested that ADAM10 also play a role in the pathogenesis of inflammatory CNS diseases, such as multiple sclerosis (MS). Demyelination is the hallmarks of MS but the mechanisms involved remain unclear. Here in this study, we examined the role that ADAM10 might play in the cuprizone-induced demyelination model. Our results demonstrated that ADAM10 expression and sAPP production were significantly reduced in the corpus callosum in response to cuprizone treatment. Overexpression of ADAM10 increased sAPP production and suppressed demyelination as well as neuroinflammation and oxidative stress in cuprizone-induced demyelination model. Pharmacological inhibition of ADAM10 activity, however, abrogates the protective effect of ADAM10 against demyelination, neuroinflammation and oxidative stress. It has been reported that CNS demyelination may induce seizure activity. Here, we found that overexpression of ADAM10 reduced seizure susceptibility in cuprizone-induced demyelination model, suggesting that ADAM10-derived sAPP suppresses demyelination and reduces seizure susceptibility via ameliorating neuroinflammation and oxidative stress in cuprizone-induced demyelination model.

PIMD: 33959710

Tract-specific MRI measures explain learning and recall differences in multiple sclerosis.

Cognitive difficulties are common and a key concern for people with multiple sclerosis. Advancing knowledge of the role of white matter pathology in multiple sclerosis-related cognitive impairment is essential as both occur early in the disease with implications for early intervention. Consequently, this cross-sectional study asked whether quantifying the relationships between lesions and specific white matter structures could better explain co-existing cognitive differences than whole brain imaging measures. Forty participants with relapse-onset multiple sclerosis underwent cognitive testing and MRI at 3 Tesla. They were classified as cognitively impaired (= 24) or unimpaired (= 16) and differed across verbal fluency, learning and recall tasks corrected for intelligence and education (corrected -values = 0.007-0.04). The relationships between lesions and white matter were characterized across six measures: conventional voxel-based T2 lesion load, whole brain tractogram load (lesioned volume/whole tractogram volume), whole bundle volume, bundle load (lesioned volume/whole bundle volume), Tractometry (diffusion-tensor and high angular resolution diffusion measures sampled from all bundle streamlines) and lesionometry (diffusion measures sampled from streamlines traversing lesions only). The tract-specific measures were extracted from corpus callosum segments (genu and isthmus), striato-prefrontal and -parietal pathways, and the superior longitudinal fasciculi (sections I, II and III). White matter measure-task associations demonstrating at least moderate evidence against the null hypothesis (Bayes Factor threshold < 0.2) were examined using independent -tests and covariate analyses (significance level <0.05). Tract-specific measures were significant predictors (all -values < 0.05) of task-specific clinical scores and diminished the significant effect of group as a categorical predictor in Story Recall (isthmus bundle load), Figure Recall (right striato-parietal lesionometry) and Design Learning (left superior longitudinal fasciculus III volume). Lesion load explained the difference in List Learning, whereas Letter Fluency was not associated with any of the imaging measures. Overall, tract-specific measures outperformed the global lesion and tractogram load measures. Variation in regional lesion burden translated to group differences in tract-specific measures, which in turn, attenuated differences in individual cognitive tasks. The structural differences converged in temporo-parietal regions with particular influence on tasks requiring visuospatial-constructional processing. We highlight that measures quantifying the relationships between tract-specific structure and multiple sclerosis lesions uncovered associations with cognition masked by overall tract volumes and global lesion and tractogram loads. These tract-specific white matter quantifications show promise for elucidating the relationships between neuropathology and cognition in multiple sclerosis.

PIMD: 33954959

N-acetylcysteine protects against cuprizone-induced demyelination: histological and immunohistochemical study.

Myelination is a sequential process that is tightly controlled by a number of intrinsic and extrinsic factors. Any CNS disease in which the neuronal myelin sheath is damaged is referred to as demyelinating disease. The present work was designed to study the histopathological, ultrastructural and immunohistochemical changes in rat brain, mainly corpus callosum (CC), following oral administration of cuprizone (CPZ), and the role of N-acetylcysteine (NAC) in reducing these changes. Demyelination was induced by CPZ administration for short (4Ws) and long (8Ws) periods. NAC was given concomitantly and sequentially for similar periods. Spontaneous recovery after cessation of CPZ followed by no medication was also investigated. At the end of each experimental period, both cerebral hemispheres were extracted and prepared for light and electron microscopic examination and immuno-histochemical study. The obtained results showed a direct proportion between the duration of CPZ administration and the severity of demyelination. The co-administration of CPZ and NAC, had a fair protective impact that was stronger than the sequential administration of the two drugs. Incomplete spontaneous remyelination was observed after cessation of CPZ, being more evident in short than in long period group, indicating that when CPZ administration is prolonged, remyelination is delayed. In the light of the above results, it could be concluded that NAC has neuroprotective effects and has the potential to be a novel therapeutic approach for the treatment of demyelinating diseases such as multiple sclerosis; however, treatment should begin as soon as the disease manifests.

PIMD: 33932559

Focal white matter lesions induce long-lasting axonal degeneration, neuroinflammation and behavioral deficits.

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) with episodes of inflammatory demyelination and remyelination. While remyelination has been linked with functional recovery in MS patients, there is evidence of ongoing tissue damage despite complete myelin repair. In this study, we investigated the long-term consequences of an acute demyelinating white matter CNS lesion. For this purpose, acute demyelination was induced by 5-week-cuprizone intoxication in male C57BL/6 J mice, and the tissues were examined after a 7-month recovery period. While myelination and oligodendrocyte densities appeared normal, ongoing axonal degeneration and glia cell activation were found in the remyelinated corpus callosum. Neuropathologies were paralleled by subtle gait abnormalities evaluated using DigiGait™ high speed ventral plane videography. Gene array analyses revealed increased expression levels of various inflammation related genes, among protein kinase c delta (PRKCD). Immunofluorescence stains revealed predominant microglia/macrophages PRKCD expression in both, cuprizone tissues and post-mortem MS lesions. These results support the hypothesis that chronic microglia/macrophages driven tissue injury represents a key aspect of progressive neurodegeneration and functional decline in MS.

PIMD: 33925560

{'sup': '18', '#text': 'Assessment of F-PBR-111 in the Cuprizone Mouse Model of Multiple Sclerosis.'}

The study aims to assess site assessment of the performance of F-PBR-111 as a neuroinflammation marker in the cuprizone mouse model of multiple sclerosis (MS). F-PBR-111 PET imaging has not been well evaluated in multiple sclerosis applications both in preclinical and clinical research. This study will help establish the potential utility of F-PBR-111 PET in preclinical MS research and future animal and future human applications. F-PBR-111 PET/CT was conducted at 3.5 weeks (= 7) and 5.0 weeks (= 7) after cuprizone treatment or sham control (= 3) in the mouse model. A subgroup of mice underwent autoradiography with cryosectioned brain tissue. T2 weighted MRI was performed to obtain the brain structural data of each mouse. F-PBR-111 uptake was assessed in multiple brain regions with PET and autoradiography images. The correlation between autoradiography and immunofluorescence staining of neuroinflammation (F4/80 and CD11b) was measured. Compared to control mice, significant F-PBR-111 uptake in the corpus callosum (< 0.001), striatum (caudate and internal capsule, < 0.001), and hippocampus (< 0.05) was identified with PET images at both 3.5 weeks and 5.0 weeks, and validated with autoradiography. No significant uptake differences were detected between 3.5 weeks and 5.0 weeks assessing these regions as a whole, although there was a trend of increased uptake at 5.0 weeks compared to 3.5 weeks in the CC. High F-PBR-111 uptake regions correlated with microglial/macrophage locations by immunofluorescence staining with F4/80 and CD11b antibodies. F-PBR-111 uptake in anatomic locations correlated with activated microglia at histology in the cuprizone mouse model of MS suggests that F-PBR-111 has potential for in vivo evaluation of therapy response and potential for use in MS patients and animal studies.

PIMD: 33903905

Brain microstructural and metabolic alterations detected in vivo at onset of the first demyelinating event.

In early multiple sclerosis, a clearer understanding of normal-brain tissue microstructural and metabolic abnormalities will provide valuable insights into its pathophysiology. We used multi-parametric quantitative MRI to detect alterations in brain tissues of patients with their first demyelinating episode. We acquired neurite orientation dispersion and density imaging [to investigate morphology of neurites (dendrites and axons)] and 23Na MRI (to estimate total sodium concentration, a reflection of underlying changes in metabolic function). In this cross-sectional study, we enrolled 42 patients diagnosed with clinically isolated syndrome or multiple sclerosis within 3 months of their first demyelinating event and 16 healthy controls. Physical and cognitive scales were assessed. At 3 T, we acquired brain and spinal cord structural scans, and neurite orientation dispersion and density imaging. Thirty-two patients and 13 healthy controls also underwent brain 23Na MRI. We measured neurite density and orientation dispersion indices and total sodium concentration in brain normal-appearing white matter, white matter lesions, and grey matter. We used linear regression models (adjusting for brain parenchymal fraction and lesion load) and Spearman correlation tests (significance level $P \leq 0.01$). Patients showed higher orientation dispersion index in normal-appearing white matter, including the corpus callosum, where they also showed lower neurite density index and higher total sodium concentration, compared with healthy controls. In grey matter, compared with healthy controls, patients demonstrated: lower orientation dispersion index in frontal, parietal and temporal cortices; lower neurite density index in parietal, temporal and occipital cortices; and higher total sodium concentration in limbic and frontal cortices. Brain volumes did not differ between patients and controls. In patients, higher orientation dispersion index in corpus callosum was associated with worse performance on timed walk test ($P = 0.009$, $B = 0.01$, 99% confidence interval = 0.0001 to 0.02), independent of brain and lesion volumes. Higher total sodium concentration in left frontal middle gyrus was associated with higher disability on Expanded Disability Status Scale ($rs = 0.5$, $P = 0.005$). Increased axonal dispersion was found in normal-appearing white matter, particularly corpus callosum, where there was also axonal degeneration and total sodium accumulation. The association between increased axonal dispersion in the corpus callosum and worse walking performance implies that morphological and metabolic alterations in this structure could mechanistically contribute to disability in multiple sclerosis. As brain volumes were neither altered nor related to disability in patients, our findings suggest that these two advanced MRI techniques are more sensitive at detecting clinically relevant pathology in early multiple sclerosis.

PIMD: 33881705

Exploratory study on neurochemical effects of low-intensity pulsed ultrasound in brains of mice.

There is now a relatively large body of evidence suggesting a relationship between dysfunction of myelin and oligodendrocytes and the etiology of several neuropsychiatric disorders, including depression and schizophrenia, and also suggesting that ultrasound methods may alleviate some of the symptoms of depression. We have applied low-intensity pulsed ultrasound (LIPUS) to the brains of mice treated with the demyelinating drug cuprizone, a drug that has been used as the basis for a rodent model relevant to a number of psychiatric and neurologic disorders including depression, schizophrenia, and multiple sclerosis. Prior to conducting the studies in mice, preliminary studies were carried out on the effects of LIPUS in vitro in neuron-like SH-SY5Y cells and primary glial cells. In subsequent studies in mice, female C57BL/6 mice were restrained in plastic tubes for 20 min daily with the ultrasound transducer near the end of the tube directly above the mouse's head. LIPUS was used at an intensity of 25 mW/cm once daily for 22 days in control mice and in mice undergoing daily repetitive restraint stress (RRS). Behavioral or neurochemical studies were done on the mice or the brain tissue obtained from them. The studies in vitro indicated that LIPUS stimulation at an intensity of 15 mW/cm delivered for 5 min daily for 3 days in an enclosed sterile cell culture plate in an incubator increased the viability of SH-SY5Y and primary glial cells. In the studies in mice, LIPUS elevated levels of doublecortin, a marker for neurogenesis, in the cortex compared to levels in the RRS mice and caused a trend in elevation of brain levels of brain-derived neurotrophic factor in the hippocampus relative to control levels. LIPUS also increased sucrose preference (a measure of the attenuation of anhedonia, a common symptom of several psychiatric disorders) in the RRS model in mice. The ability of LIPUS administered daily to rescue damaged myelin and oligodendrocytes was studied in mice treated chronically with cuprizone for 35 days. LIPUS increased cortex and corpus callosum levels of myelin basic protein, a protein marker for mature oligodendrocytes, and neural/glial antigen 2, a protein marker for oligodendrocyte precursor cells, relative to levels in the cuprizone + sham animals. These results of this exploratory study suggest that future comprehensive time-related studies with LIPUS on brain chemistry and behavior related to neuropsychiatric disorders are warranted. Exploratory Study on Neurochemical Effects of Low Intensity Pulsed Ultrasound in Brains of Mice. Upper part of figure: LIPUS device and in-vitro cell experimental set-up. The center image is the LIPUS generating box; the image in the upper left shows the cell experiment set-up; the image in the upper right shows a zoomed-in sketch for the cell experiment; the image in the lower left shows the set-up of repetitive restraint stress (RRS) with a mouse; the image in the lower middle shows the set-up of LIPUS treatment of a mouse; the image in the lower right shows a zoomed-in sketch for the LIPUS treatment of a mouse.

PIMD: 33841545

{'i': 'Melilotus Officinalis', '#text': 'Healing Influence of Herbal Extract on Experimental Autoimmune Encephalomyelitis in C57BL/6 Mice.'}

The present study was designed to primarily examine the therapeutic potential of the herbal extract of for the treatment of multiple sclerosis in the experimental autoimmune encephalomyelitis (EAE) model of the disease. The animal model was induced in C57BL/6 female mice, and then the herbal extract was intraperitoneally administered for a total of 21 days after the first day of post-immunization. The phenotypic signs, a gene expression profile of inflammatory cytokines, antioxidant state, and pathological hallmarks of the disease in the corpus callosum were evaluated. The prophylactic administration of attenuates the clinical signs of the disease. It significantly declined the gene expression of pro-inflammatory cytokines like IL-6, TNF-α, and IFN-γ. This herbal extract also surged the gene expression, as an anti-inflammatory cytokine. The gene expression of Glutathione peroxidase and Catalase (antioxidant enzymes) was meaningfully higher in the treatment group. Pathological evaluation of corpus callosum cross-sections by Luxol Fast Blue staining revealed preserved myelin sheath in the treated group compared to the EAE mice. The results of our assay confirmed that immunomodulatory and antioxidant features of the herbal extract of ameliorated the EAE severity. This study finding disclosed the therapeutic efficiency of this compound in MS treatment.

PIMD: 33837066

{'sup': '18', '#text': 'Longitudinal Imaging of T Cells and Inflammatory Demyelination in a Preclinical Model of Multiple Sclerosis Using F-FAraG PET and MRI.'}

Lymphocytes and innate immune cells are key drivers of multiple sclerosis (MS) and are the main target of MS disease-modifying therapies (DMT). Ex vivo analyses of MS lesions have revealed cellular heterogeneity and variable T cell levels, which may have important implications for patient stratification and choice of DMT. Although MRI has proven valuable to monitor DMT efficacy, its lack of specificity for cellular subtypes highlights the need for complementary methods to improve lesion characterization. Here, we evaluated the potential of 2'-deoxy-2'-F-fluoro-9-β-d-arabinofuranosylguanine (F-FAraG) PET imaging to noninvasively assess infiltrating T cells and to provide, in combination with MRI, a novel tool to determine lesion types. We used a novel MS mouse model that combines cuprizone and experimental autoimmune encephalomyelitis to reproducibly induce 2 brain inflammatory lesion types, differentiated by their T cell content. F-FAraG PET imaging, T2-weighted MRI, and T1-weighted contrast-enhanced MRI were performed before disease induction, during demyelination with high levels of innate immune cells, and after T cell infiltration. Fingolimod immunotherapy was used to evaluate the ability of PET and MRI to detect therapy response. Ex vivo immunofluorescence analyses for T cells, microglia/macrophages, myelin, and blood-brain barrier (BBB) integrity were performed to validate the in vivo findings. F-FAraG signal was significantly increased in the brain and spinal cord at the time point of T cell infiltration. F-FAraG signal from white matter (corpus callosum) and gray matter (cortex, hippocampus) further correlated with T cell density. T2-weighted MRI detected white matter lesions independently of T cells. T1-weighted contrast-enhanced MRI indicated BBB disruption at the time point of T cell infiltration. Fingolimod treatment prevented motor deficits and decreased T cell and microglia/macrophage levels. In agreement, F-FAraG signal was decreased in the brain and spinal cord of fingolimod-treated mice; T1-weighted contrast-enhanced MRI revealed intact BBB, whereas T2-weighted MRI findings remained unchanged. The combination of MRI and F-FAraG PET enables detection of inflammatory demyelination and T cell infiltration in an MS mouse model, providing a new way to evaluate lesion heterogeneity during disease progression and after DMT. On clinical translation, these methods hold great potential for stratifying patients, monitoring MS progression, and determining therapy responses.

PIMD: 33828603

Evaluation of neuroprotective effects of alpha-tocopherol in cuprizone-induced demyelination model of multiple sclerosis.

Multiple sclerosis (MS) is an autoimmune disorder characterized by demyelination and axonal loss. Quantitative estimation of behavioral, locomotor, and histological changes following the use of alpha-tocopherol (AT) in the animal model of MS have not been reported. The present study was planned to evaluate whether AT can improve sensorimotor dysfunction and reduce demyelination in the cuprizone (CPZ)-induced rat model of MS.Female rats (8 weeks) were fed with cuprizone diet for 5 weeks followed by intraperitoneal injections of alpha-tocopherol (100 mg/Kg) or PBS for 2 weeks (groups E1 and E2, n = 8). Group C (n = 8) was fed with normal pellets followed by intraperitoneal doses of PBS. Open-field test and beam walking were carried out on every 10 day. The mean area of demyelination in the corpus callosum was quantified in Luxol fast blue (LFB) stained histological sections of the forebrain. Qualitative grading for relative changes in the stains of myelinated fibers was also done.During withdrawal of CPZ, AT treatment increased the average speed by 22% in group E1, compared to group E2 (< 0.05). The mean time to walk the beam was reduced in group E1 by 2.6% compared to group E2 (< 0.05). The rearing frequency was increased in group E1 during week 6-7 compared to that in the period of CPZ treatment. The mean area of demyelination in the corpus callosum showed a 12% reduction in group E1 compared to group E2 (< 0.05).Short-term AT therapy showed improvement in motor dysfunction and reduction of demyelination in the animal model of MS.

PIMD: 33826184

Delayed access to conscious processing in multiple sclerosis: Reduced cortical activation and impaired structural connectivity.

Although multiple sclerosis (MS) is frequently accompanied by visuo-cognitive impairment, especially functional brain mechanisms underlying this impairment are still not well understood. Consequently, we used a functional MRI (fMRI) backward masking task to study visual information processing stratifying unconscious and conscious in MS. Specifically, 30 persons with MS (pwMS) and 34 healthy controls (HC) were shown target stimuli followed by a mask presented 8-150 ms later and had to compare the target to a reference stimulus. Retinal integrity (via optical coherence tomography), optic tract integrity (visual evoked potential; VEP) and whole brain structural connectivity (probabilistic tractography) were assessed as complementary structural brain integrity markers. On a psychophysical level, pwMS reached conscious access later than HC (50 vs. 16 ms, $p < .001$). The delay increased with disease duration ($p < .001$, $\beta = .37$) and disability ($p < .001$, $\beta = .24$), but did not correlate with conscious information processing speed (Symbol digit modality test, $\beta = .07$, $p = .817$). No association was found for VEP and retinal integrity markers. Moreover, pwMS were characterized by decreased brain activation during unconscious processing compared with HC. No group differences were found during conscious processing. Finally, a complementary structural brain integrity analysis showed that a reduced fractional anisotropy in corpus callosum and an impaired connection between right insula and primary visual areas was related to delayed conscious access in pwMS. Our study revealed slowed conscious access to visual stimulus material in MS and a complex pattern of functional and structural alterations coupled to unconscious processing of/delayed conscious access to visual stimulus material in MS.

PIMD: 33807060

Contribution of Gray Matter Atrophy and White Matter Damage to Cognitive Impairment in Mildly Disabled Relapsing-Remitting Multiple Sclerosis Patients.

Cognitive impairment (CI) is frequently present in multiple sclerosis patients. Despite ongoing research, the neurological substrates have not been fully elucidated. In this study we investigated the contribution of gray and white matter in the CI observed in mildly disabled relapsing-remitting multiple sclerosis (RRMS) patients. For that purpose, 30 patients with RRMS (median EDSS = 2), and 30 age- and sex-matched healthy controls were studied. CI was assessed using the symbol digit modalities test (SDMT) and the memory alteration test. Brain magnetic resonance imaging, diffusion tensor imaging (DTI), voxel-based morphometry (VBM), brain segmentation, thalamic vertex analysis, and connectivity-based thalamic parcellation analyses were performed. RRMS patients scored significantly lower in both cognitive tests. In the patient group, significant atrophy in the thalami was observed. Multiple regression analyses revealed associations between SDMT scores and GM volume in both hemispheres in the temporal, parietal, frontal, and occipital lobes. The DTI results pointed to white matter damage in all thalamocortical connections, the corpus callosum, and several fasciculi. Multiple regression and correlation analyses suggested that in RRMS patients with mild disease, thalamic atrophy and thalamocortical connection damage may lead to slower cognitive processing. Furthermore, white matter damage at specific fasciculi may be related to episodic memory impairment.

PIMD: 33794337

17β-Estradiol Reduces Demyelination in Cuprizone-fed Mice by Promoting M2 Microglia Polarity and Regulating NLRP3 Inflammasome.

Estrogen produces a beneficial role in animal models of multiple sclerosis (MS). The effect of 17β-estradiol therapy on microglia polarization and neuroinflammation in the corpus callosum of the cuprizone-induced demyelination model has not been elucidated. In this study, mice were given 0.2% cuprizone (CPZ) for 5 weeks to induce demyelination during which they received 50 ng of 17β-estradiol (EST), injected subcutaneously in the neck region, twice weekly. Data revealed that treatment with 17β-estradiol therapy (CPZ+EST) improved neurological behavioral deficits, displayed by a significant reduction in escape latencies, in comparison to untreated CPZ mice. Also, administration of 17β-estradiol caused a decrease in demyelination levels and axonal injury, as demonstrated by staining with Luxol fast blue, immunofluorescence to myelin basic protein, and transmission electron microscopy analysis. In addition, at the transcriptional level in the brain, mice treated with 17β-estradiol (CPZ+EST) showed a decrease in the levels of M1-assosicted microglia markers (CD86, iNOS and MHC-II) whereas M2-associated genes (Arg-1, CD206 and Trem-2) were increased, compared to CPZ mice. Moreover, administration of 17β-estradiol resulted in a significant reduction (3-fold) in transcript levels of NLRP3 inflammasome and its downstream product IL-18, compared to controls. In summary, this study demonstrated for the first time that exogenous 17β-estradiol therapy robustly leads to the reduction of M1 phenotype, stimulation of polarized M2 microglia, and repression of NLRP3 inflammasome in the corpus callosum of CPZ demyelination model of MS. The positive effects of 17β-estradiol on microglia and inflammasome seems to facilitate and accelerate the remyelination process.

PIMD: 33794147

Remyelination is enhanced by Astragalus polysaccharides through inducing the differentiation of oligodendrocytes from neural stem cells in cuprizone model of demyelination.

Demyelination is the hallmark of multiple sclerosis (MS). Promoting remyelination is an important strategy to treat MS. Our previous study showed that Astragalus polysaccharides (APS), the main bioactive component of Astragalus membranaceus, could prevent demyelination in experimental autoimmune encephalomyelitis mice. To investigate the effects of APS on remyelination and the underlying mechanisms, in this study we set up a cuprizone-induced demyelination model in mice and treated them with APS. It was found that APS relieved the neurobehavioral dysfunctions caused by demyelination, and efficaciously facilitated remyelination in vivo. In order to determine whether the mechanism of enhancing remyelination was associated with the differentiation of neural stem cells (NSCs), biomarkers of NSCs, astrocytes, oligodendrocytes and neurons were measured in the corpus callosum tissues of mice through Real-time PCR, Western blot and immunohistochemistry assays. Data revealed that APS suppressed the stemness of NSCs, reduced the differentiation of NSCs into astrocytes, and promoted the differentiation into oligodendrocytes and neurons. This phenomenon was confirmed in the differentiation model of C17.2 NSCs cultured in vitro. Since Sonic hedgehog signaling pathway has been proven to be crucial to the differentiation of NSCs into oligodendrocytes, we examined expression levels of the key molecules in this pathway in vivo and in vitro, and eventually found APS activated this signaling pathway. Together, our results demonstrated that APS probably activated Sonic hedgehog signaling pathway first, then induced NSCs to differentiate into oligodendrocytes and promoted remyelination, which suggested that APS might be a potential candidate in treating MS.

PIMD: 33787958

Microstructural White Matter Alterations in Cognitively Impaired Patients at Early Stages of Multiple Sclerosis.

As conventional quantitative magnetic resonance imaging (MRI) parameters are weakly associated with cognitive impairment (CI) in early multiple sclerosis (MS), we explored microstructural white matter alterations in early MS or clinically isolated syndrome (CIS) comparing patients with or without CI.Based on a preceding tract-based spatial statistics analysis (3 Tesla MRI) which contrasted 106 patients with early MS or CIS and 49 healthy controls, diffusion metrics (fractional anisotropy, FA, mean diffusivity, MD) were extracted from significant clusters using an atlas-based approach. The FA and MD were compared between patients with (Ci_P n = 14) and without (Cp_P n = 81) cognitive impairment in a subset of patients who underwent CI screening.The FA was reduced in Ci_P compared to Cp_P in the splenium of corpus callosum (p = 0.001), right parahippocampal cingulum (p = 0.002) and fornix cres./stria terminalis (0.042), left posterior corona radiata (p = 0.012), bilateral cerebral peduncles, medial lemniscus and in cerebellar tracts. Increased MD was detected in the splenium of corpus callosum (p = 0.01). The CI-related localizations overlapped only partially with MS lesions.Microstructural white matter alterations at disease onset were detectable in Ci_P compared to Cp_P in known cognitively relevant fiber tracts, indicating the relevance of early treatment initiation in MS and CIS.

PIMD: 33746698

RAFF-4, Magnetization Transfer and Diffusion Tensor MRI of Lysophosphatidylcholine Induced Demyelination and Remyelination in Rats.

Remyelination is a naturally occurring response to demyelination and has a central role in the pathophysiology of multiple sclerosis and traumatic brain injury. Recently we demonstrated that a novel MRI technique entitled Relaxation Along a Fictitious Field (RAFF) in the rotating frame of rank n (RAFFn) achieved exceptional sensitivity in detecting the demyelination processes induced by lysophosphatidylcholine (LPC) in rat brain. In the present work, our aim was to test whether RAFF4, along with magnetization transfer (MT) and diffusion tensor imaging (DTI), would be capable of detecting the changes in the myelin content and microstructure caused by modifications of myelin sheets around axons or by gliosis during the remyelination phase after LPC-induced demyelination in the corpus callosum of rats. We collected MRI data with RAFF4, MT and DTI at 3 days after injection (demyelination stage) and at 38 days after injection (remyelination stage) of LPC (= 12) or vehicle (= 9). Cell density and myelin content were assessed by histology. All MRI metrics detected differences between LPC-injected and control groups of animals in the demyelination stage, on day 3. In the remyelination phase (day 38), RAFF4, MT parameters, fractional anisotropy, and axial diffusivity detected signs of a partial recovery consistent with the remyelination evident in histology. Radial diffusivity had undergone a further increase from day 3 to 38 and mean diffusivity revealed a complete recovery correlating with the histological assessment of cell density attributed to gliosis. The combination of RAFF4, MT and DTI has the potential to differentiate between normal, demyelinated and remyelinated axons and gliosis and thus it may be able to provide a more detailed assessment of white matter pathologies in several neurological diseases.

PIMD: 33720130

Positron Emission Tomography Imaging for In Vivo Measuring of Myelin Content in the Lysolecithin Rat Model of Multiple Sclerosis.

Multiple sclerosis (MS) is a neuroinflammatory disease with expanding axonal and neuronal degeneration and demyelination in the central nervous system, leading to motor dysfunctions, psychical disability, and cognitive impairment during MS progression. Positron emission tomography (PET) is an imaging technique able to quantify in vivo cellular and molecular alterations. Radiotracers with affinity to intact myelin can be used for in vivo imaging of myelin content changes over time. It is possible to detect either an increase or decrease in myelin content, what means this imaging technique can detect demyelination and remyelination processes of the central nervous system. In this protocol we demonstrate how to use PET imaging to detect myelin changes in the lysolecithin rat model, which is a model of focal demyelination lesion (induced by stereotactic injection) (i.e., a model of multiple sclerosis disease). C-PIB PET imaging was performed at baseline, and 1 week and 4 weeks after stereotaxic injection of lysolecithin 1% in the right striatum (4 µL) and corpus callosum (3 µL) of the rat brain, allowing quantification of focal demyelination (injection site after 1 week) and the remyelination process (injection site at 4 weeks). Myelin PET imaging is an interesting tool for monitoring in vivo changes in myelin content which could be useful for monitoring demyelinating disease progression and therapeutic response.

PIMD: 33714029

Identification of novel myelin repair drugs by modulation of oligodendroglial differentiation competence.

In multiple sclerosis loss of myelin and oligodendrocytes impairs saltatory signal transduction and leads to neuronal loss and functional deficits. Limited capacity of oligodendroglial precursor cells to differentiate into mature cells is the main reason for inefficient myelin repair in the central nervous system. Drug repurposing constitutes a powerful approach for identification of pharmacological compounds promoting this process.A phenotypic compound screening using the subcellular distribution of a potent inhibitor of oligodendroglial cell differentiation, namely p57kip2, as differentiation competence marker was conducted. Hit compounds were validated in terms of their impact on developmental cell differentiation and myelination using both rat and human primary cell cultures and organotypic cerebellar slice cultures, respectively. Their effect on spontaneous remyelination was then investigated following cuprizone-mediated demyelination of the corpus callosum.A number of novel small molecules able to promote oligodendroglial cell differentiation were identified and a subset was found to foster human oligodendrogenesis as well as myelination ex vivo. Among them the steroid danazol and the anthelminthic parbendazole were found to increase myelin repair.We provide evidence that early cellular processes involved in differentiation decisions are applicable for the identification of regeneration promoting drugs and we suggest danazol and parbendazole as potent therapeutic candidates for demyelinating diseases.This work was supported by the Jürgen Manchot Foundation, Düsseldorf; Research Commission of the Medical Faculty of Heinrich-Heine-University Düsseldorf; Christiane and Claudia Hempel Foundation; Stifterverband/Novartisstiftung; James and Elisabeth Cloppenburg, Peek and Cloppenburg Düsseldorf Stiftung and International Progressive MS Alliance (BRAVEinMS).

PIMD: 33708131

Effect and Mechanism of Catalpol on Remyelination via Regulation of the NOTCH1 Signaling Pathway.

Promoting the differentiation of oligodendrocyte precursor cells (OPCs) is important for fostering remyelination in multiple sclerosis. Catalpol has the potential to promote remyelination and exert neuroprotective effects, but its specific mechanism is still unclear. Recent studies have shown that the NOTCH1 signaling pathway is involved in mediating OPC proliferation and differentiation. In this study, we elucidated that catalpol promoted OPC differentiation and vitro and explored the regulatory role of catalpol in specific biomolecular processes. Following catalpol administration, better and faster recovery of body weight and motor balance was observed in mice with cuprizone (CPZ)-induced demyelination. Luxol fast blue staining (LFB) and transmission electron microscopy (TEM) showed that catalpol increased the myelinated area and improved myelin ultrastructure in the corpus callosum in demyelinated mice. In addition, catalpol enhanced the expression of CNPase and MBP, indicating that it increased OPC differentiation. Additionally, catalpol downregulated the expression of NOTCH1 signaling pathway-related molecules, such as JAGGED1, NOTCH1, NICD1, RBPJ, HES5, and HES1. We further demonstrated that , catalpol enhanced the differentiation of OPCs into OLs and inhibited NOTCH1 signaling pathway activity. Our data suggested that catalpol may promote OPC differentiation and remyelination through modulation of the NOTCH1 pathway. This study provides new insight into the mechanism of action of catalpol in the treatment of multiple sclerosis.

PIMD: 33680032

Protective Effects of a Nano-Formulation of Curcumin against Cuprizone-Induced Demyelination in the Mouse Corpus Callosum.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS), characterized by neuroinflammation, oligodendrocytes (OLs) loss, and demyelination Curcumin, a natural phenolic substance, has been shown to have significant therapeutic properties in various neurodegenerative diseases, including MS. In our laboratory by loading curcumin in dendrosome nanoparticles we improved its solubility and bioavailability. Our previous study showed anti-inflammatory and anti-oxidative effects of dendrosomal nano-curcumin (DNC) in experimental autoimmune encephalomyelitis (EAE) model of MS. Here, by using a toxic demyelination model, induced by cuprizone (CPZ), we investigated the protective effect of DNC on oligodendroglial lineage cells (OLLC) and myelin preservation in context of acute demyelination. CPZ is a copper chelator, thus its intake reduces the mitochondrial activity, activates oxidative stress response, leading to specific OLs death, due to their high-energy consumption. We also evaluated DNC effect on activation of astrocytes and microglia, which are enriched in both MS and CPZ demyelinated lesions. Our results demonstrated that DNC treatment protected Oligodendrocyte lineage cells (OLLCs) against CPZ toxin. Besides DNC treatment suppressed accumulation of astrocytes and microglia in CC of CPZ-fed mice, compared to PBS treated onse. Moreover, DNC treatment lead to higher index of luxol fast bluefast blue (LFB) and myelin-specific proteins, myelin basic protein (MBP) intensity in the corpus callosum (CC), as indicators of myelin content. These results suggest a potent pleiotropic therapeutic efficiency for DNC for protection of myelinating cells, possibly via suppression of astrocytes and microglia.

PIMD: 33587820

Deep Learning Corpus Callosum Segmentation as a Neurodegenerative Marker in Multiple Sclerosis.

Corpus callosum atrophy is a sensitive biomarker of multiple sclerosis (MS) neurodegeneration but typically requires manual 2D or volumetric 3D-based segmentations. We developed a supervised machine learning algorithm, DeepnCCA, for corpus callosum segmentation and relate callosal morphology to clinical disability using conventional MRI scans collected in clinical routine.In a prospective study of 553 MS patients with 704 acquisitions, 200 unique 2D T -weighted MRI scans were delineated to develop, train, and validate DeepnCCA. Comparative FreeSurfer segmentations were obtained in 504 3D T -weighted scans. Both FreeSurfer and DeepnCCA outputs were correlated with clinical disability. Using principal component analysis of the DeepnCCA output, the morphological changes were explored in relation to clinical disease burden.DeepnCCA and manual segmentations had high similarity (Dice coefficients 98.1 .11%, 89.3 .76%, for intracranial and corpus callosum area, respectively through 10-fold cross-validation). DeepnCCA had numerically stronger correlations with cognitive and physical disability as compared to FreeSurfer: Expanded disability status scale (EDSS) ±6 months (r = -.22 P = .002; r = -.17, P = .013), future EDSS (r = -.26, P<.001; r = -.17, P = .012), and future symbol digit modalities test (r = .26, P = .001; r = .24, P = .003). The corpus callosum became thinner with increasing cognitive and physical disability. Increasing physical disability, additionally, significantly correlated with a more angled corpus callosum.DeepnCCA (https://github.com/plattenmichael/DeepnCCA/) is an openly available tool that can provide fast and accurate corpus callosum measurements applicable to large MS cohorts, potentially suitable for monitoring disease progression and therapy response.

PIMD: 33517175

ELTD1 as a biomarker for multiple sclerosis: Pre-clinical molecular-targeted studies in a mouse experimental autoimmune encephalomyelitis model.

Multiple sclerosis (MS) and glioblastoma (GBM) are two distinct diseases that affect the central nervous system (CNS). However, perturbation in CNS vasculature are hallmarks of both diseases. ELTD1 (epidermal growth factor, latrophilin, and 7 transmembrane domain containing protein 1 on chromosome 1) is associated with vascular development, and has been linked with tumor angiogenesis. In glioblastomas, we detected over-expression of ELTD1, and found that an antibody targeting ELTD1 could increase animal survival and decrease tumor volumes in a xenograft GBM model. RNA-seq analysis of the preclinical data in the model for GBM identified that some of the molecular pathways affected by the anti-ELTD1 antibody therapy are also found to be associated with MS. In this study, we used molecular-targeted (mt) MR imaging and immunohistochemistry to assess ELTD1 levels in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. Specifically, we found that ELTD1 is readily detected in the brains of mice with EAE and is predominantly found in the corpus callosum. In addition, we found that the blood-brain barrier (BBB) was compromised in the brains of EAE mice using contrast-enhanced MRI (CE-MRI), as well as altered relative cerebral blood flow (rCBF) in the brains and cervical spinal cords of these mice using perfusion imaging, compared to controls. These findings indicate that ELTD1 may be a promising biomarker for CNS-inflammation in MS.

PIMD: 33484378

Cerebral Vasoreactivity as an Indirect MRI Marker of White Matter Tracts Alterations in Multiple Sclerosis.

Patients with multiple sclerosis (MS) show a diffuse cerebral perfusion decrease, presumably related to multiple metabolism and vascular alterations. It is assumed that white matter fiber alterations cause a localized cerebral vasoreactivity (CVR) disruption through astrocytes metabolism alteration, leading to hypoperfusion. We proposed to (1) evaluate the CVR disruptions in MS, (2) in relation to white matter lesions and (3) compare CVR disruptions maps with standard imaging biomarkers. Thirty-five MS patients (10 progressive, 25 relapsing-remitting) and 22 controls underwent MRI with hypercapnic challenge, DTI imaging and neuropsychological assessment. Areas with disrupted CVR were assessed using a general linear model. Resulting maps were associated with clinical scores, compared between groups, and related to DTI metrics and white matter lesions. MS patients showed stronger disrupted CVR within supratentorial white matter, linking the left anterior insula to both the precentral gyrus and the right middle and superior frontal gyrus through the corpus callosum ($P < 0.05$, FWE corrected). Patient's verbal intellectual quotient was negatively associated with a pathway linking both hippocampi to the ispilateral prefrontal cortex ($P < 0.05$, FWE corrected). Disrupted CVR maps unrelated to DTI metrics and white matter lesions. We have demonstrated for the first time that white matter alterations can be indirectly identified through surrounding vessel alterations, and are related to clinical signs of MS. This offers a new, likely independent marker to monitor MS and supports a mediator role of the astrocytes in the fibers/vessels relationship.

PIMD: 33373835

Quantitative evaluation of callosal abnormalities in relapsing-remitting multiple sclerosis using diffusion tensor imaging: A systemic review and meta-analysis.

Although the changes of diffusion tensor imaging (DTI) in corpus callosum (CC) in patients with relapsing-remitting multiple sclerosis (RRMS) has been reported, the results are controversial. We aimed to determine the damage to the CC in patients with RRMS using DTI.A systematic search of English databases (PubMed, Embase, Cochrane Library, and Scopus) was performed. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) values of DTI were compared between RRMS patients and healthy controls (HC) using Stata 12.0.A total of 461 patients and 365 HC from 15 studies were included. Compared with HC, the FA values of the whole CC (SMD -1.894, P < 0.001), genu (SMD -0.830, P < 0.001) and splenium (SMD -1.431, P < 0.001) of CC were significantly reduced in patients with RRMS. Moreover, the MD values of the whole CC (SMD 1.213, P < 0.001), genu (SMD 0.657, P < 0.001) and splenium (SMD 0.830, P < 0.001) of CC were significantly increased in patients with RRMS. Additionally, the AD values (SMD 0.635, P < 0.001) and RD values (SMD 1.480, P < 0.001) were significantly increased in the whole CC in patients with RRMS. The meta-regression analysis revealed that the male ratio showed a significant effect on the FA reduction in the splenium CC in RRMS patients.These results indicated that DTI parameters were potential biomarkers with increased sensitivity for detecting pathological damage in the CC in patients with RRMS.

PIMD: 33369182

{'sup': '®', '#text': 'Nestorone , a 19nor-progesterone derivative boosts remyelination in an animal model of demyelination.'}

We previously showed that Nestorone (NES), a synthetic progestin structurally related to progesterone, stimulated remyelination of the corpus callosum in a Cuprizone (CUP) mouse model of demyelination in intact females by promoting replenishment with mature oligodendrocytes (OL) (Glia. 2015;63:104-117). Here, we further investigated the underlying mechanisms of this promyelinating effect.We explored whether NES, applied subcutaneously through Alzet mini-osmotic pumps, regulates specific transcription factors involved in oligodendrocyte progenitor cell (OPC) proliferation and their differentiation into mature OL, using RT-qPCR and Western Blot analysis.Our present data show that in comparison to controls, a one-week treatment with NES, through Alzet mini-osmotic pumps, enhanced the production of three relevant transcription factor mRNAs encoding Olig2, Myt1, and Sox17. After 3 weeks, NES treatment reversed the effect of CUP on the levels of corresponding Olig2, Myt1, and Sox17 proteins. Moreover, in mice receiving NES + Estradiol (E2) co-treatment, levels of Olig2, Myt1, and Sox17 proteins did not change as compared to NES alone.NES alone or with E2 increased the levels of transcription factors, essential for myelin synthesis.

PIMD: 33368776

Multimodal MRI Response to Fingolimod in Multiple Sclerosis: A Nonrandomized, Single Arm, Observational Study.

Fingolimod has a favorable effect on conventional MRI measures; however, its neuroprotective effect is not clear. We aim to investigate changes of conventional and advanced MRI measures in lesions and normal-appearing white matter (NAWM) over 2 years in fingolimod-treated patients.Fifty relapsing-remitting multiple sclerosis patients and 27 healthy controls were enrolled in the study and underwent baseline, 1-year, and 2-year 3T MRI scans. T2 lesion volume, whole brain volume, cortical gray matter volume, white matter volume, corpus callosum area, percentage brain volume change (PBVC), Expanded Disability Status Scale, gadolinium-enhancing lesions, PBVC, magnetization transfer ratio (MTR), and diffusion tensor imaging metrics (fractional anisotropy [FA] and median diffusivity [MD]) in lesions and NAWM were calculated. Longitudinal changes were examined using one-way repeated measures ANOVA. Bonferroni correction for multiple testing was used when appropriate.Conventional MRI measures were unchanged in both groups. Lesion MTR increased significantly ($P < .001$), but NAWM-MTR remained unchanged. Lesion FA improved significantly in year 1 ($P = .003$) and over the study duration ($P = .05$). Lesion MD changed significantly from baseline to year 1 ($P < .001$) and remained stable over 2 years. NAWM-FA was significant from baseline to year 1 ($P = .002$) and from baseline to year 2 ($P < .001$). NAWM-MD was significant only from baseline to year 1 ($P = .001$).These findings suggest a possible neuroreparative effect of fingolimod on the MS lesions and NAWM. Larger and longer randomized studies are required to confirm these results.

PIMD: 33348120

Impairments of white matter tracts and connectivity alterations in five cognitive networks of patients with multiple sclerosis.

MS is associated with structural and functional brain alterations leading to cognitive impairments across multiple domains including attention, memory, and speed of information processing. Here, we analyzed the white matter damage and topological organization of white matter tracts in specific brain regions responsible for cognition in MS.Brain DTI, rs-fMRI, T1, T2, and T2-FLAIR were acquired for 22 MS subjects and 22 healthy controls. Automatic brain parcellation was performed on T1-weighted images. Skull-stripped T1-weighted intensity inverted images were co-registered to the b0 image. Diffusion-weighted images were processed to perform whole brain tractography. The rs-fMRI data were processed, and the connectivity matrixes were analyzed to identify significant differences in the network of nodes between the two groups using NBS analysis. In addition, diffusion entropy maps were produced from DTI data sets using in-house software.MS subjects exhibited significantly reduced mean FA and entropy in 38 and 34 regions, respectively, out of a total of 54 regions. The connectivity values in both structural and functional analyses were decreased in most regions of the default mode network and in four other cognitive networks in MS subjects compared to healthy controls. MS also induced significant reduction in the normalized hippocampus and corpus callosum volumes; the normalized hippocampus volume was significantly correlated with EDSS scores.MS subjects have significant white matter damage and reduction of FA and entropy in various brain regions involved in cognitive networks. Structural and functional connectivity within the default mode network and an additional four cognitive networks exhibited significant changes compared with healthy controls.

PIMD: 33303506

Rare case of Marchiafava-Bignami disease due to thiamine deficiency and malnutrition.

Marchiafava-Bignami disease (MBD) is a rare, toxic demyelinating disorder of the central nervous system associated with chronic alcoholism and malnutrition. The clinical presentation is varied and non-specific, including symptoms of acute dementia, impaired consciousness, dysarthria, hemiparesis, pyramidal tract signs, seizure activity, ataxia and signs of interhemispheric disconnection. The differential diagnosis of MBD may include Wernicke's encephalopathy, multiple sclerosis, encephalitis, infectious or paraneoplastic leucoencephalopathy, infarction, Alzheimer's disease, multi-infarct dementia and frontotemporal lobar degeneration (Pick) disease. The diagnosis of MBD is dependent on MRI findings of hyperintensity of the corpus callosum on T2 and fluid-attenuated inversion recovery T2 sequences, with or without extracallosal lesions. The use of MRI in diagnosis has allowed for early initiation of treatment with parenteral thiamine, and improved the prognosis of MBD from frequently fatal to a mortality of less than 8%. Administration of thiamine within 14 days of symptom onset has demonstrated statistically better outcomes over delayed treatment. We present a case report of MBD diagnosed in a 72-year-old woman who presented with ataxia and slurred speech, in an effort to highlight the importance of obtaining MRI in patients presenting with behavioural disturbance and neurological findings, as well as discuss the relationship between thiamine supplementation and demyelinating diseases in the central nervous system.

PIMD: 33282858

Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1) Is a Negative Regulator of Oligodendrocyte Progenitor Cell Differentiation in the Adult Mouse Brain.

Low-density lipoprotein receptor-related protein 1 (LRP1) is a large, endocytic cell surface receptor that is highly expressed by oligodendrocyte progenitor cells (OPCs) and LRP1 expression is rapidly downregulated as OPCs differentiate into oligodendrocytes (OLs). We report that the conditional deletion of from adult mouse OPCs ( ) increases the number of newborn, mature myelinating OLs added to the corpus callosum and motor cortex. As these additional OLs extend a normal number of internodes that are of a normal length, -deletion increases adult myelination. OPC proliferation is also elevated following deletion , however, this may be a secondary, homeostatic response to increased OPC differentiation, as our experiments show that LRP1 is a direct negative regulator of OPC differentiation, not proliferation. Deleting from adult OPCs also increases the number of newborn mature OLs added to the corpus callosum in response to cuprizone-induced demyelination. These data suggest that the selective blockade of LRP1 function on adult OPCs may enhance myelin repair in demyelinating diseases such as multiple sclerosis.

PIMD: 33279637

The Intellicage system provides a reproducible and standardized method to assess behavioral changes in cuprizone-induced demyelination mouse model.

Multiple sclerosis is a neurodegenerative disorder characterized by myelin loss in the brain parenchyma. To mimic the disease, mice are fed a cuprizone-supplemented diet for 5 weeks, which leads to demyelination of white and grey matter regions, with the corpus callosum being the most susceptible to cuprizone intoxication. Although this model is highly exploited, classical behavioural tests showed inconsistent results.In our study, we aimed to use the automated system Intellicage to phenotype the behaviour of cuprizone-fed mice.Mice were continuously monitored during the 5 weeks of intoxication in their home cages, with minimal interference from the experimenter. Mice were assessed for spontaneous activity, fine movements, and impulsivity.Consistently, cuprizone-fed mice showed reduced activity and impulsivity throughout the test period. These behavioral results were confirmed by repeating the battery of behavioral tests in a second cohort of cuprizone-fed mice. Our results suggest that the behavioural phenotyping of cuprizone-fed mice using Intellicage is reproducible and sensitive enough to detect changes normally missed in standard behavioral test batteries.Using a reproducible and standardized method to assess behavioral changes in mice intoxicated with cuprizone is crucial to better understand the disease as well as the functional outcome of treatments.

PIMD: 33253366

Non-invasive quantification of inflammation, axonal and myelin injury in multiple sclerosis.

The aim of this study was to determine the feasibility of diffusion basis spectrum imaging in multiple sclerosis at 7 T and to investigate the pathological substrates of tissue damage in lesions and normal-appearing white matter. To this end, 43 patients with multiple sclerosis (24 relapsing-remitting, 19 progressive), and 21 healthy control subjects were enrolled. White matter lesions were classified in T1-isointense, T1-hypointense and black holes. Mean values of diffusion basis spectrum imaging metrics (fibres, restricted and non-restricted fractions, axial and radial diffusivities and fractional anisotropy) were measured from whole brain white matter lesions and from both lesions and normal appearing white matter of the corpus callosum. Significant differences were found between T1-isointense and black holes (P ranging from 0.005 to <0.001) and between lesions' centre and rim ($P < 0.001$) for all the metrics. When comparing the three subject groups in terms of metrics derived from corpus callosum normal appearing white matter and T2-hyperintense lesions, a significant difference was found between healthy controls and relapsing-remitting patients for all metrics except restricted fraction and fractional anisotropy; between healthy controls and progressive patients for all metrics except restricted fraction and between relapsing-remitting and progressive multiple sclerosis patients for all metrics except fibres and restricted fractions (P ranging from 0.05 to <0.001 for all). Significant associations were found between corpus callosum normal-appearing white matter fibres fraction/non-restricted fraction and the Symbol Digit Modality Test (respectively, $r = 0.35$, $P = 0.043$; $r = -0.35$, $P = 0.046$), and between black holes radial diffusivity and Expanded Disability Status Score ($r = 0.59$, $P = 0.002$). We showed the feasibility of diffusion basis spectrum imaging metrics at 7 T, confirmed the role of the derived metrics in the characterization of lesions and normal appearing white matter tissue in different stages of the disease and demonstrated their clinical relevance. Thus, suggesting that diffusion basis spectrum imaging is a promising tool to investigate multiple sclerosis pathophysiology, monitor disease progression and treatment response.

PIMD: 33245472

Coenzyme Q10 enhances remyelination and regulate inflammation effects of cuprizone in corpus callosum of chronic model of multiple sclerosis.

Multiple Sclerosis (MS) is a chronic, progressive demyelinating disease of the central nervous system that causes the most disability in young people, besides trauma. Coenzyme Q10 (CoQ10)-also known as ubiquinone-is an endogenous lipid-soluble antioxidant in the mitochondrial oxidative respiratory chain which can reduce oxidative stress and inflammation, the processes associated with demyelination in MS. Cuprizone (CPZ) intoxication is a well-established model of inducing MS, best for studying demyelination-remyelination. In this study, we examined for the first time the role of CoQ10 in preventing demyelination and induction of remyelination in the chronic CPZ model of MS. 40 male mice were divided into four groups. 3 group chewed CPZ-containing food for 12 weeks to induce MS. After 4 weeks, one group were treated with CoQ10 (150 mg/kg/day) by daily gavage until the end of the experiment, while CPZ poisoning continued. At the end of 12 weeks, tail suspension test (TST) and open field test (OFT) was taken and animals were sacrificed to assess myelin basic protein (MBP), oligodendrocyte transcription factor-1 (Olig1), tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) by real-time polymerase chain reaction (real-time PCR) and total antioxidant capacity (TAC) and superoxide dismutase (SOD) by Elisa test. Luxol fast blue (LFB) staining was used to evaluate histological changes. CoQ10 administration promoted remyelination in histological findings. MBP and Olig-1 expression were increased significantly in CoQ10 treated group compare to the CPZ-intoxicated group. CoQ10 treatment alleviated stress oxidative status induced by CPZ and dramatically suppress inflammatory biomarkers. CPZ ingestion made no significant difference between normal control group and the CPZ-intoxicated group in TST and OFT. CoQ10 can enhance remyelination in the CPZ model and potentially might have same effects in MS patients.

PIMD: 33214945

An Unusual Presentation of Multiple Sclerosis in a Middle-Aged Woman: A Case Report and Literature Review.

An intense itching localized to dermatomes is a rare symptom of multiple sclerosis (MS). Herein, we report a case of a 45-year-old female who presented with severe itching and tingling sensation, gait disturbance, and bilateral paresthesia for one week. She also had a history of multiple admission in the hospital due to recurrent walking abnormalities and numbness and tingling of both hands associated with intermittent psychiatric symptoms. The neurological examination revealed spastic quadriparesis with lower limb muscles affected more than the upper limbs, numbness, and sensory loss in the upper extremities in the glove and stocking pattern. Magnetic resonance imaging (MRI) revealed multiple small rounded periventricular plaques in both hemispheres and along the long axis of the corpus callosum (fluid-attenuated inversion recovery/FLAIR sequence), and cerebrospinal fluid analysis revealed the presence of oligoclonal bands, suggestive of MS. She was commenced on methylprednisolone and carbamazepine, leading to progressive resolution of her signs and symptoms. She was discharged with monthly natalizumab, and she was doing well on her follow-up.

PIMD: 33208084

Increasing Progenitor Cell Proliferation in the Sub-Ventricular Zone: A Therapeutic Treatment for Progressive Multiple Sclerosis?

The purpose of this study was to determine if pharmacological treatment could increase progenitor cell proliferation in the Sub-ventricular Zone of aged rats. Previous work had shown that increasing progenitor cell proliferation in this region correlated well (R2=0.78; p= 0.0007) with functional recovery in a damaged corpus callosum (white matter tract), suggesting that progenitor cell proliferation results in oligodendrocytes in this region.10 month old male and female Sprague Dawley rats were fed the drugs for 30 days in cookie dough, then immunocytochemistry was performed on coronal brain sections, using Ki67 labeling to determine progenitor cell proliferation.Female rats showed low endogenous (control) progenitor cell proliferation, significantly different from male rats (P<0.0001), at this age. Ascorbic Acid (20 mg/kg, daily for 30 days) increased progenitor cell proliferation overall, but maintained the innate gender difference in stem cell proliferation (P=0.001). Prozac (5 mg/kg, daily for 30 days) increased progenitor cell proliferation for females but decreased stem cell proliferation for males, again showing a gender difference (P<0.0001). Simvastatin (1 mg/kg for 30 days) also increased progenitor cell proliferation in females and decreased progenitor cell proliferation in males, leading to a significant gender difference.The three drug combinations (fluoxetine, simvastatin, and ascorbic acid, patent # 9,254,281) led to ~ 4 fold increase in progenitor cell proliferation in females, while male progenitor cell proliferation was highest with 50 mg/kg ascorbic acid. However, the ascorbic acid increase in proliferation appears to be only on the sides of the ventricles, which is not the region that normally gives rise to oligodendrocytes.There are innate gender differences in progenitor cell proliferation at the Sub-Ventricular Zone at middle age in rats, possibly due to the loss of estrogen in females. We also see notable gender differences in progenitor cell proliferation in the Sub ventricular Zone in response to common drugs, such as fluoxetine, simvastatin and Vitamin C (ascorbic acid).

PIMD: 33173493

A Case of HaNDL with Low Cerebrospinal Fluid Level of Neurofilament Light Chain.

Diagnosis of the syndrome of headache and neurological deficits with cerebrospinal fluid (CSF) lymphocytosis (HaNDL) is based on clinical features, and no diagnostic biomarkers are available. We present a case presenting with characteristic features of HaNDL and an MRI lesion in the splenium of corpus callosum. CSF neurofilament light chain (NFL) levels were assessed in this patient together with 7 additional HaNDL patients, 18 multiple sclerosis (MS) patients, and 15 primary headache patients. Both HaNDL and primary headache patients showed significantly lower NFL levels than MS patients. Our results suggest that increased CSF levels of NFL and neuroaxonal loss are not characteristic features of HaNDL. Neurological disorders mimicking HaNDL often present with increased levels of NFL, and thus CSF measurement of NFL might be useful in differential diagnosis of HaNDL.

PIMD: 33158440

Deficiency of microglial Hv1 channel is associated with activation of autophagic pathway and ROS production in LPC-induced demyelination mouse model.

Multiple sclerosis (MS) is an immune-mediated demyelinated disease of the central nervous system. Activation of microglia is involved in the pathogenesis of myelin loss.This study is focused on the role of Hv1 in regulating demyelination and microglial activation through reactive oxygen species (ROS) production after lysophosphatidylcholine (LPC)-mediated demyelination. We also explored autophagy in this process.A model of demyelination using two-point LPC injection into the corpus callosum was established. LFB staining, immunofluorescence, Western blot, and electron microscopy were used to study the severity of demyelination. Microglial phenotype and autophagy were detected by immunofluorescence and Western blot. Morris water maze was used to test spatial learning and memory ability.We have identified that LPC-mediated myelin damage was reduced by Hv1 deficiency. Furthermore, we found that ROS and autophagy of microglia increased in the demyelination region, which was also inhibited by Hv1 knockout.These results suggested that microglial Hv1 deficiency ameliorates demyelination through inhibition of ROS-mediated autophagy and microglial phenotypic transformation.

PIMD: 33106352

Ferroptosis Mediates Cuprizone-Induced Loss of Oligodendrocytes and Demyelination.

Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS. Cuprizone (CZ), a copper chelator, is widely used to study demyelination and remyelination in the CNS, in the context of MS. However, the mechanisms underlying oligodendrocyte (OL) cell loss and demyelination are not known. As copper-containing enzymes play important roles in iron homeostasis and controlling oxidative stress, we examined whether chelating copper leads to disruption of molecules involved in iron homeostasis that can trigger iron-mediated OL loss. We show that giving mice (male) CZ in the diet induces rapid loss of OL in the corpus callosum by 2 d, accompanied by expression of several markers for ferroptosis, a relatively newly described form of iron-mediated cell death. In ferroptosis, iron-mediated free radicals trigger lipid peroxidation under conditions of glutathione insufficiency, and a reduced capacity to repair lipid damage. This was further confirmed using a small-molecule inhibitor of ferroptosis that prevents CZ-induced loss of OL and demyelination, providing clear evidence of a copper-iron connection in CZ-induced neurotoxicity. This work has wider implications for disorders, such as multiple sclerosis and CNS injury. Cuprizone (CZ) is a copper chelator that induces demyelination. Although it is a widely used model to study demyelination and remyelination in the context of multiple sclerosis, the mechanisms mediating demyelination is not fully understood. This study shows, for the first time, that CZ induces demyelination via ferroptosis-mediated rapid loss of oligodendrocytes. This work shows that chelating copper with CZ leads to the expression of molecules that rapidly mobilize iron from ferritin (an iron storage protein), that triggers iron-mediated lipid peroxidation and oligodendrocyte loss (via ferroptosis). Such rapid mobilization of iron from cellular stores may also play a role in cell death in other neurologic conditions.

PIMD: 33085075

Recommendations of the Polish Medical Society of Radiology and the Polish Society of Neurology for a protocol concerning routinely used magnetic resonance imaging in patients with multiple sclerosis.

Magnetic resonance imaging (MRI) is a widely used method for the diagnosis of multiple sclerosis that is essential for the detection and follow-up of the disease. OBJECTIVE: The Polish Medical Society of Radiology (PLTR) and the Polish Society of Neurology (PTN) present the second version of their recommendations for investigations routinely conducted in magnetic resonance imaging departments in patients with multiple sclerosis. This version includes new data and practical comments for electroradiology technologists and radiologists. The recommended protocol aims to improve the MRI procedure and, most importantly, to standardise the method of conducting scans in all MRI departments. This is crucial for the initial diagnostics necessary for establishing a diagnosis, as well as for MS patient monitoring, which directly translates into significant clinical decisions. INTRODUCTION: Multiple sclerosis (MS) is a chronic immune mediated inflammatory demyelinating disease of the central nervous system (CNS), the aetiology of which is still unknown. The nature of the disease lies in a CNS destruction process disseminated in time (DIT) and space (DIS). MRI detects focal lesions in the white and grey matter with high sensitivity (although with significantly lower specificity in the latter). It is also the best tool to assess brain atrophy in patients with MS in terms of grey matter volume (GMV) and white matter volume (WMV) as well as local atrophy (by measuring the volume of thalamus, corpus callosum, subcortical nuclei, and hippocampus) as parameters that correlate with disability progression and cognitive dysfunctions. Progress in MR techniques, as well as advances in postprocessing the obtained data, has driven the dynamic development of computer programs that allow for a more repeatable assessment of brain atrophy in both cross-sectional and longitudinal studies. MR imaging is unquestionably the best diagnostic tool available to follow up the course of the disease and support clinicians in choosing the most appropriate treatment strategy for their MS patient. However, to diagnose and follow up MS patients on the basis of MRI in accordance with the latest standards, the MRI study must adhere to certain quality criteria. Such criteria are the subject of this paper.

PIMD: 33080467

The role of glycogen synthase kinase 3 beta in multiple sclerosis.

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that leads to progressive neurological disability due to axonal deterioration. Although MS presents profound heterogeneity in the clinical course, its underlying central mechanism is active demyelination and neurodegeneration associated with inflammation. Multiple autoimmune and neuroinflammatory pathways are involved in the demyelination process of MS. Analysis of MS lesions has shown that inflammatory genes are upregulated. Glycogen synthase kinase-3 (GSK-3) is part of the mitogen-activated protein kinase (MAPK) family and has important roles in many signaling cascades. GSK-3 is a highly conserved serine/threonine protein kinase expressed in both the central and the peripheral nervous systems. GSK-3 modulates several biological processes through phosphorylation of protein kinases, including cell signaling, neuronal growth, apoptosis and production of pro-inflammatory cytokines and interleukins, allowing adaptive changes in events such as cellular proliferation, migration, inflammation, and immunity. GSK-3 occurs in mammals in two isoforms GSK-3α and GSK-3β, both of which are common in the brain, although GSK-3α is found particularly in the cerebral cortex, cerebellum, striated hippocampus and Purkinje cells, while GSK-3β is found in all brain regions. In patients with chronic progressive MS, expression of GSK-3β is elevated in several brain regions such as the corpus callosum and cerebral cortex. GSK-3β inhibition may play a role in glial cell activation, reducing pathological pain induced by nerve injury by formalin injection. According to the role of GSK-3β in pathological conditions, the aim of this article is review of the role of GSK-3β in multiple sclerosis and inflammation of neurons.

PIMD: 33068322

BALB/c mice infected with Angiostrongylus cantonensis: A new model for demyelination in the brain.

In this study, we present a new model for demyelination of the central nervous system (CNS). BALB/c mice were infected with Angiostrongylus cantonensis and analyzed 7, 14, and 21 days postinfection. Neurological scale evaluation, magnetic resonance imaging (MRI), histology, real-time quantitative polymerase chain reaction, and western blotting were all performed on days 7, 14, and 21. The results showed that the neurological functions and weight of A. cantonensis-infected mice decreased markedly after 21 days of infection. MRI showed subdural effusion and white high signals in the corpus callosum in both T1WI and T2WI, while hematoxylin and eosin and luxol fast blue staining showed hemorrhage and demyelination in the corpus callosum. Transmission electron microscopy revealed that the ultrastructure of the myelin sheath in the corpus callosum was dispersed or disintegrated. The percentage of myelinated axons was significantly decreased, and the g-ratio was lower than that in the normal group. Both protein and mRNA levels of myelin basic protein decreased markedly at 21 days postinfection. Immunofluorescence revealed that the number of CC1 positive cells in the corpus callosum also decreased, which confirmed the damage of A. cantonensis to oligodendrocytes. Our experiments confirmed that A. cantonensis infection caused demyelination in the CNS of BALB/c mice after 21 days, and its clinical manifestations and pathological changes were similar to those of multiple sclerosis and other CNS demyelination models. Thus, mice infected with A. cantonensis could be used as a new model to study acute demyelination of the CNS.

PIMD: 33035669

Machine learning based white matter models with permeability: An experimental study in cuprizone treated in-vivo mouse model of axonal demyelination.

The intra-axonal water exchange time (τ), a parameter associated with axonal permeability, could be an important biomarker for understanding and treating demyelinating pathologies such as Multiple Sclerosis. Diffusion-Weighted MRI (DW-MRI) is sensitive to changes in permeability; however, the parameter has so far remained elusive due to the lack of general biophysical models that incorporate it. Machine learning based computational models can potentially be used to estimate such parameters. Recently, for the first time, a theoretical framework using a random forest (RF) regressor suggests that this is a promising new approach for permeability estimation. In this study, we adopt such an approach and for the first time experimentally investigate it for demyelinating pathologies through direct comparison with histology. We construct a computational model using Monte Carlo simulations and an RF regressor in order to learn a mapping between features derived from DW-MRI signals and ground truth microstructure parameters. We test our model in simulations, and find strong correlations between the predicted and ground truth parameters (intra-axonal volume fraction f: R =0.99, τ: R =0.84, intrinsic diffusivity d: R =0.99). We then apply the model in-vivo, on a controlled cuprizone (CPZ) mouse model of demyelination, comparing the results from two cohorts of mice, CPZ (N=8) and healthy age-matched wild-type (WT, N=8). We find that the RF model estimates sensible microstructure parameters for both groups, matching values found in literature. Furthermore, we perform histology for both groups using electron microscopy (EM), measuring the thickness of the myelin sheath as a surrogate for exchange time. Histology results show that our RF model estimates are very strongly correlated with the EM measurements (ρ = 0.98 for f, ρ = 0.82 for τ). Finally, we find a statistically significant decrease in τ in all three regions of the corpus callosum (splenium/genu/body) of the CPZ cohort (<τ>=310ms/330ms/350ms) compared to the WT group (<τ>=370ms/370ms/380ms). This is in line with our expectations that τ is lower in regions where the myelin sheath is damaged, as axonal membranes become more permeable. Overall, these results demonstrate, for the first time experimentally and in vivo, that a computational model learned from simulations can reliably estimate microstructure parameters, including the axonal permeability .

PIMD: 32996165

The effect of microglial ablation and mesenchymal stem cell transplantation on a cuprizone-induced demyelination model.

Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system with symptoms such as neuroinflammation, astrocytosis, microgliosis, and axonal degeneration. Mesenchymal stem cells (MSCs) with their immunomodulation, differentiation, and neuroprotection abilities can influence the remyelination process. The goal of this study is to investigate the impact of microglial ablation and MSCs transplantation on remyelination processes in the corpus callosum (CC) of the cuprizone demyelination model. For the induction of a chronic demyelination model, C57BL6 mice were fed with chow containing 0.2% cuprizone (wt/wt) for 12 weeks. For the depletion of microglia, PLX3397 was used as a colony-stimulating factor 1 receptor inhibitor for 21 days. MSCs were injected to the right lateral ventricle and after 2 weeks, the mice were killed. We assessed glial cells using specific markers such as APC, Iba-1, and GFAP using the immunohistochemistry method. Remyelination was evaluated by Luxol fast blue (LFB) staining and transmission electron microscope (TEM). The specific genes of microglia and MSCs were evaluated by a quantitative real-time polymerase chain reaction. According to the results of the study, 21 days of PLX3397 treatment significantly reduced microglial cells, and MSCs transplantation decreased the number of astrocytes, whereas the oligodendrocytes population increased significantly in PLX + MSC group in comparison with the cuprizone mice. Furthermore, PLX and MSC treatment elevated levels of remyelination compared with the cuprizone group, as confirmed by LFB staining and TEM analysis. The molecular results showed that MSC transplantation significantly decreased the number of microglia through the CX3CL1/CX3CR1 axis. These results revealed that PLX3397 treatment and MSCs injection reduced microgliosis and astrocytosis. It also increased the oligodendrocytes population by enhancing remyelination in the CC of the cuprizone model of MS.

PIMD: 32990740

Associations Between Findings From Myelin Water Imaging and Cognitive Performance Among Individuals With Multiple Sclerosis.

Cognitive impairment is a debilitating symptom of multiple sclerosis (MS) that affects up to 70% of patients. An improved understanding of the underlying pathology of MS-related cognitive impairment would provide considerable benefit to patients and clinicians.To determine whether there is an association between myelin damage in tissue that appears completely normal on standard clinical imaging, but can be detected by myelin water imaging (MWI), with cognitive performance in MS.In this cross-sectional study, participants with MS and controls underwent cognitive testing and magnetic resonance imaging (MRI) from August 23, 2017, to February 20, 2019. Participants were recruited through the University of British Columbia Hospital MS clinic and via online recruitment advertisements on local health authority websites. Cognitive testing was performed in the MS clinic, and MRI was performed at the adjacent academic research neuroimaging center. Seventy-three participants with clinically definite MS fulfilling the 2017 revised McDonald criteria for diagnosis and 22 age-, sex-, and education-matched healthy volunteers without neurological disease were included in the study. Data analysis was performed from March to November 2019.MWI was performed at 3 T with a 48-echo, 3-dimensional, gradient and spin-echo (GRASE) sequence. Cognitive testing was performed with assessments drawn from cognitive batteries validated for use in MS.The association between myelin water measures, a measurement of the T2 relaxation signal from water in the myelin bilayers providing a specific marker for myelin, and cognitive test scores was assessed using Pearson correlation. Three white matter regions of interest-the cingulum, superior longitudinal fasciculus (SLF), and corpus callosum-were selected a priori according to their known involvement in MS-related cognitive impairment.For the 95 total participants, the mean (SD) age was 49.33 (11.44) years. The mean (SD) age was 50.2 (10.7) years for the 73 participants with MS and 46.4 (13.5) for the 22 controls. Forty-eight participants with MS (66%) and 14 controls (64%) were women. The mean (SD) years of education were 14.7 (2.2) for patients and 15.8 (2.5) years for controls. In MS, significant associations were observed between myelin water measures and scores on the Symbol Digit Modalities Test (SLF, r = -0.490; 95% CI, -0.697 to -0.284; P < .001; corpus callosum, r = -0.471; 95% CI, -0.680 to -0.262; P < .001; and cingulum, r = -0.419; 95% CI, -0.634 to -0.205; P < .001), Selective Reminding Test (SLF, r = -0.444; 95% CI, -0.660 to -0.217; P < .001; corpus callosum, r = -0.411; 95% CI, -0.630 to -0.181; P = .001; and cingulum, r = -0.361; 95% CI, -0.602 to -0.130; P = .003), and Controlled Oral Word Association Test (SLF, r = -0.317; 95% CI, -0.549 to -0.078; P = .01; and cingulum, r = -0.335; 95% CI, -0.658 to -0.113; P = .006). No significant associations were found in controls.This study used MWI to demonstrate that otherwise normal-appearing brain tissue is diffusely damaged in MS, and the findings suggest that myelin water measures are associated with cognitive performance. MWI offers an in vivo biomarker feasible for use in clinical trials investigating cognition, providing a means for monitoring changes in myelination and its association with symptom worsening or improvement.

PIMD: 32926951

Signal alterations of glutamate-weighted chemical exchange saturation transfer MRI in lysophosphatidylcholine-induced demyelination in the rat brain.

To compare in vivo glutamate-weighted chemical exchange saturation transfer (GluCEST-weighted) signal changes between in a rat model of demyelinated multiple sclerosis and control groups.Using a pre-clinical 7 T magnetic resonance imaging (MRI) system, CEST imaging was applied to a toxin (lysophosphatidylcholine; LPC) induced rat (MS) and control (CTRL) groups to compare in vivo glutamate signal changes. The GluCEST-weighted signals were analyzed based on the magnetization transfer ratio asymmetry approach at 3.0 ppm on the region-of-interests (ROIs) in the corpus callosum and hippocampus at each hemispheric region.GluCEST-weighted signals were significantly changed between the CTRL and MS groups, while higher glutamate signals were indicated in the MS than the CTRL group ([MS / CTRL]; hippocampus: [6.159 ± 0.790 / 4.336 ± 0.446] and corpus callosum: [-3.545 ± 0.945 / -6.038 ± 0.620], all $p = 0.001$).Our results show increased GluCEST-weighted signals in the LPC-induced demyelination rat brain compared with control. GluCEST-weighted imaging could be a useful tool for defining a biomarker to estimate the glutamate-related metabolism in MS.

PIMD: 32922313

Probable Autoimmune Depression in a Patient With Multiple Sclerosis and Antineuronal Antibodies.

In a subgroup of patients with mood disorders, clear-cut organic disorders are responsible for depressive symptoms (e.g., autoimmune diseases such as multiple sclerosis or systemic lupus erythematosus). In these cases, an organic affective disorder can be diagnosed.The authors present the case of a 59-year-old male patient who developed a severe depressive episode over approximately 6 months and was, therefore, admitted to the hospital. In retrospect, he reported that, at age 39, he suffered from self-limiting sensory disturbances and muscle weakness in both legs. The current magnetic resonance imaging of his brain showed several conspicuous FLAIR-hyperintense supratentorial white matter lesions compatible with chronic inflammatory brain disease. Imaging of the spinal axis revealed no clear spinal lesions. Cerebrospinal fluid (CSF) analyses showed CSF-specific oligoclonal bands. Therefore, multiple sclerosis was diagnosed. Further CSF analyses, using tissue-based assays with indirect immunofluorescence on unfixed murine brain tissue, revealed a (peri-)nuclear signal and a strong neuritic signal of many neurons, especially on granule cells in the cerebellum, hippocampus, and olfactory bulb, as well as in the corpus callosum. Additionally, antinuclear antibody (ANA) titers of 1:12,800 and a lymphopenia were detected in blood tests. Further system clarification showed no suspicion of rheumatic or oncological disease. Anti-inflammatory treatment led to rapid and sustained improvement.The present patient suffered from a probable "autoimmune depression" in the context of newly diagnosed multiple sclerosis with typical MRI and CSF pathologies, alongside mild concomitant latent systemic autoimmune process (with high-titer ANAs and lymphopenia) and unknown antineuronal antibodies. The case report illustrates that a depressive syndrome suggestive of primary idiopathic depressive disorder may be associated with an autoimmune brain involvement. The detection of such organic affective disorders is of high clinical relevance for affected patients, as it enables alternative and more causal treatment approaches.

PIMD: 32920871

Dicrocoelium ova can block the induction phase of experimental autoimmune encephalomyelitis.

This study aimed at investigating the impact of Dicrocoelium ova on experimental autoimmune encephalomyelitis (EAE) treatment in C57BL6 mice.Twenty-eight C57BL/6 mice were assigned into four groups as PBS, prophylaxis (P), treatment1 (T1) and treatment2 (T2). Prior to induction of EAE in prophylaxis group and on days 7 and 18 in T1 and T2 groups, respectively, Dicrocoelium eggs were injected intraperitoneally to each mouse. The clinical score, weight changes and incidence time of EAE were recorded. IFN-γ and IL-4 expression is quantified on spleen cells. Also, histopathological study by (H&E) and Toluidine-Blue (TB), and Luxol Fast Blue (LFB) were performed. The data were analysed using SPSS version 21. Mean disease scores were significantly lower in P and T1 groups than the PBS group (P = .01). IFN-γ was lower in P and T1 groups than the PBS group. The highest level of IL-4 was observed in T1 group. The total number of neuroglia cells of corpus callosum was similar in all groups, but the density increased in T1 group compared to the PBS group (P = .03).Dicrocoelium eggs have a great potential to stimulate immunomodulation towards treatment of EAE during the initial phase.

PIMD: 32892382

Shikonin ameliorates experimental autoimmune encephalomyelitis (EAE) via immunomodulatory, anti-apoptotic and antioxidative activity.

Multiple sclerosis is a common autoimmune inflammatory disease of the central nervous system. There are several underlying mechanisms for the pathogenesis of the disease, including inflammation, oligodendrocyte apoptosis and oxidative stress.The mechanism of action of shikonin was investigated in the C57BL/6 experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis.The results revealed that EAE induction significantly increased the extent of demyelination in the corpus callosum tissues of the animals, while treatment of the mice with shikonin significantly decreased the extent of demyelination. Real-time polymerase chain reaction-based analysis of the brain samples from the EAE mice revealed significant enhancement in the expression levels of tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and Bax genes as well as a reduction in the expression levels of transforming growth factor-ß (TGF-β) and Bcl2. But, shikonin treatment significantly reduced the expression levels of TNF-α, IFN-γ and Bax. On the other hand, the expression levels of TGF-β and Bcl2 as well as the activity of glutathione peroxidase-1 (GPX-1) enzyme were significantly increased following the shikonin treatment.This study emphasized the immune-modulatory and antioxidative effects of shikonin, which may have an important healing effect on the severity of EAE.

PIMD: 32814050

Fractalkine-Dependent Microglial Pruning of Viable Oligodendrocyte Progenitor Cells Regulates Myelination.

Oligodendrogenesis occurs during early postnatal development, coincident with neurogenesis and synaptogenesis, raising the possibility that microglia-dependent pruning mechanisms that modulate neurons regulate myelin sheath formation. Here we show a population of ameboid microglia migrating from the ventricular zone into the corpus callosum during early postnatal development, termed "the fountain of microglia," phagocytosing viable oligodendrocyte progenitor cells (OPCs) before onset of myelination. Fractalkine receptor-deficient mice exhibit a reduction in microglial engulfment of viable OPCs, increased numbers of oligodendrocytes, and reduced myelin thickness but no change in axon number. These data provide evidence that microglia phagocytose OPCs as a homeostatic mechanism for proper myelination. A hallmark of hypomyelinating developmental disorders such as periventricular leukomalacia and of adult demyelinating diseases such as multiple sclerosis is increased numbers of oligodendrocytes but failure to myelinate, suggesting that microglial pruning of OPCs may be impaired in pathological states and hinder myelination.

PIMD: 32798053

Alexithymia in multiple sclerosis: Clinical and radiological correlations.

Alexithymia, meaning no words for emotions is a common problem that could affect up to 53% of patients in multiple sclerosis (MS).To determine the frequency of alexithymia in MS and investigate MS-related abnormalities in structural magnetic resonance imaging (MRI) and their associations with fatigue and cognitive functions.Ninety-five patients at all stages of the disease were examined: 21 with clinically isolated syndromes (CIS), 30 with relapsing-remitting MS (RRMS), 21 with primary (PP) and 23 with secondary progressive MS (SPMS). Alexithymia was measured with the Toronto alexithymia scale (TAS-20) and correlated to cognitive functions, depression, and fatigue. Voxel-based morphometry MRI was analyzed to determine lesion load, cerebral and regional atrophy.Fifty-seven of patients had alexithymia with no significant difference between the clinical phenotypes. Alexithymic patients differed from non-alexithymic patients on fatigue, depression and information processing speed. Compared to non-alexithymic patients, alexithymic patients had decreased volumes of cerebral and cerebellar white matter and there was a significant relationship between alexithymia and decreased brainstem, thalamic and corpus callosum volume.Regardless of the phenotype of MS, alexithymia is associated with atrophy of cerebral and cerebellar white matter, brainstem, corpus callosum, and thalami.

PIMD: 32792656

Advanced MRI features in relapsing multiple sclerosis patients with and without CSF oligoclonal IgG bands.

Oligoclonal IgG bands (OCB) in cerebrospinal fluid (CSF) are important in diagnosis of multiple sclerosis (MS). We evaluated the MRI features of clinically definite MS subjects with and without CSF-OCB. Relapsing MS subjects were recruited from a prospective registry in a university center. CSF-OCB were detected using isoelectric focusing and IgG-specific immunofixation. MRI metrics including brain volumes, lesion volumes and microstructural measures, were analyzed by FMRIB Software Library (FSL) and Statistical Parametric Mapping (SPM). Seventy-five subjects with relapsing MS were analyzed. Forty-four (59%) subjects had an interval MRI at around 1 year. CSF-OCB were detected in 46 (61%) subjects. The OCB-positive group had a higher proportion of cerebellar lesions than the OCB-negative group (23.9% vs. 3.4%, $p = 0.057$). Except for amygdala volumes which were lower in the OCB-positive group ($p = 0.034$), other regional brain volumes including the subcortical deep gray matter and corpus callosum were similar. The two groups also showed comparable brain atrophy rate. For DTI, the OCB-positive group showed significantly higher mean diffusivity (MD) value in perilesional normal-appearing white matter ($p = 0.043$). Relapsing MS patients with and without CSF-OCB shared similar MRI features regarding volumetric analyses and DTI microstructural integrity.

PIMD: 32755334

Innovative methods measure the neural correlates of proprioception in multiple sclerosis.

The authors of the recently published article "Position sense deficits at the lower limbs in early multiple sclerosis: clinical and neural correlates" (Iandolo R, Bommarito G, Falcitano L, Schiavi S, Piaggio N, Mancardi GL, Casadio M, Inglese M. 34: 260-270, 2020) provide strong evidence for the neural correlates leading to deficits in proprioception in multiple sclerosis. We believe their findings and innovative methodology show promise for how proprioception is measured in this and other clinical populations. We also suggest that further work should investigate the role of the corpus callosum in proprioceptive balance control.

PIMD: 32748319

White matter correlates of slowed information processing speed in unimpaired multiple sclerosis patients with young age onset.

Slowed information processing speed is among the earliest markers of cognitive impairment in multiple sclerosis (MS) and has been associated with white matter (WM) structural integrity. Localization of WM tracts associated with slowing, but not significant impairment, on specific cognitive tasks in pediatric and young age onset MS can facilitate early and effective therapeutic intervention. Diffusion tensor imaging data were collected on 25 MS patients and 24 controls who also underwent the Symbol Digit Modalities Test (SDMT) and the computer-based Cogstate simple and choice reaction time tests. Fractional anisotropy (FA), mean (MD), radial (RD) and axial (AD) diffusivities were correlated voxel-wise with processing speed measures. All DTI metrics of several white matter tracts were significantly different between groups ($p < 0.05$). Notably, higher MD, RD, and AD, but not FA, in the corpus callosum correlated with lower scores on both SDMT and simple reaction time. Additionally, all diffusivity metrics in the left corticospinal tract correlated negatively with SDMT scores, whereas only MD in the right superior fronto-occipital fasciculus correlated with simple reaction time. In conclusion, subtle slowing of processing speed is correlated with WM damage in the visual-motor processing pathways in patients with young age of MS onset.

PIMD: 32733354

Inflammation and Corticospinal Functioning in Multiple Sclerosis: A TMS Perspective.

Transcranial magnetic stimulation (TMS) has been employed in multiple sclerosis (MS) to assess the integrity of the corticospinal tract and the corpus callosum and to explore some physiological properties of the motor cortex. Specific alterations of TMS measures have been strongly associated to different pathophysiological mechanisms, particularly to demyelination and neuronal loss. Moreover, TMS has contributed to investigate the neurophysiological basis of MS symptoms, particularly those not completely explained by conventional structural damage, such as fatigue. However, variability existing between studies suggests that alternative mechanisms should be involved. Knowledge of MS pathophysiology has been enriched by experimental studies in animal models (i.e., experimental autoimmune encephalomyelitis) demonstrating that inflammation alters synaptic transmission, promoting hyperexcitability and neuronal damage. Accordingly, TMS studies have demonstrated an imbalance between cortical excitation and inhibition in MS. In particular, cerebrospinal fluid concentrations of different proinflammatory and anti-inflammatory molecules have been associated to corticospinal hyperexcitability, highlighting that inflammatory synaptopathy may represent a key pathophysiological mechanism in MS. In this perspective article, we discuss whether corticospinal excitability alterations assessed with TMS in MS patients could be useful to explain the pathophysiological correlates and their relationships with specific MS clinical characteristics and symptoms. Furthermore, we discuss evidence indicating that, in MS patients, inflammatory synaptopathy could be present since the early phases, could specifically characterize relapses, and could progressively increase during the disease course.

PIMD: 32714402

Tyrosine Kinase Receptors Axl and MerTK Mediate the Beneficial Effect of Electroacupuncture in a Cuprizone-Induced Demyelinating Model.

Electroacupuncture has been shown to promote remyelination in a demyelinating model of multiple sclerosis (MS) through enhanced microglial clearance of degraded myelin debris. However, the mechanisms involved in this process are yet to be clearly elucidated. It has been revealed that TAM receptor tyrosine kinases (Tyro3, Axl, and MerTK) play pivotal roles in regulating multiple features of microglia, including the phagocytic function and myelin clearance. Therefore, the aim of this study is to further confirm whether electroacupuncture improves functional recovery in this model and to characterise the involvement of the TAM receptor during this process. In addition to naive control mice, a cuprizone-induced demyelinating model was established, and long-term electroacupuncture treatment was administrated. To evaluate the efficiency of functional recovery following demyelination, we performed beam-walking test and rotarod performance test; to objectify the degree of remyelination, we performed transmission electron microscopy and protein quantification of mature oligodendrocyte markers. Oil Red O staining was used to evaluate the deposit of myelin debris. We confirmed that, in cuprizone-treated mice, electroacupuncture significantly ameliorates motor-coordinative dysfunction and counteracts demyelinating processes, with less deposit of myelin debris accumulating in the corpus callosum. Surprisingly, mRNA expression of TAM receptors was significantly upregulated after electroacupuncture treatment, and we further confirmed an increased protein expression of Axl and MerTK after electroacupuncture treatment, indicating their involvement during electroacupuncture treatment. Finally, LDC1267, a selective TAM kinase inhibitor, abolished the therapeutic effect of electroacupuncture on motor-coordinative dysfunction. Overall, our data demonstrate that electroacupuncture could mitigate the progression of demyelination by enhancing the TAM receptor expression to facilitate the clearance of myelin debris. Our results also suggest that electroacupuncture may be a potential curative treatment for MS patients.

PIMD: 32683399

Corpus callosum index correlates with brain volumetry and disability in multiple sclerosis patients.

To analyze the correlation between corpus callosum index (CCI), brain volumetry, and disability in multiple sclerosis (MS) patients. The brain volumetry consists of the corpus callosum, cortical gray matter, subcortical gray matter, and white matter volumes.This was a retrospective cross-sectional study from October 2018 to February 2019 of 30 patients with MS aged 20 to 61 years old. Brain volumetry was performed using FreeSurfer software. The CCI were measured manually using conventional best mid-sagittal T1W brain MRI. The anterior, posterior, and medium segments were measured and divided to its greatest anteroposterior diameter. Higher CCI values indicated greater corpus callosum volumes. Clinical evaluation was comprised of MS subtype, age of onset, relapse frequency and Expanded Disability Status Scale (EDSS).Thirty MS patients with median of age 22 years were included. Relapsing-remitting (RRMS) subtype were 73.3%. Very significant correlations were shown between the CCI and corpus callosum volume (CCV) ($r=0.79$; $p<0.0001$) and cerebral white matter volume ($r=0.81$; $p<0.0001$). Significant correlations were shown between the CCI and cortical gray matter volume ($r=0.64$; $p<0.0001$) and subcortical gray matter volume ($r=0.69$; $p<0.0001$). The CCI was positively correlated with age of onset and inversely with EDSS. The CCV and CCI were smaller in secondary progressive MS (SPMS).The CCI is easy and fast to obtain in conventional MRI and significantly correlated with brain volumetry, age of onset and disability in MS patients.

PIMD: 32662738

Measurement of white matter fiber-bundle cross-section in multiple sclerosis using diffusion-weighted imaging.

When investigating white matter (WM) microstructure, the axonal fiber orientation should be considered. Constrained spherical deconvolution (CSD) is a diffusion-weighted imaging (DWI) method that estimates distribution of fibers within each imaging voxel.To study fiber-bundle cross-section (FC) as measured by CSD in multiple sclerosis (MS) patients versus healthy controls (HCs).DWI and three-dimensional (3D) T-weighted magnetic resonance imaging (MRI) were obtained from 45 MS patients and 45 HCs. We applied fixel-based morphometry analysis to assess differences of FC in MS against HCs and voxel-based analysis of fractional anisotropy (FA).We found a significant widespread reduction of WM FC in MS compared to HCs. The decrease in FA was less extensive, mainly located in regions with high lesion occurrence such as the periventricular WM and the corpus callosum. Progressive MS patients showed a significant FC reduction in the right anterior cingulum, bilateral cerebellum, and in several mesencephalic and diencephalic regions compared to relapsing-remitting MS patients.The CSD method can be applied in MS for a fiber-specific study of WM microstructure and quantification of FC. Fixel-based findings offered greater anatomical specificity and biological interpretability by identifying tract-specific differences and allowed substantial abnormalities to be detected.

PIMD: 32659734

Measurements of the corpus callosum index and fractional anisotropy of the corpus callosum and their cutoff values are useful to assess global brain volume loss in multiple sclerosis.

Recent studies suggest that parameters of the corpus callosum (CC), such as the CC index (CCI) and fractional anisotropy (FA) of the CC, may be related to the degree of brain volume loss (BVL) in MS patients; however, cutoff values that determine the degree of BVL have not been set.Seventy-five MS patients and 21 healthy controls (HCs) underwent volumetric MRI examinations. MS patients were also evaluated for T2 lesion load, the CCI, and FA of the CC. Among the 75 MS patients, 20 had undergone cognitive assessments with the Symbol Digit Modalities Test (SDMT). After 75 MS patients were categorized into mild, moderate, or severe BVL subgroups according to our previous report, we performed receiver operating characteristic analysis to determine the cutoff values of CCI and FA, categorizing the MS patients into the three subgroups.The volume of the CC was significantly reduced in MS patients compared to that in HCs. The CCI and FA were significantly associated with EDSS, disease duration, clinical phenotype, T2-lesion load, and whole brain volume. The FA was significantly correlated with the SDMT score. We identified optimal cutoff values for the CCI and FA of 0.32 (85% sensitivity, 92% specificity) and 0.39 (100% sensitivity, 92% specificity), respectively, which discriminated the severe BVL group from others, and 0.385 (84% sensitivity, 74% specificity) and 0.45 (81% sensitivity, 89% specificity), respectively, which discriminated the mild BVL group from others.The CCI and FA cutoff values may be useful for evaluating the degree of MS brain atrophy in clinical practice.

PIMD: 32638202

Calorie restriction promotes remyelination in a Cuprizone-Induced demyelination mouse model of multiple sclerosis.

Over the past few decades several attempts have been made to introduce a potential and promising therapy for Multiple sclerosis (MS). Calorie restriction (CR) is a dietary manipulation to reduce calorie intake which has been shown to improve neuroprotection and attenuate neurodegenerative disorders. Here, we evaluated the effect of 33% CR regimen for 4 weeks on the remyelination capacity of Cuprizone (CPZ) induced demyelination in a mouse model of MS. Results showed that CR induced a significant increase in motor coordination and balance performance in CPZ mice. Also, luxol fast blue (LFB) staining showed that CR regimen significantly improved the remyelination in the corpus callosum of CPZ + CR mice compared to the CPZ group. In addition, CR regimen significantly increased the transcript expression levels of BDNF, Sox2, and Sirt1 in the corpus callosum of CPZ mice, while decreasing the p53 levels. Moreover, CR regimen significantly decreased the apoptosis rate. Furthermore, astrogliosis (GFAP + astrocytes) and microgliosis (Iba-1 + microglia) were significantly decreased by CR regimen while oligodendrogenesis (Olig2+) and Sirt1 + cell expression were significantly increased in the corpus callosum of CPZ + CR mice compared to the CPZ group. In conclusion, CR regimen can promote remyelination potential in a CPZ-demyelinating mouse model of MS by increasing oligodendrocyte generation while decreasing their apoptosis.

PIMD: 32636463

A time-dependent diffusion MRI signature of axon caliber variations and beading.

MRI provides a unique non-invasive window into the brain, yet is limited to millimeter resolution, orders of magnitude coarser than cell dimensions. Here, we show that diffusion MRI is sensitive to the micrometer-scale variations in axon caliber or pathological beading, by identifying a signature power-law diffusion time-dependence of the along-fiber diffusion coefficient. We observe this signature in human brain white matter and identify its origins by Monte Carlo simulations in realistic substrates from 3-dimensional electron microscopy of mouse corpus callosum. Simulations reveal that the time-dependence originates from axon caliber variation, rather than from mitochondria or axonal undulations. We report a decreased amplitude of time-dependence in multiple sclerosis lesions, illustrating the potential sensitivity of our method to axonal beading in a plethora of neurodegenerative disorders. This specificity to microstructure offers an exciting possibility of bridging across scales to image cellular-level pathology with a clinically feasible MRI technique.

PIMD: 32617658

Cognitive impairment in benign multiple sclerosis: a multiparametric structural and functional MRI study.

The substrates of cognitive impairment in benign MS (BMS) still need to be identified. We investigated whether cognitive impairment in BMS patients is associated with specific patterns of brain structural and functional abnormalities.Thirty-seven BMS patients (EDSS score ≤ 3.0 and disease duration ≥ 15 years) and 50 healthy controls (HC) were studied. In BMS patients, a cognitive impairment index (CII) was derived. Gray matter (GM) volumes, white matter (WM) fractional anisotropy (FA) and resting-state (RS) functional connectivity (FC) were investigated for whole-brain relevant regions (cortex, lobes, subcortical nuclei, fiber tracts) and functional networks. Univariate and multivariate analyses identified independent predictors of cognitive impairment.In BMS, median CII was 9 (IQR: 4-16). Compared to HC, BMS patients showed reduced WM FA, GM atrophy and increased RS FC in fronto-temporo-parietal regions. At multivariate analysis, percentage of T2-lesions of the corpus callosum, reduced posterior corona radiata (PCR) FA and caudate nucleus atrophy were independent predictors of worse CII. A multivariate model identified reduced PCR FA ($R = 0.39$; $p = 0.001$) as the only predictor of CII.Cognitive impairment in BMS is associated with structural damage of relevant brain areas. WM damage of parietal regions was the predominant predictor of worse cognitive performance in these patients.

PIMD: 32612727

Recommendations of the Polish Medical Society of Radiology and the Polish Society of Neurology for the routinely used magnetic resonance imaging protocol in patients with multiple sclerosis.

Magnetic resonance imaging (MRI) is a widely used method for the diagnosis of multiple sclerosis (MS) that is essential for the detection and follow-up of the disease. The Polish Medical Society of Radiology (PLTR) and the Polish Society of Neurology (PTN) present the second version of the recommendations for examinations routinely conducted in magnetic resonance imaging departments in patients with MS, which include new data and practical comments for electroradiology technicians and radiologists. The recommended protocol aims to improve the MRI procedure and, most importantly, to standardise the method of conducting scans in all MRI departments. This is crucial for the initial diagnostics that are necessary to establish a diagnosis as well as monitor patients with MS, which directly translates into significant clinical decisions. MS is a chronic idiopathic inflammatory demyelinating disease of the central nervous system (CNS), the aetiology of which is still unknown. The nature of the disease lies in the CNS destruction process disseminated in time and space. MRI detects focal lesions in the white and grey matter with high sensitivity (with significantly less specificity in the latter). It is also the best tool to assess brain atrophy in patients with MS in terms of grey matter volume and white matter volume as well as local atrophy (by measuring the volume of thalamus, corpus callosum, subcortical nuclei, hippocampus) as parameters that correlate with disability progression and cognitive dysfunctions. Progress in magnetic resonance techniques, as well as the abilities of postprocessing the obtained data, has become the basis for the dynamic development of computer programs that allow for a more repeatable assessment of brain atrophy in both cross-sectional and longitudinal studies. MRI is unquestionably the best diagnostic tool used to follow up the course of the disease and to treat patients with MS. However, to diagnose and follow up the patients with MS on the basis of MRI in accordance with the latest standards, an MRI study must meet certain quality criteria, which are the subject of this paper.

PIMD: 32599064

Effects of EHP-101 on inflammation and remyelination in murine models of Multiple sclerosis.

Multiple Sclerosis (MS) is characterized by a combination of inflammatory and neurodegenerative processes in the spinal cord and the brain. Natural and synthetic cannabinoids such as VCE-004.8 have been studied in preclinical models of MS and represent promising candidates for drug development. VCE-004.8 is a multitarget synthetic cannabidiol (CBD) derivative acting as a dual Peroxisome proliferator-activated receptor-gamma/Cannabinoid receptor type 2 (PPARγ/CB) ligand agonist that also activates the Hypoxia-inducible factor (HIF) pathway. EHP-101 is an oral lipidic formulation of VCE-004.8 that has shown efficacy in several preclinical models of autoimmune, inflammatory, fibrotic, and neurodegenerative diseases. EHP-101 alleviated clinical symptomatology in EAE and transcriptomic analysis demonstrated that EHP-101 prevented the expression of many inflammatory genes closely associated with MS pathophysiology in the spinal cord. EHP-101 normalized the expression of several genes associated with oligodendrocyte function such as Teneurin 4 (Tenm4) and Gap junction gamma-3 (Gjc3) that were downregulated in EAE. EHP-101 treatment prevented microglia activation and demyelination in both the spinal cord and the brain. Moreover, EAE was associated with a loss in the expression of Oligodendrocyte transcription factor 2 (Olig2) in the corpus callosum, a marker for oligodendrocyte differentiation, which was restored by EHP-101 treatment. In addition, EHP-101 enhanced the expression of glutathione S-transferase pi (GSTpi), a marker for mature oligodendrocytes in the brain. We also found that a diet containing 0.2% cuprizone for six weeks induced a clear loss of myelin in the brain measured by Cryomyelin staining and Myelin basic protein (MBP) expression. Moreover, EHP-101 also prevented cuprizone-induced microglial activation, astrogliosis and reduced axonal damage. Our results provide evidence that EHP-101 showed potent anti-inflammatory activity, prevented demyelination, and enhanced remyelination. Therefore, EHP-101 represents a promising drug candidate for the potential treatment of different forms of MS.

PIMD: 32594382

Mesenchymal Stem Cells Ameliorate Cuprizone-Induced Demyelination by Targeting Oxidative Stress and Mitochondrial Dysfunction.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system. The main causes of MS disease progression, demyelination, and tissue damage are oxidative stress and mitochondrial dysfunction. Hence, the latter are considered as important therapeutic targets. Recent studies have demonstrated that mesenchymal stem cells (MSCs) possess antioxidative properties and are able to target mitochondrial dysfunction. Therefore, we investigated the effect of transplanting Wharton's jelly-derived MSCs in a demyelination mouse model of MS in which mice were fed cuprizone (CPZ) for 12 weeks. CPZ is a copper chelator that impairs the activity of cytochrome oxidase, decreases oxidative phosphorylation, and produces degenerative changes in oligodendrocytes, leading to toxic demyelination similar to those found in MS patients. Results showed that MSCs caused a significant increase in the percentage of myelinated areas and in the number of myelinated fibers in the corpus callosum of the CPZ + MSC group, compared to the CPZ group, as assessed by Luxol fast blue staining and transmission electron microscopy. In addition, transplantation of MSCs significantly increased the number of oligodendrocytes while decreasing astrogliosis and microgliosis in the corpus callosum of the CPZ + MSC group, evaluated by immunofluorescence. Moreover, the mechanism by which MSCs exert these physiological effects was found to be through abolishing the effect of CPZ on oxidative stress markers and mitochondrial dysfunction. Indeed, malondialdehyde significantly decreased while glutathione and superoxide dismutase significantly increased in CPZ + MSC mice group, in comparison witth the CPZ group alone. Furthermore, cell therapy with MSC transplantation increased the expression levels of mitochondrial biogenesis transcripts PGC1α, NRF1, MFN2, and TFAM. In summary, these results demonstrate that MSCs may attenuate MS by promoting an antioxidant response, reducing oxidative stress, and improving mitochondrial homeostasis.

PIMD: 32532336

Myelination- and immune-mediated MR-based brain network correlates.

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS), characterized by inflammatory and neurodegenerative processes. Despite demyelination being a hallmark of the disease, how it relates to neurodegeneration has still not been completely unraveled, and research is still ongoing into how these processes can be tracked non-invasively. Magnetic resonance imaging (MRI) derived brain network characteristics, which closely mirror disease processes and relate to functional impairment, recently became important variables for characterizing immune-mediated neurodegeneration; however, their histopathological basis remains unclear.In order to determine the MRI-derived correlates of myelin dynamics and to test if brain network characteristics derived from diffusion tensor imaging reflect microstructural tissue reorganization, we took advantage of the cuprizone model of general demyelination in mice and performed longitudinal histological and imaging analyses with behavioral tests. By introducing cuprizone into the diet, we induced targeted and consistent demyelination of oligodendrocytes, over a period of 5 weeks. Subsequent myelin synthesis was enabled by reintroduction of normal food.Using specific immune-histological markers, we demonstrated that 2 weeks of cuprizone diet induced a 52% reduction of myelin content in the corpus callosum (CC) and a 35% reduction in the neocortex. An extended cuprizone diet increased myelin loss in the CC, while remyelination commenced in the neocortex. These histologically determined dynamics were reflected by MRI measurements from diffusion tensor imaging. Demyelination was associated with decreased fractional anisotropy (FA) values and increased modularity and clustering at the network level. MRI-derived modularization of the brain network and FA reduction in key anatomical regions, including the hippocampus, thalamus, and analyzed cortical areas, were closely related to impaired memory function and anxiety-like behavior.Network-specific remyelination, shown by histology and MRI metrics, determined amelioration of functional performance and neuropsychiatric symptoms. Taken together, we illustrate the histological basis for the MRI-driven network responses to demyelination, where increased modularity leads to evolving damage and abnormal behavior in MS. Quantitative information about in vivo myelination processes is mirrored by diffusion-based imaging of microstructural integrity and network characteristics.

PIMD: 32524994

CD44 expression in the cuprizone model.

Numerous studies report that changes in extracellular matrix components and receptors, such as CD44, contribute to immune cell recruitment and thus lesion formation in multiple sclerosis (MS). In the present study, we used the cuprizone model to elucidate the expression pattern of CD44 in a toxin-induced MS model. Therefore, tissues of cuprizone-intoxicated mice were analyzed by real-time qRT-PCR and immunohistochemical staining against CD44. Co-localization analyses of CD44-positive cells with glial cell markers were performed by immunofluorescence labeling and in-situ hybridization. To investigate the functional importance of CD44 expression for myelination and glial cell activation, Cd44-deficient mice were used. In this study we demonstrate that CD44 expression is induced in a time-dependent manner in an autoimmune-independent model of MS. Up-regulation of CD44 expression was primarily associated to the superficial and perivascular glia limitans and demyelinated white matter structures, particularly the corpus callosum. In the demyelinated corpus callosum, CD44 was localized on GFAP astrocytes and IBA1 microglial cells. Despite a robust expression induction, Cd44-deficiency did not ameliorate cuprizone-induced pathology. Although further studies will be needed to examine the functional relevance of CD44 in the cuprizone model, the spatial and temporal expression pattern of CD44 will pave the way to evaluate its precise role in different (immune and non-immune) pathological conditions.

PIMD: 32519512

Impaired cognition is related to microstructural integrity in relapsing remitting multiple sclerosis.

Cognitive impairment is common in multiple sclerosis (MS). However, the relationship between cognitive deficits and microstructural abnormalities in Chinese MS patients remains unclear. We aimed to investigate the importance of microstructural abnormalities and the associations with cognitive impairment in Chinese MS patients.Three-dimensional T1-weighted magnetic resonance imaging (MRI) scans were obtained from 36 relapsing remitting MS patients. Diffusion tensor imaging (DTI) scans were acquired for 29 (81%) patients. Cognitive impairment was assessed using a comprehensive neuropsychological battery. Patients were classified into cognitively impaired (CI) group and cognitively preserved (CP) group. Using volBrain and FSL software, we assessed white matter lesion burden, white matter (WM) and gray matter (GM) volumetric as well as microstructural diffusivity. MRI variables explaining cognitive impairment were analyzed.Fifteen (42%) patients were classified as CI. Verbal learning and memory was the most commonly impaired domain (n = 16, 44%). CI patients had lower mean skeleton fractional anisotropy (FA) value than CP patients (275.45 vs. 283.61 × 10 , P = 0.023). The final predicting model including demographic variables and global skeleton mean diffusivity (MD) explained 43.6% of variance of the presence of cognitive impairment (β = 0.131, P = 0.041). CI patients showed a widespread change of microstructural integrity comparing to CP patients, which was rarely overlapping with lesion probability map. Microstructural abnormalities in corpus callosum were associated with performance in verbal learning and memory, processing speed and selective attention (P < 0.05).Loss of microstructural integrity demonstrated by DTI helps explain cognitive dysfunction in Chinese MS patients.

PIMD: 32517808

Transplantation of induced neural stem cells (iNSCs) into chronically demyelinated corpus callosum ameliorates motor deficits.

Multiple Sclerosis (MS) causes neurologic disability due to inflammation, demyelination, and neurodegeneration. Immunosuppressive treatments can modify the disease course but do not effectively promote remyelination or prevent long term neurodegeneration. As a novel approach to mitigate chronic stage pathology, we tested transplantation of mouse induced neural stem cells (iNSCs) into the chronically demyelinated corpus callosum (CC) in adult mice. Male C57BL/6 mice fed 0.3% cuprizone for 12 weeks exhibited CC atrophy with chronic demyelination, astrogliosis, and microglial activation. Syngeneic iNSCs were transplanted into the CC after ending cuprizone and perfused for neuropathology 2 weeks later. Magnetic resonance imaging (MRI) sequences for magnetization transfer ratio (MTR), diffusion-weighted imaging (T2), and diffusion tensor imaging (DTI) quantified CC pathology in live mice before and after iNSC transplantation. Each MRI technique detected progressive CC pathology. Mice that received iNSCs had normalized DTI radial diffusivity, and reduced astrogliosis post-imaging. A motor skill task that engages the CC is Miss-step wheel running, which demonstrated functional deficits from cuprizone demyelination. Transplantation of iNSCs resulted in marked recovery of running velocity. Neuropathology after wheel running showed that iNSC grafts significantly increased host oligodendrocytes and proliferating oligodendrocyte progenitors, while modulating axon damage. Transplanted iNSCs differentiated along astrocyte and oligodendrocyte lineages, without myelinating, and many remained neural stem cells. Our findings demonstrate the applicability of neuroimaging and functional assessments for pre-clinical interventional trials during chronic demyelination and detect improved function from iNSC transplantation. Directly reprogramming fibroblasts into iNSCs facilitates the future translation towards exogenous autologous cell therapies.

PIMD: 32503176

Could the Heat Shock Proteins 70 Family Members Exacerbate the Immune Response in Multiple Sclerosis? An in Silico Study.

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system. It represents one of the main causes of neurological disability in young people. In MS, the autoimmune response is directed against myelin antigens but other possible bio-molecular markers are investigated. The aim of this work was, through an in silico study, the evaluation of the transcriptional modifications between healthy subjects and MS patients in six brain areas (corpus callosum, hippocampus, internal capsule, optic chiasm, frontal and parietal cortex) in order to identify genes representative of the disease. Our results show the upregulation of the Heat Shock Proteins (HSPs) , , , , and of the HSP70 family, among which and are upregulated in all the brain areas. HSP70s are molecular chaperones indispensable for protein folding, recently associated with immune system maintenance. The little overexpression of the HSPs protects the cells from stress but extreme upregulation can contribute to the MS pathogenesis. We also investigated the genes involved in the immune system that result in overall upregulation in the corpus callosum, hippocampus, internal capsule, optic chiasm and are absent in the cortex. Interestingly, the genes of the immune system and the HSP70s have comparable levels of expression.

PIMD: 32436171

Structural changes in the brain of patients with relapsing-remitting multiple sclerosis compared to controls: a MRI-based stereological study.

Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system characterized by demyelination, inflammation, gliosis, and axonal loss. Nowadays, increasing scientific reports have focused on neurodegenerative processes and structural changes of the disease underlying pathogenesis.The aim of this study is a structural analysis of brain magnetic resonance images (MRIs) in patients with relapsing-remitting multiple sclerosis (RRMS) comparing with normal individuals.This case-control study was carried out on MRIs of 20 patients with RRMS and 20 healthy controls in Zahedan, Iran. MR images with 4-mm slice thickness and 0.5-mm intervals in three anatomical planes (coronal, sagittal, axial) were acquired. Then, stereological parameters, including volume and volume density of different parts of the brain, based on Cavalries' point counting method were measured in both groups. Data analyses were performed using Mann-Whitney U and Pearson's correlation tests.The results of the study showed that there were no significant differences in total brain, hemispheres, gray matter, and basal nuclei volume and volume density between the two groups (p 0.05). However, the left hemisphere, cerebellum, lateral ventricles, brainstem, corpus callosum, and white matter volume in RRMS patients were significantly lower than those in controls (p 0.05).The findings showed that quantitative assessments based on stereological method on brain MRIs facilitate clarifying neuropathology of the disease. Also, it can be helpful as a simple index for following up the clinical situation and assessing therapeutic efficiency in MS patients. It may provide a precise treatment approach and justification of symptoms in patients with MS.

PIMD: 32419416

Clinically isolated syndrome and multiple sclerosis in children: a single center study.

This study was conducted to determine the differences in clinical and radiological features at the first demyelinating event in children with clinically isolated syndrome (CIS) and multiple sclerosis (MS).This was a single center retrospective cohort study of the children with CIS followed-up at Istanbul University Faculty of Medicine, Department of Pediatric Neurology, between 2010 and 2018. Children with CIS who were assessed at 3, 6, 12 and 24 months following their first identified demyelinating event were included. Demographic data, mode of presentation and the presence of the oligoclonal band in the cerebrospinal fluid (CSF) were abstracted from the medical records. Magnetic resonance imaging of the brain and spinal cord was analyzed for the location, number, size and gadolinium enhancement of the lesions.A total of 51 patients` data was assessed, 38 patients at a mean age of 12.3 years were enrolled in the study. Twenty-seven children (71%) evolved into clinically definite MS after a mean follow-up of 11 months. Older age at first demyelinating event and the presence of the oligoclonal band in CSF were tended to be more common in patients with MS than patients with CIS ($p < 0.05$). The increased number of T2-hyperintense lesion and the presence of the lesion in periventricular, infratentorial and corpus callosum were associated with a tendency for development of MS ($p < 0.05$).Older age at first demyelinating event, the presence of the oligoclonal band in CSF, the number and localization of T2-hyperintense lesion were associated with a tendency for development of MS.

PIMD: 32413277

The Median Eminence, A New Oligodendrogenic Niche in the Adult Mouse Brain.

The subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus are known as neurogenic niches. We show that the median eminence (ME) of the hypothalamus comprises BrdU newly proliferating cells co-expressing NG2 (oligodendrocyte progenitors) and RIP (pre-myelinating oligodendrocytes), suggesting their differentiation toward mature oligodendrocytes (OLs). ME cells can generate neurospheres (NS) in vitro, which differentiate mostly to OLs compared with SVZ-NS that typically generate neurons. Interestingly, this population of oligodendrocyte progenitors is increased in the ME from experimental autoimmune encephalomyelitis (EAE)-affected mice. Notably, the thrombospondin 1 (TSP1) expressed by astrocytes, acts as negative regulator of oligodendrogenesis in vitro and is downregulated in the ME of EAE mice. Importantly, transplanted ME-NS preferentially differentiate to MBP OLs compared with SVZ-NS in Shiverer mice. Hence, discovering the ME as a new site for myelin-producing cells has a great importance for advising future therapy for demyelinating diseases and spinal cord injury.

PIMD: 32378482

Theory of mind network in multiple Sclerosis: A double disconnection mechanism.

The relationship between cognitive and affective theory of mind (ToM), clinical variables, and brain tissue injury is still a subject of debate in multiple sclerosis (MS). By adopting a ToM Networks model, we investigated ToM performance, and brain imaging correlates in relapsing-remitting (RR) and progressive (Pr) MS. 16RR, 19Pr, and 21 healthy controls were assessed with both cognitive (CToM) and affective ToM (AToM) tests and neuropsychological tools and were evaluated with MRI. Cortical thickness, sub-cortical volumetry, and tract-based-spatial-statistics were analyzed. Our results reported a CToM deficit in Pr, correlated with attention. While no relation between gray matter and CToM was observed, a widespread correlation between CToM and normal-appearing white matter was found. In particular, we registered a significant positive correlation between CToM and fractional anisotropy in Superior and Inferior Longitudinal Fasciculus and right thalamic radiation tracts. Moreover, an inverse correlation between CToM and mean diffusivity of the right fronto-occipital fasciculus, bilateral superior longitudinal fasciculus, cortico-spinal, left uncinate, corpus callosum, and forceps minor tracts was also observed. This work highlighted a double disconnection mechanism in Pr MS affecting communication both (1) inside the ToM network and (2) between the ToM network and cognitive execution areas, likely explaining the deficit in cognitive ToM.

PIMD: 32328718

Cognitive impairment in early MS: contribution of white matter lesions, deep grey matter atrophy, and cortical atrophy.

Cognitive impairment (CI) is a frequent and debilitating symptom in MS. To better understand the neural bases of CI in MS, this magnetic resonance imaging (MRI) study aimed to identify and quantify related structural brain changes and to investigate their relation to each other.We studied 51 patients with CI and 391 patients with cognitive preservation (CP). We analyzed three-dimensional T1-weighted and FLAIR scans at 3 Tesla. We determined mean cortical thickness as well as volumes of cortical grey matter (GM), deep GM including thalamus, cerebellar cortex, white matter, corpus callosum, and white matter lesions (WML). We also analyzed GM across the whole brain by voxel-wise and surface-based techniques.Mean disease duration was 5 years. Comparing MS patients with CI and CP, we found higher volumes of WML, lower volumes of deep and cortical GM structures, and lower volumes of the corpus callosum (all corrected p values < 0.05). Effect sizes were largest for WML and thalamic volume (standardized ß values 0.25 and - 0.25). By logistic regression analysis including both WML and thalamic volume, we found a significant effect only for WML volume. Inclusion of the interaction term of WML and thalamic volume increased the model fit and revealed a highly significant interaction of WML and thalamic volume. Moreover, voxel-wise and surface-based comparisons of MS patients with CI and CP showed regional atrophy of both deep and cortical GM independent of WML volume and overall disability, but effect sizes were lower.Although several mechanisms contribute to CI already in the early stage of MS, WML seem to be the main driver with thalamic atrophy primarily intensifying this effect.

PIMD: 32314194

Improvement of Remyelination in Demyelinated Corpus Callosum Using Human Adipose-Derived Stem Cells (hADSCs) and Pregnenolone in the Cuprizone Rat Model of Multiple Sclerosis.

Adipose-derived stem cells (ASCs) have neuroprotective effects, and their repair ability has been approved in neurodegenerative studies. Pregnenolone as a neurosteroid plays significant roles in neurogenesis. We aimed to consider the effect of ADSCs and pregnenolone injection on the multiple sclerosis (MS) model created by cuprizone. Male Wistar rats (n = 36) were fed with an ordinary diet or a diet with cuprizone (0.6%) for 3 weeks. H-ADSCs were taken from patients with lipoaspirate surgery. The rats were divided into six groups (n = 6): healthy, MS, sham, pregnenolone injection, ADSCs injection, pregnenolone and ADSCs injection. Behavioral test, histological examination and TEM were conducted. The specific markers for myelin and cell differentiation were assessed using immunohistochemistry staining. Additionally, the measure of MBP and MOG gene expression and the amount of related proteins were determined using real-time RT-PCR and ELISA techniques, respectively. Histologic results showed that induced demyelination in corpus callosum fibers. TEM revealed an increased thickness of myelin in fibers in the treated groups ($P < 0.05$). Injection of hADSC and pregnenolone significantly increased the expression levels of MBP and MOG ($P < 0.001$). The mean percentage of MOG and MBP markers were significantly increased in the treated groups compared to MS and sham groups ($P < 0.05$). Moreover, the OD level of MBP and MOG proteins showed that their values in the ADSCs/pregnenolone group were close to those of the control group without a significant difference. Our data indicated the remyelination potency and cell differentiation can improve with ADSCs and pregnenolone treatments in the multiple sclerosis model which created by cuprizone in rats.

PIMD: 32290524

Delayed Demyelination and Impaired Remyelination in Aged Mice in the Cuprizone Model.

To unravel the failure of remyelination in multiple sclerosis (MS) and to test promising remyelinating treatments, suitable animal models like the well-established cuprizone model are required. However, this model is only standardized in young mice. This does not represent the typical age of MS patients. Furthermore, remyelination is very fast in young mice, hindering the examination of effects of remyelination-promoting agents. Thus, there is the need for a better animal model to study remyelination. We therefore aimed to establish the cuprizone model in aged mice. 6-month-old C57BL6 mice were fed with different concentrations of cuprizone (0.2-0.6%) for 5-6.5 weeks. De- and remyelination in the medial and lateral parts of the corpus callosum were analyzed by immunohistochemistry. Feeding aged mice 0.4% cuprizone for 6.5 weeks resulted in the best and most reliable administration scheme with virtually complete demyelination of the corpus callosum. This was accompanied by a strong accumulation of microglia and near absolute loss of mature oligodendrocytes. Subsequent remyelination was initially robust but remained incomplete. The remyelination process in mature adult mice better represents the age of MS patients and offers a better model for the examination of regenerative therapies.

PIMD: 32272486

Proteomic changes during experimental de- and remyelination in the corpus callosum.

In the cuprizone model of multiple sclerosis, de- and remyelination can be studied without major interference from the adaptive immune responses. Since previous proteomic studies did not focus on the corpus callosum, where cuprizone causes the most pronounced demyelination, we performed a bottom up proteomic analysis on this brain region.Eight week-old mice treated with 0.2% cuprizone, for 4 weeks and controls (C) were sacrificed after termination of the treatment (4wD), and 2 (2dR) or 14 (2wR) days later. Homogenates of dissected corpus callosum were analysed by quantitative proteomics. For data processing, clustering, gene ontology analysis, and regulatory network prediction, we used Perseus, PANTHER and Ingenuity Pathway Analysis softwares, respectively.We identified 4886 unmodified, single- or multi phosphorylated and/or gycosylated (PTM) proteins. Out of them, 191 proteins were differentially regulated in at least one experimental group. We found 57 proteins specific for demyelination, 27 for early- and 57 for late remyelinationwhile 36 proteins were affected in two, and 23 proteins in all three groups. Phosphorylation represented 92% of the post translational modifications among differentially regulated modified (PTM) proteins with decreased level, while it was only 30% of the PTM proteins with increased level. Gene ontology analysis could not classify the demyelination specific proteins into any biological process category, while allocated the remyelination specific ones to nervous system development and myelination as the most specific subcategory. We also identified a protein network in experimental remyelination, and the gene orthologues of the network were differentially expressed in remyelinating multiple sclerosis brain lesions consistent with an early remyelination pattern.Proteomic analysis seems more informative for remyelination than demyelination in the cuprizone model.

PIMD: 32246177

A validation study of manual atrophy measures in patients with Multiple Sclerosis.

Manual measures such as corpus callosum index, normalized corpus callosum area, and width of the third ventricle are potential biomarkers for brain atrophy. In this work, we investigate their suitability to assess the neurodegenerative component of multiple sclerosis (MS) by comparing them to volumetric measures and expanded disability status scale (EDSS).Fifty-eight patients with a clinically isolated syndrome, 48 MS patients treated with interferon β, and 26 treated with natalizumab underwent a brain MRI at baseline and after 1 year. Manual measures were evaluated by two observers using Jim v.6.0 at both time points. Volumetric tools (SIENA/x and Freesurfer) were used to calculate normalized brain volume, brain parenchymal fraction, annualized percentage of brain volume change, corpus callosum volume, ventricle volume, and volume of the third ventricle. Statistical analyses were performed with SPSS v.13.Usage of corpus callosum volume and third ventricle volume to validate normalized corpus callosum area and width of the third ventricle, respectively, showed very good correlations ($r = 0.85$, $r = 0.83$; $p < 0.01$). Width of the third ventricle, corpus callosum index, and normalized corpus callosum area correlations were significant with EDSS in all patients and moderate to strong with normalized brain volume and brain parenchymal fraction in natalizumab-treated patients (respectively $r = -0.54$, $r = -0.61$; $r = 0.55$, $r = 0.67$; and $r = 0.58$, $r = 0.67$; with $p < 0.05$).Width of the third ventricle and normalized corpus callosum area seem the more robust manual measures regarding correlation with volumetric measures and EDSS, especially in patients with more advanced disease.

PIMD: 32201679

Multiphasic acute disseminated encephalomyelitis and differential with early onset multiple sclerosis.

Multiple sclerosis is considered the most frequent demyelinating disorder of the Central Nervous System (CNS) among young adults, yet is very rare before 10 years old. Acute disseminated encephalomyelitis is a monophasic, polysymptomatic disorder that involves the CNS white matter with demyelinating lesions, which usually occurs after systemic viral infections. These two demyelinating diseases can present initially as an acute focal neurological syndrome and they can be difficult to distinguish. We describe a case of a nine-year-old girl that presented initially with dysphonia, gait ataxia, eyelid myokymia and brainstem disturbances. This was her second episode; the first episode was at the age of four years old. She recovered without neurological sequelae. The brain magnetic resonance imaging (MRI) demonstrated multiple demyelinating lesions in the white matter, cortical regions of the frontal lobe, periventricular distribution, internal capsule, corpus callosum and cerebellum. The purpose of the presentation of this case was to highlight the similarities between these two entities, since the clinical picture and neuroimaging are difficult to distinguish, mainly in relation to the first episode.

PIMD: 32184863

Myelin Protection by Ursolic Acid in Cuprizone-Induced Demyelination in Mice.

Neuronal survival in multiple sclerosis (MS) and other demyelinating diseases depends on the preservation of myelin and remyelination of axons. Myelin protection is the main purpose to decrease myelin damage in the central nervous system (CNS). Ursolic acid (UA) as a natural product in apple is suggested to protect neural cells. This study is the first to demonstrate an effect for UA on CNS myelin loss induced by cuprizone toxin. In the current study, we hypothesized that daily treatment with UA in drinking water (1 mg/mL) prevents myelin damage by 6 weeks administration of CPZ in mice pellet which lead to corpus callosum axonal demyelination. We assessed the myelin content and the number of myelinating cells in corpus callosum by FluoroMyelin and luxol fast blue staining as well as by immunostaining against MBP and Olig2. Our finding indicated that UA could decrease the extent of demyelination area and enhanced myelin stain intensity within CC and protected oligodendrocyte lineage cells against cuprizone toxin. We could conclude that myelinated structures could be protected by UA in corpus callosum, which provide favorable evidence for the possibility of application of UA in demyelinating diseases and traumatic injuries.

PIMD: 32170811

Streamline density and lesion volume reveal a postero-anterior gradient of corpus callosum damage in multiple sclerosis.

Although interhemispheric disconnection significantly contributes to disability in multiple sclerosis (MS), the topography, timeline and relationship of callosal damage accrual with hemispheric damage are still unclear.Streamline density and the presence of focal lesions in five callosal subregions were computed in 55 people with MS [13 relapsing-remitting (RRMS), 20 secondary progressive (SPMS), 22 primary progressive (PPMS)] and 24 healthy controls.Streamline density decrease was identified in SPMS in all corpus callosum (CC) subregions, in PPMS in the posterior CC and mid-posterior CC and in RRMS in the posterior CC. CC density was independently predicted by CC lesion volume and hemispheric lesion volume and independently predicted visuospatial memory, Expanded Disability Status Scale, manual dexterity and ambulation.The reduction in CC density across phenotypes suggests an earlier involvement of the posterior regions, followed only at a later stage by involvement of the anterior portions of the CC. Such interhemispheric disconnection seems to develop as a consequence of white matter macroscopic damage and exerts a relevant impact on motor and, to a lesser extent, cognitive disability.

PIMD: 32163190

In vivo silencing of miR-125a-3p promotes myelin repair in models of white matter demyelination.

In the last decade, microRNAs have been increasingly recognized as key modulators of glial development. Recently, we identified miR-125a-3p as a new player in oligodendrocyte physiology, regulating in vitro differentiation of oligodendrocyte precursor cells (OPCs). Here, we show that miR-125a-3p is upregulated in active lesions of multiple sclerosis (MS) patients and in OPCs isolated from the spinal cord of chronic experimental autoimmune encephalomyelitis (EAE) mice, but not in those isolated from the spontaneously remyelinating corpus callosum of lysolecithin-treated mice. To test whether a sustained expression of miR-125a-3p in OPCs contribute to defective remyelination, we modulated miR-125a-3p expression in vivo and ex vivo after lysolecithin-induced demyelination. We found that lentiviral over-expression of miR-125a-3p impaired OPC maturation, whereas its downregulation accelerated remyelination. Transcriptome analysis and luciferase reporter assay revealed that these effects are partly mediated by the direct interaction of miR-125a-3p with Slc8a3, a sodium-calcium membrane transporter, and identified novel candidate targets, such as Gas7, that we demonstrated necessary to correctly address oligodendrocytes to terminal maturation. These findings show that miR-125a-3p upregulation negatively affects OPC maturation in vivo, suggest its role in the pathogenesis of demyelinating diseases and unveil new targets for future promyelinating protective interventions.

PIMD: 32147502

Deciphering the neural underpinnings of alexithymia in multiple sclerosis.

Alexithymia is a personality construct that could occur in up to 53 % of patients with multiple sclerosis (MS). It entails difficulties in identifying and describing one's feelings and an externally oriented thinking. The current work aims to assess the neural underpinnings of alexithymia in this population.Forty-five patients with MS filled in the Toronto Alexithymia Scale (n = 17 with high alexithymia and n = 28 with low alexithymia). Brain magnetic resonance imaging was obtained for each patient and a morphometry algorithm (MorphoBox) was applied to calculate regional brain volumes. All patients underwent a clinical and neuropsychological evaluation which included measures for anxiety, depression, fatigue, daytime sleepiness, and basic and social cognition.Compared to patients with low alexithymia, patients with high alexithymia had significantly higher fatigue and depression ratings, and lower empathy scores. In addition, they had lower volumes of corpus callosum, deep white matter, pallidum bilaterally, and left thalamus. In the whole cohort, alexithymia scores were inversely correlated with gray matter (thalamus and pallidum bilaterally) and white matter volumes (corpus callosum and bilateral deep white matter) after controlling for covariates (ps<0.05).This study offers insights on the neuropsychological and neural substrates of alexithymia in MS. The current findings are consistent with alexithymia reports in other clinical populations, and suggest an association between alexithymia and atrophy of thalami, pallidum, corpus callosum and deep white matter in MS. Further research is needed to enhance the understanding of alexithymia mechanisms in this clinical context.

PIMD: 32087534

A novel role of cardiac inwardly rectifying potassium channels explaining autonomic cardiovascular dysfunctions in a cuprizone-induced mouse model of multiple sclerosis.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS), believed to have an autoimmune etiology. MS patients showed an increased cardiovascular (CV) risk probably related to an impairment in the autonomic control of CV functions, but the underlying molecular mechanisms are not completely elucidated. Inwardly-rectifying potassium (Kir) channels play a key role in cardiac excitability by contributing to the repolarization phase of action potential and were recently identified as target of the autoantibody response in MS patients. Therefore, we investigated the role of cardiac Kir channels in the CV dysfunctions occurring in MS. Cardiac functions were evaluated by electrocardiographic recordings (ECG) in cuprizone-fed C57BL/6 mice, a classic demyelination animal model. Gene expression profiling of cardiac Kir2.2, Kir4.1 and Kir6.2 channels was performed using real-time PCR in mice. Cuprizone-induced mouse model was confirmed by immunohistochemistry analysis showing demyelination in the corpus callosum. ECG recordings from mice showed a significant decreased duration of the P wave and RR interval as well as an increase of the heart rate in cuprizone-treated mice as compared with the controls. Significant increased relative expression levels of Kcnj11 and Kcnj12, encoding for Kir6.2 and Kir2.2 channels respectively, were observed in mouse heart tissue, whereas no differences were found in mRNA levels of Kir4.1 channel as compared with controls. For the first time, these findings provided valuable insights into the potential role of Kir channels in cardiac problems associated with MS.

PIMD: 32048246

Metformin accelerates myelin recovery and ameliorates behavioral deficits in the animal model of multiple sclerosis via adjustment of AMPK/Nrf2/mTOR signaling and maintenance of endogenous oligodendrogenesis during brain self-repairing period.

Multiple sclerosis (MS) is a devastating autoimmune disorder characterized by oligodendrocytes (OLGs) loss and demyelination. In this study, we have examined the effects of metformin (MET) on the oligodendrogenesis, redox signaling, apoptosis, and glial responses during a self-repairing period (1-week) in the animal model of MS.For induction of demyelination, C57BL/6 J mice were fed a 0.2% cuprizone (CPZ) for 5 weeks. Thereafter, CPZ was removed for 1-week and molecular and behavioral changes were monitored in the presence or absence of MET (50 mg/kg body weight/day).MET remarkably increased the localization of precursor OLGs (NG2/O4 cells) and subsequently the renewal of mature OLGs (MOG cells) in the corpus callosum via AMPK/mammalian target of rapamycin (mTOR) pathway. Moreover, we observed a significant elevation in the antioxidant responses, especially in mature OLGs (MOG/nuclear factor erythroid 2-related factor 2 (Nrf2) cells) after MET intervention. MET also reduced brain apoptosis markers and lessened motor dysfunction in the open-field test. While MET was unable to decrease active astrogliosis (GFAP mRNA), it reduced microgliosis by down-regulation of Mac-3 mRNA a marker of pro-inflammatory microglia/macrophages. Molecular modeling studies, likewise, confirmed that MET exerts its effects via direct interaction with AMPK.Altogether, our study reveals that MET effectively induces lesion reduction and elevated molecular processes that support myelin recovery via direct activation of AMPK and indirect regulation of AMPK/Nrf2/mTOR pathway in OLGs. These findings facilitate the development of new therapeutic strategies based on AMPK activation for MS in the near future.

PIMD: 32028846

Position Sense Deficits at the Lower Limbs in Early Multiple Sclerosis: Clinical and Neural Correlates.

. Position sense, defined as the ability to identify joint and limb position in space, is crucial for balance and gait but has received limited attention in patients with multiple sclerosis (MS). We investigated lower limb position sense deficits, their neural correlates, and their effects on standing balance in patients with early MS. . A total of 24 patients with early relapsing-remitting MS and 24 healthy controls performed ipsilateral and contralateral matching tasks with the right foot during functional magnetic resonance imaging. Corpus callosum (CC) integrity was estimated with diffusion tensor imaging. Patients also underwent an assessment of balance during quiet standing. We investigated differences between the 2 groups and the relations among proprioceptive errors, balance performance, and functional/structural correlates. . During the contralateral matching task, patients demonstrated a higher matching error than controls, which correlated with the microstructural damage of the CC and with balance ability. In contrast, during the ipsilateral task, the 2 groups showed a similar matching performance, but patients displayed a functional reorganization involving the parietal areas. Neural activity in the frontoparietal regions correlated with the performance during both proprioceptive matching tasks and quiet standing. Patients with early MS had subtle, clinically undetectable, position sense deficits at the lower limbs that, nevertheless, affected standing balance. Functional changes allowed correct proprioception processing during the ipsilateral matching task but not during the more demanding bilateral task, possibly because of damage to the CC. These findings provide new insights into the mechanisms underlying disability in MS and could influence the design of neurorehabilitation protocols.

PIMD: 31953431

Dose-dependent effect of cannabinoid WIN-55,212-2 on myelin repair following a demyelinating insult.

Dysfunctions in the endocannabinoid system have been associated with experimental animal models and multiple sclerosis patients. Interestingly, the endocannabinoid system has been reported to confer neuroprotection against demyelination. The present study aims to assess the effects of the cannabinoid agonist WIN-55,212-2 in cuprizone fed animals on myelin repair capacity. Animals exposed to cuprizone were simultaneously treated withWIN-55,212-2, behaviorally tested and finally the corpus callosum was exhaustively studied by Western blotting, qRT-PCR and a myelin staining procedure. We report that the long-term administration of WIN-55,212-2 reduced the global amount of CB protein. Histological analysis revealed clear demyelination after being fed cuprizone for three weeks. However, cuprizone-fed mice subjected to 0.5 mg/Kg of WIN-55,212-2 displayed no differences when compared to controls during demyelination, although there was a robust increase in the myelinated axons during the remyelination phase. These animals displayed better performance on contextual fear conditioning which was in turn non-attributable to an antinociceptive effect. In contrast, a 1 mg/Kg dosage caused a remarkable demyelination accompanied by limited potential for myelin repair. Upon drug administration while mice ongoing demyeliniation, the expression of Aif1 (microglia) and Gfap (astrocytes) followed a dose-dependent manner whereas the expression of both markers was apparently attenuated during remyelination. Treatment with vehicle or 0.5 mg/Kg of the drug during demyelination increased the expression of Pdgfra (oligodendrocyte precursor cells) but this did not occur when 1 mg/Kg was administered. In conclusion, the drug at 0.5 mg/Kg did not alter myelin architecture while 1 mg/Kg had a deleterious effect in this model.

PIMD: 31887455

Towards microstructure-informed material models for human brain tissue.

Emerging evidence suggests that the mechanical behavior of the brain plays a critical role in development, disease, and aging. Recent studies have begun to characterize the mechanical behavior of gray and white matter tissue and to identify sets of material models that best reproduce the stress-strain behavior of different brain regions. Yet, these models are mainly phenomenological in nature, their parameters often lack clear physical interpretation, and they fail to correlate the mechanical behavior to the underlying microstructural composition. Here we make a first attempt towards identifying general relations between microstructure and mechanics with the ultimate goal to develop microstructurally motivated constitutive equations for human brain tissue. Using histological staining, we analyze the microstructure of brain specimens from different anatomical regions, the cortex, basal ganglia, corona radiata, and corpus callosum, and identify the regional stiffness and viscosity under multiple loading conditions, simple shear, compression, and tension. Strikingly, our study reveals a negative correlation between cell count and stiffness, a positive correlation between myelin content and stiffness, and a negative correlation between proteoglycan content and stiffness. Additionally, our analysis shows a positive correlation between lipid and proteoglycan content and viscosity. We demonstrate how understanding the microstructural origin of the macroscopic behavior of the brain can help us design microstructure-informed material models for human brain tissue that inherently capture regional heterogeneities. This study represents an important step towards using brain tissue stiffness and viscosity as early diagnostic markers for clinical conditions including chronic traumatic encephalopathy, Alzheimer's and Parkinson's disease, or multiple sclerosis. STATEMENT OF SIGNIFICANCE: The complex and heterogeneous mechanical properties of brain tissue play a critical role for brain function. To understand and predict how brain tissue properties vary in space and time, it will be key to link the mechanical behavior to the underlying microstructural composition. Here we use histological staining to quantify area fractions of microstructural components of mechanically tested specimens and evaluate their individual contributions to the nonlinear macroscopic mechanical response. We further propose a microstructure-informed material model for human brain tissue that inherently captures regional heterogeneities. The current work provides unprecedented insights into the biomechanics of human brain tissue, which are highly relevant to develop refined computational models for brain tissue behavior or to advance neural tissue engineering.

PIMD: 31837111

Vitamin D increases remyelination by promoting oligodendrocyte lineage differentiation.

Several experimental studies have suggested the potential remyelinating effects of vitamin D (VitD) supplements regardless of the presence of VitD deficiency. This study aims to analyze neurogenesis in a model of toxic demyelination in order to evaluate the effects of VitD on demyelination and remyelination.We used 24 male Wistar rats that had received surgical lesions to the corpus callosum and were injected with lysolecithin. Rats were divided into three groups: Group 1 included eight rats with lesions to the corpus callosum but not lysolecithin injections (sham group), group 2 included eight rats with lesions to the corpus callosum that were injected with lysolecithin (lysolecithin group), and group 3 included eight rats with lesions that were injected with lysolecithin and received VitD (VitD group). We analyzed neurogenesis both in the subventricular zone and at the lesion site.Administration of VitD promotes the proliferation and differentiation of neural stem cells in the subventricular zone and the migration of these cells to the lesion site in the corpus callosum; these cells subsequently differentiate into oligodendrocyte lineage cells and produce myelin basic protein. This phenomenon was not caused by microglial activation, which was less marked in rats receiving VitD. Megalin expression did not increase at the lesion site, which suggests that VitD is internalized by other mechanisms.Our results support the hypothesis that regardless of the presence of VitD deficiency, treatment with VitD may contribute to remyelination by promoting the proliferation of oligodendrocyte precursor cells.

PIMD: 31762132

Myelin Damage in Normal Appearing White Matter Contributes to Impaired Cognitive Processing Speed in Multiple Sclerosis.

Cognitive impairment is a core symptom in multiple sclerosis (MS). Damage to normal appearing white matter (NAWM) is likely involved. We sought to determine if greater myelin heterogeneity in NAWM is associated with decreased cognitive performance in MS.A total of 27 participants with MS and 13 controls matched for age, sex, and education underwent myelin water imaging (MWI) from which the myelin water fraction (MWF) was calculated. Corpus callosum, superior longitudinal fasciculus, and cingulum were chosen as regions of interest (ROIs) a priori based on their involvement in MS-related cognitive impairment. Cognitive performance was assessed using the Symbol Digit Modalities Test (SDMT). Pearson

s product moment correlations were performed to assess relationships between cognitive performance and myelin heterogeneity (variance of MWF within an ROI).In MS, myelin heterogeneity in all three ROIs was significantly associated with performance on the SDMT. These correlations ranged from moderate (r = -.561) to moderately strong (r = -.654) and were highly significant (P values ranged from .001 to .0002). Conversely, myelin heterogeneity was not associated with SDMT performance in controls in any ROI (P > .108).Increased myelin heterogeneity in NAWM is associated with decreased cognitive processing speed performance in MS.

PIMD: 31750599

MRI-Based Manual versus Automated Corpus Callosum Volumetric Measurements in Multiple Sclerosis.

Corpus callosum atrophy is a neurodegenerative biomarker in multiple sclerosis (MS). Manual delineations are gold standard but subjective and labor intensive. Novel automated methods are promising but require validation. We aimed to compare the robustness of manual versus automatic corpus callosum segmentations based on FreeSurfer.Nine MS patients (6 females, age 38 ± 13 years, disease duration 7.3 ± 5.2 years) were scanned twice with repositioning using 3-dimensional T -weighted magnetic resonance imaging on three scanners (two 1.5 T and one 3.0 T), that is, six scans/patient, on the same day. Normalized corpus callosum areas were measured independently by a junior doctor and neuroradiologist. The cross-sectional and longitudinal streams of FreeSurfer were used to segment the corpus callosum volume.Manual measurements had high intrarater (junior doctor .96 and neuroradiologist .96) and interrater agreement (.94), by intraclass correlation coefficient ($P < .001$). The coefficient of variation was lowest for longitudinal FreeSurfer (.96% within scanners; 2.0% between scanners) compared to cross-sectional FreeSurfer (3.7%, $P = .001$; 3.8%, $P = .058$) and the neuroradiologist (2.3%, $P = .005$; 2.4%, $P = .33$). Longitudinal FreeSurfer was also more accurate than cross-sectional (Dice scores 83.9 ± 7.5% vs. 78.9 ± 8.4%, $P < .01$ relative to manual segmentations). The corpus callosum measures correlated with physical disability (longitudinal FreeSurfer $r = -.36$, $P < .01$; neuroradiologist $r = -.32$, $P < .01$) and cognitive disability (longitudinal FreeSurfer $r = .68$, $P < .001$; neuroradiologist $r = .64$, $P < .001$).FreeSurfer's longitudinal stream provides corpus callosum measures with better repeatability than current manual methods and with similar clinical correlations. However, due to some limitations in accuracy, caution is warranted when using FreeSurfer with clinical data.

PIMD: 31749760

Temporal Dynamics of Diffusion Metrics in Early Multiple Sclerosis and Clinically Isolated Syndrome: A 2-Year Follow-Up Tract-Based Spatial Statistics Study.

Tract-based spatial statistics (TBSS) is suitable for the assessment of voxel-wise changes in fiber integrity in WM tracts in the entire brain. Longitudinal TBSS analyses of early multiple sclerosis (MS) using 3 Tesla magnetic resonance imaging (MRI) are not common. To characterize microstructural WM alterations at initial diagnosis in clinically isolated syndrome (CIS) and early MS at baseline and longitudinally over 2 years. DTI (Diffusion tensor imaging) at 3 Tesla was used to evaluate 106 therapy-naive patients with CIS or definite MS at baseline and at 1-year (= 83) and 2-year (= 43) follow-up compared to healthy controls (HC, = 49). TBSS was used for voxel-wise analyses of the DTI indices of fractional anisotropy (FA) and radial, mean, and axial diffusivity (RD, MD, AD) for cross-sectional and longitudinal comparisons. Mean values of FA, RD, and cluster voxel numbers were extracted from significant clusters using an atlas-based approach. Correlations with disability (EDSS) were calculated for FA and RD changes related to affected brain regions. Reductions in FA compared to HC were found at baseline in patients with CIS and RRMS and involved most supra- and infratentorial WM tracts. In the cerebellum and cerebral peduncles, these changes negatively correlated with EDSS after 2 years. FA changes in patients with CIS and RRMS evolved in the second year, particularly in the descending projection pathways and the cerebellum, and were significantly associated with EDSS. RD alterations compared to HC were undetectable in patients at baseline but were observed after 1 year and were exacerbated during the second year in all major supratentorial WM tracts, the corpus callosum, and the cerebellum. FA did not change between baseline and year 1 follow-up, but longitudinal investigation between the first and second year revealed combined dynamic FA and RD changes in the corpus callosum and corona radiata. TBSS of diffusion metrics at initial diagnosis and at 2-year follow-up showed microstructural WM pathology and associations between FA reduction and future disability, respectively. Combined longitudinal changes in FA and RD occurred in specific structures, where RD increases likely reflected progressing axonal degeneration. The distinct temporal dynamics of FA and RD, implying constancy during the first year, supports early therapeutic intervention for CIS and RRMS.

PIMD: 31705326

Biopsy histopathology in the diagnosis of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP).

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is an inherited rare disease affecting young adults. We present the clinical, imaging, and neuropathological results of our case series, emphasizing biopsy histology combined with clinical information will increase the accuracy of early diagnosis.In total, 4 females and 2 male ALSP patients with onset at ages 24-45 years were enrolled. Clinical manifestations, neuroimaging, and histopathology as well as gene mutation were analyzed and compared with literature.Clinical manifestations include cognitive decline with/without psycho-behavior problems and movement disorders including paralysis, hemiplegia, parkinsonism, and pyramidal tract injury, as well as dysarthria, dysphagia, and sensory disturbances. MRI showed multiple periventricular and subcortical white matter lesions, involving the corpus callosum, with no enhancement, but with persistent hyperintensity on diffuse-weighted imaging. Histology showed widespread white matter damage and pale stain, especially destroyed axons with spheroids and funicular axons which were stained with neurofilament and ubiquitin. Foamy and pigmented macrophages were another typical change. CSF1R mutation was found in 4 of them. All of the patients were misdiagnosed and treated for a long time for multiple sclerosis, cerebral infarction, normal pressure hydrocephalus, etc. CONCLUSION: ALSP will cause rapidly progressing dementia with/without movement disorders in young adults. The definite diagnosis should be based on a comprehensive analysis of clinical manifestations, and neuroimaging, histology, and genetic results. Early biopsy will add to the accuracy of the diagnosis.

PIMD: 31696586

Is the walk ratio a window to the cerebellum in multiple sclerosis? A structural magnetic resonance imaging study.

Existing research studies have demonstrated a relationship between magnetic resonance imaging (MRI) neuroimaging measures and walking speed in people with multiple sclerosis (PwMS). However, to date there are no data as to the brain structures involved in gait coordination and control in PwMS. Therefore, the aim of our study was to investigate the association between walk ratio, an indicator of gait coordination, and related brain structures in PwMS.A brain MRI was performed by a 3.0-T MR scanner in conjunction with a volumetric analysis based on three-dimensional T1-weighted images. Regions of interest were volumes of the hippocampus, amygdala, putamen, caudate, pallidum, thalamus, cerebellum and the corpus callosum regions. Walking speed and walk ratio, defined as step length divided by step rate, was measured whilst walking on an electronic walkway.In all, 343 PwMS (41.1 ± 13.4 years, 69.1% female, median Expanded Disability Status Scale 2.5) were included in the study. A significant association was found between the left cerebellum volume and walk ratio after controlling for age, gender, total cranial volume and disability; R = 0.379, P = 0.002. A similar association was found between the right cerebellum volume and walk ratio, R = 0.364, P = 0.002. No correlations were observed between walk ratio and the thalamus, basal ganglia, hippocampus, amygdala and the corpus callosum volumes. No association was found between walking speed and all brain measures.The walk ratio should be considered when evaluating and assessing PwMS presenting with ataxia. Furthermore, it is also hypothesized that a low walk ratio indicates a lower cerebellum volume in the MS population.

PIMD: 31654116

Patterns of regional brain volume loss in multiple sclerosis: a cluster analysis.

Although whole and individual regional brain volume loss have been separately reported to correlate with disability in multiple sclerosis (MS), hierarchical cluster analyses of the whole and regional brain to find their pattern in MS are few.We cross-sectionally conducted high-resolution, T1-weighted volumetric MRI examinations in 75 MS patients and 21 healthy controls (HCs) to measure the volumes of whole brain and a total of 56 brain regions of interest. Using a hierarchical cluster analysis with multivariate imaging data, we classified the patients into clusters according to their brain-volume patterns. Principal component analysis was also applied. Clinical features and brain volumes were then compared among the MS clusters.The MS patients were categorized into three major clusters (Clusters 1, 2, and 3) with increasing disability in that order. Principal component analysis also identified Clusters 1, 2 and 3. Whole brain volume and supratentorial regional brain volumes, including thalamus and corpus callosum, decreased severely in Cluster 3 and moderately in Cluster 2, while equally preserved in Cluster 1 and the HCs. Only the volumes of the ventral diencephalon and T1 white matter hypointensities significantly differed in Clusters 1, 2 and 3 and HCs. In contrast, the volumes of the cerebellar cortex and brainstem were significantly different between Clusters 3 and 1, whereas there were no significant differences between Clusters 1 and 2 and Clusters 2 and 3.We identified brain regions that exhibit different degree of atrophy in a background of global brain atrophy in MS.

PIMD: 31620963

Metformin-induced AMPK activation stimulates remyelination through induction of neurotrophic factors, downregulation of NogoA and recruitment of Olig2+ precursor cells in the cuprizone murine model of multiple sclerosis.

Oligodendrocytes (OLGs) damage and myelin distraction is considered as a critical step in many neurological disorders especially multiple sclerosis (MS). Cuprizone (cup) animal model of MS targets OLGs degeneration and frequently used to the mechanistic understanding of de- and remyelination. The aim of this study was exploring the effects of metformin on the OLGs regeneration, myelin repair and profile of neurotrophic factors in the mice brain after cup-induced acute demyelination.Mice (C57BL/6 J) were fed with chow containing 0.2% cup for 5 weeks to induce specific OLGs degeneration and acute demyelination. Next, the cup was withdrawn to allow one-week recovery (spontaneous remyelination). At the end of this period, mature OLGs markers, myelin-associated neurite outgrowth inhibitor protein A (NogoA), premature specific OLGs transcription factor (Olig2), anti-apoptosis marker (survivin), neurotrophic factors, and AMPK activation were monitored in the presence or absence of metformin (50 mg/kg body weight/day) in the corpus callosum (CC).Our finding indicated that consumption of metformin during the recovery period potentially induced an active form of AMPK (p-AMPK) and promoted repopulation of mature OLGs (MOG cells, MBP cells) in CC through up-regulation of BDNF, CNTF, and NGF as well as down-regulation of NogoA and recruitment of Olig2 precursor cells.This study for the first time reveals that metformin-induced AMPK, a master regulator of energy homeostasis, activation following toxic demyelination could potentially accelerate regeneration and supports spontaneous demyelination. These findings suggest the development of new therapeutic strategies based on AMPK activation for MS in the near future. Graphical abstract An overview of the possible molecular mechanisms of action of metformin-mediated remyelinationa.

PIMD: 31603846

[Neuromyelitis optica].

Neuromyelitis optica (NMO) is an autoimmune, inflammatory and de myelinat ing disorder of the central nervous system with a predilection for the optic nerves and spinal cord. In 2004 the association of NMO with an antibody against the water channel aquaporin 4 (anti-AQP4) was published as a different pathology from multiple sclerosis (MS). Currently the term NMO spectrum disorders (NMOSD) is proposed, because the manifestations of the disease can be more extensive, affecting in addition to the optic nerve and spinal cord, the area postrema of the dorsal medulla, brainstem, diencephalon and typical brain areas (periependymal, corpus callosum, internal capsule and subcortical white matter). NMOSD is also applied to patients who meet the NMO criteria and are negative for AQP4-IgG. Within the latter group, the presence of another antibody, anti-MOG, has been detected in 20%, with a different physiopathological mechanism, but with a similar clinic and a better prognosis. The immunosuppressive treatment in the attack, as well as the long-term treatment in the cases that are indicated, is fundamental to avoid sequelaes and recurrences. The correct diagnosis of this entity is essential since it can be aggravated with the use of drugs useful in the treatment of MS. In this publication we will review the pathophysiology, clinical and diagnostic criteria of NMOSD, and discuss the different therapeutic options.

PIMD: 31588688

Diffusion basis spectrum imaging for identifying pathologies in MS subtypes.

Diffusion basis spectrum imaging (DBSI) combines discrete anisotropic diffusion tensors and the spectrum of isotropic diffusion tensors to model the underlying multiple sclerosis (MS) pathologies. We used clinical MS subtypes as a surrogate of underlying pathologies to assess DBSI as a biomarker of pathology in 55 individuals with MS. Restricted isotropic fraction (reflecting cellularity) and fiber fraction (representing apparent axonal density) were the most important DBSI metrics to classify MS using brain white matter lesions. These DBSI metrics outperformed lesion volume. When analyzing the normal-appearing corpus callosum, the most significant DBSI metrics were fiber fraction, radial diffusivity (reflecting myelination), and nonrestricted isotropic fraction (representing edema). This study provides preliminary evidence supporting the ability of DBSI as a potential noninvasive biomarker of MS neuropathology.

PIMD: 31515218

White Matter Abnormalities in Multiple Sclerosis Evaluated by Quantitative Synthetic MRI, Diffusion Tensor Imaging, and Neurite Orientation Dispersion and Density Imaging.

A number of MR-derived quantitative metrics have been suggested to assess the pathophysiology of MS, but the reports about combined analyses of these metrics are scarce. Our aim was to assess the spatial distribution of parameters for white matter myelin and axon integrity in patients with relapsing-remitting MS by multiparametric MR imaging.Twenty-four patients with relapsing-remitting MS and 24 age- and sex-matched controls were prospectively scanned by quantitative synthetic and 2-shell diffusion MR imaging. Synthetic MR imaging data were used to retrieve relaxometry parameters (R1 and R2 relaxation rates and proton density) and myelin volume fraction. Diffusion tensor metrics (fractional anisotropy and mean, axial, and radial diffusivity) and neurite orientation and dispersion index metrics (intracellular volume fraction, isotropic volume fraction, and orientation dispersion index) were retrieved from diffusion MR imaging data. These data were analyzed using Tract-Based Spatial Statistics.Patients with MS showed significantly lower fractional anisotropy and myelin volume fraction and higher isotropic volume fraction in widespread white matter areas. Areas with different isotropic volume fractions were included within areas with lower fractional anisotropy. Myelin volume fraction showed no significant difference in some areas with significantly decreased fractional anisotropy in MS, including in the genu of the corpus callosum and bilateral anterior corona radiata, whereas myelin volume fraction was significantly decreased in some areas where fractional anisotropy showed no significant difference, including the bilateral posterior limb of the internal capsule, external capsule, sagittal striatum, fornix, and uncinate fasciculus.We found differences in spatial distribution of abnormality in fractional anisotropy, isotropic volume fraction, and myelin volume fraction distribution in MS, which might be useful for characterizing white matter in patients with MS.

PIMD: 31484353

Stereological Investigation of Regional Brain Volumes after Acute and Chronic Cuprizone-Induced Demyelination.

Brain volume measurement is one of the most frequently used biomarkers to establish neuroprotective effects during pre-clinical multiple sclerosis (MS) studies. Furthermore, whole-brain atrophy estimates in MS correlate more robustly with clinical disability than traditional, lesion-based metrics. However, the underlying mechanisms leading to brain atrophy are poorly understood, partly due to the lack of appropriate animal models to study this aspect of the disease. The purpose of this study was to assess brain volumes and neuro-axonal degeneration after acute and chronic cuprizone-induced demyelination. C57BL/6 male mice were intoxicated with cuprizone for up to 12 weeks. Brain volume, as well as total numbers and densities of neurons, were determined using design-based stereology. After five weeks of cuprizone intoxication, despite severe demyelination, brain volumes were not altered at this time point. After 12 weeks of cuprizone intoxication, a significant volume reduction was found in the corpus callosum and diverse subcortical areas, particularly the internal capsule and the thalamus. Thalamic volume loss was accompanied by glucose hypermetabolism, analyzed by [F]-fluoro-2-deoxy-d-glucose (18F-FDG) positron-emission tomography. This study demonstrates region-specific brain atrophy of different subcortical brain regions after chronic cuprizone-induced demyelination. The chronic cuprizone demyelination model in male mice is, thus, a useful tool to study the underlying mechanisms of subcortical brain atrophy and to investigate the effectiveness of therapeutic interventions.

PIMD: 31421546

Ginkgolide K supports remyelination via induction of astrocytic IGF/PI3K/Nrf2 axis.

Although several therapies are approved, none promote re-myelination in multiple sclerosis (MS) patients, limiting their ability for sustained recovery. Thus, treatment development in MS has the opportunity to tackle the challenges, including experimental therapies targeting neuroprotection and re-myelination. Here, we provide a novel therapeutic target for Ginkgolide K (GK) that is now becoming a very critical natural compound to treat demyelination and neurodegeneration. GK improves behavioral dysfunction and demyelination in cuprizone (CPZ) model, followed by the migration and enrichment of astrocytes in the corpus callosum. Both in vitro and in vivo experiments demonstrates that GK triggers the upregulation of Nrf2/HO-1 in astrocytes and inhibition of p-NF-kB/p65, which is associated with the outcome of anti-inflammation and anti-oxidation by suppressing the production of IL-6 and TNFα as well as nitric oxide and iNOS in astrocytes. Further findings suggest that IGF/PI3K, but not BDNF, was induced in the corpus callosum after GK treatment, revealing that Nrf2 activation inhibited caspase-3 and apoptosis in O4+ oligodendrocytes possibly through IGF/PI3K signaling molecules. Since the current immunomodulatory therapies for MS have failed to prevent patients from entering the progressive phase of the disease, thus targeting Nrf2 in astrocytes with GK would be an ideal strategy for myelin protection and regeneration.

PIMD: 31418910

Quantitative brain relaxation atlases for personalized detection and characterization of brain pathology.

To exploit the improved comparability and hardware independency of quantitative MRI, databases of MR physical parameters in healthy tissue are required, to which tissue properties of patients can be compared. In this work, normative values for longitudinal and transverse relaxation times in the brain were established and tested in single-subject comparisons for detection of abnormal relaxation times.Relaxometry maps of the brain were acquired from 52 healthy volunteers. After spatially normalizing the volumes into a common space, T and T inter-subject variability within the healthy cohort was modeled voxel-wise. A method for a single-subject comparison against the atlases was developed by computing z-scores with respect to the established healthy norms. The comparison was applied to two multiple sclerosis and one clinically isolated syndrome cases for a proof of concept.The established atlases exhibit a low variation in white matter structures (median RMSE of models equal to 32 ms for T and 4 ms for T), indicating that relaxation times are in a narrow range for normal tissues. The proposed method for single-subject comparison detected relaxation time deviations from healthy norms in the example patient data sets. Relaxation times were found to be increased in brain lesions (mean z-scores >5). Moreover, subtle and confluent differences (z-scores ~2-4) were observed in clinically plausible regions (between lesions, corpus callosum).Brain T and T quantitative norms were derived voxel-wise with low variability in healthy tissue. Example patient deviation maps demonstrated good sensitivity of the atlases for detecting relaxation time alterations.

PIMD: 31363836

Detrimental and protective action of microglial extracellular vesicles on myelin lesions: astrocyte involvement in remyelination failure.

Microglia are highly plastic immune cells which exist in a continuum of activation states. By shaping the function of oligodendrocyte precursor cells (OPCs), the brain cells which differentiate to myelin-forming cells, microglia participate in both myelin injury and remyelination during multiple sclerosis. However, the mode(s) of action of microglia in supporting or inhibiting myelin repair is still largely unclear. Here, we analysed the effects of extracellular vesicles (EVs) produced in vitro by either pro-inflammatory or pro-regenerative microglia on OPCs at demyelinated lesions caused by lysolecithin injection in the mouse corpus callosum. Immunolabelling for myelin proteins and electron microscopy showed that EVs released by pro-inflammatory microglia blocked remyelination, whereas EVs produced by microglia co-cultured with immunosuppressive mesenchymal stem cells promoted OPC recruitment and myelin repair. The molecular mechanisms responsible for the harmful and beneficial EV actions were dissected in primary OPC cultures. By exposing OPCs, cultured either alone or with astrocytes, to inflammatory EVs, we observed a blockade of OPC maturation only in the presence of astrocytes, implicating these cells in remyelination failure. Biochemical fractionation revealed that astrocytes may be converted into harmful cells by the inflammatory EV cargo, as indicated by immunohistochemical and qPCR analyses, whereas surface lipid components of EVs promote OPC migration and/or differentiation, linking EV lipids to myelin repair. Although the mechanisms through which the lipid species enhance OPC maturation still remain to be fully defined, we provide the first demonstration that vesicular sphingosine 1 phosphate stimulates OPC migration, the first fundamental step in myelin repair. From this study, microglial EVs emerge as multimodal and multitarget signalling mediators able to influence both OPCs and astrocytes around myelin lesions, which may be exploited to develop novel approaches for myelin repair not only in multiple sclerosis, but also in neurological and neuropsychiatric diseases characterized by demyelination.

PIMD: 31362166

{'sup': '11', '#text': '[C]PIB PET imaging can detect white and grey matter demyelination in a non-human primate model of progressive multiple sclerosis.'}

Multiple sclerosis (MS) is a demyelinating and inflammatory disease of the central nervous system. Its diagnosis is clinical, often confirmed by magnetic resonance imaging. This image modality, however, is not ideal for discrimination of demyelination in grey and white matter regions from inflammatory lesions. Positron Emission Tomography (PET), using specific radiopharmaceuticals, can be a tool to differentiate between these processes. The radiopharmaceutical [C]PIB is widely used for detection of β-amyloid plaques, but has also been suggested for the analysis of myelin content due to its consistent uptake in white matter. The aim of this study was to evaluate [C]PIB PET imaging as a tool for detecting demyelinated regions in white and grey matter of non-human primate model of progressive MS.Experimental autoimmune encephalomyelitis (EAE) was induced in marmosets by injection of recombinant human myelin oligodendrocyte glycoprotein (rhMOG) emulsified in either Incomplete Freund's Adjuvant (IFA) or Complete Freund's Adjuvant (CFA). [C]PIB PET images were acquired prior to immunization (baseline) and after symptoms were present (end of experiment). Brain tissue was isolated for histochemical analysis.All rhMOG/IFA-treated and rhMOG/CFA-treated animals showed clinical signs of EAE. The rhMOG/CFA group presented a significant [C]PIB uptake reduction only in the left motor cortex (9%, P□=□0.011). For the rhMOG/IFA group, significant decrease in [C]PIB uptake was observed in the whole brain (15%, P□=□0.015), in the right hemisphere of body of corpus callosum (34%, P□=□0.02), splenium of corpus callosum (38%, P□=□0.004), hippocampus (19%, P□=□0.036), optic tract (13%, P□=□0.025), thalamus (14%, P□=□0.041), Globus pallidus (23%, P□=□0.017), head of caudate nucleus (25%, P□=□0.045), tail of caudate nucleus (29%, P□=□0.003), putamen (28%, P□=□0.047) and left hemisphere of body of corpus callosum (14%, P□=□0.037) and head of caudate nucleus (23%, P□=□0.023). [C]PIB uptake significantly correlated with luxol fast blue histology (myelin marker), both in the rhMOG/IFA (r= 0.32, P < 0.0001) and the rhMOG/CFA group (r= 0.46, P < 0.0001).[C]PIB PET imaging is an efficient tool for detecting demyelination in grey and white matter, in a non-human primate model of progressive MS.

PIMD: 31357085

Cordycepin (3'-deoxyadenosine) promotes remyelination via suppression of neuroinflammation in a cuprizone-induced mouse model of demyelination.

Multiple sclerosis (MS) is an inflammatory demyelination disease characterized by autoimmune damage to the central nervous system. In this disease, failure of remyelination could cause persistent disability. Cordycepin, also known as 3'-deoxyadenosine, exerts anti-inflammatory, anti-oxidic, anti-apoptotic and neuroprotective effects. The cuprizone (CPZ) model has been widely used to study MS as it mimics some characteristics of demyelination disease. To determine whether cordycepin promotes remyelination and functional recovery after CPZ-induced demyelination, we administered cordycepin to the CPZ-induced demyelination mice. Cordycepin reversed CPZ-induced loss of body weight and rescued motor dysfunction in the model mice. Cordycepin effectively promoted remyelination and enhanced MBP expression in the corpus callosum. Cordycepin also inhibited the CPZ-induced increase in the number of Iba1-positive microglia, GFAP-positive astrocytes and Olig2-positive oligodendroglial precursor cells in the corpus callosum and cerebral cortex. Pro-inflammatory cytokine expression (IL-1β and IL-6) was inhibited while anti-inflammatory cytokine IL-4 and neurotrophic factor BDNF release was elevated in the corpus callosum and hippocampus after cordycepin treatment. In addition, we also found that cordycepin ameliorated CPZ-induced body weight loss, motor dysfunction, demyelination, glial cells activation and pro-inflammatory cytokine expression in the corpus callosum and hippocampus. Our results suggest that cordycepin may represent a useful therapeutic agent in demyelination-related diseases via suppression of neuroinflammation.

PIMD: 31351476

Systemic TLR2 tolerance enhances central nervous system remyelination.

Multiple sclerosis (MS) is a central nervous system (CNS) autoimmune disease characterized by both inflammatory demyelination and impaired remyelination. Studies indicate that Toll-like receptor 2 (TLR2) signaling contributes to both the inflammatory component and the defective remyelination in MS. While most MS therapeutics target adaptive immunity, we recently reported that reducing TLR2 signaling in innate immune cells by inducing TLR2 tolerance attenuates adoptively transferred experimental autoimmune encephalomyelitis. Given that previous reports suggest TLR2 signaling also inhibits myelin repair, the objective of this study was to assess how reducing TLR2 signaling through TLR2 tolerance induction affects CNS myelin repair.Chow containing 0.2% cuprizone was fed to male and female wild-type (WT) C57BL/6 mice or TLR2-deficient (TLR2) mice for 5 weeks to induce demyelination. During a 2-week remyelination period following discontinuation of cuprizone, WT mice received either low dose TLR2 ligands to induce systemic TLR2 tolerance or vehicle control (VC). Remyelination was evaluated via electron microscopy and immunohistochemical analysis of microglia and oligodendrocytes in the corpus callosum. Statistical tests included 2-way ANOVA and Mann-Whitney U analyses.Inducing TLR2 tolerance in WT mice during remyelination significantly enhanced myelin recovery, restoring unmyelinated axon frequency and myelin thickness to baseline levels compared to VC-treated mice. Mechanistically, enhanced remyelination in TLR2 tolerized mice was associated with a shift in corpus callosum microglia from a pro-inflammatory iNOS phenotype to a non-inflammatory/pro-repair Arg1 phenotype. This result was confirmed in vitro by inducing TLR2 tolerance in WT microglia cultures. TLR2 mice, without TLR2 tolerance induction, also significantly enhanced myelin recovery compared to WT mice, adding confirmation that reduced TLR2 signaling is associated with enhanced remyelination.Our results suggest that reducing TLR2 signaling in vivo by inducing TLR2 tolerance significantly enhances myelin repair. Furthermore, the enhanced remyelination resulting from TLR2 tolerance induction is associated with a shift in corpus callosum microglia from a pro-inflammatory iNOS phenotype to a non-inflammatory/pro-repair Arg1 phenotype. While deletion of TLR2 would be an impractical approach in vivo, reducing innate immune signaling through TLR2 tolerance induction may represent a novel, two-pronged approach for treating both inflammatory and myelin repair components of MS.

PIMD: 31251832

The Spatial and Temporal Characters of Demyelination and Remyelination in the Cuprizone Animal Model.

Multiple sclerosis (MS) is the most common central nervous system disease due to demyelination in young adults, and currently, there is no cure. Some experimental animal models were generated to mimic specific aspects of MS pathological characteristics. Among them, the cuprizone (CPZ)-induced mouse demyelination model presents heterogeneous pathologies with both focal and diffuse lesions. Considering that MS is a progressive disease, it is important to study the spatial and temporal characters of de- and remyelination in MS animal models. However, such data especially in some brain regions such as lateral septal area, fimbria of hippocampus, and hippocampus are still lacking. In this study, we investigated the alterations of myelin in these areas in parallel to the changes in corpus callosum using coronal sections. We found that the progression of demyelinating varied in different brain regions in C57BL/6J mice treated with CPZ for 1 to 5 weeks. This result suggests that each brain region has a distinct sensitivity to CPZ intoxication. Interestingly, activated microglia appeared not only in the active demyelinating areas but also in the non-myelinolysis regions. After CPZ withdrawal, significant remyelination was started in corpus callosum as early as 3 days. The completion of remyelination in the entire brain regions took 3 weeks. Our study detailed characterized the dynamics of myelin alterations and microglial status in the brain of the CPZ model. This information is valuable to facilitate further MS studies utilizing the CPZ model. Anat Rec, 302:2020-2029, 2019. © 2019 American Association for Anatomy.

PIMD: 31226301

Diffusion tensor imaging identifies aspects of therapeutic estrogen receptor β ligand-induced remyelination in a mouse model of multiple sclerosis.

Diffusion tensor imaging (DTI) has been shown to detect white matter degeneration in multiple sclerosis (MS), a neurodegenerative autoimmune disease that presents with diffuse demyelination of the central nervous system. However, the utility of DTI in evaluating therapeutic remyelination has not yet been well-established. Here, we assessed the ability of DTI to distinguish between remyelination and neuroprotection following estrogen receptor β ligand (Indazole chloride, IndCl) treatment, which has been previously shown to stimulate functional remyelination, in the cuprizone (CPZ) diet mouse model of MS. Adult C57BL/6 J male and female mice received a normal diet (control), demyelination-inducing CPZ diet (9wkDM), or CPZ diet followed by two weeks of a normal diet (i.e., remyelination period) with either IndCl (RM + IndCl) or vehicle (RM + Veh) injections. We evaluated tissue microstructure of the corpus callosum utilizing in vivo and ex vivo DTI and immunohistochemistry (IHC) for validation. Compared to control mice, the 9wkDM group showed decreased fractional anisotropy (FA), increased radial diffusivity (RD), and no changes in axial diffusivity (AD) both in vivo and ex vivo. Meanwhile, RM + IndCl groups showed increased FA and decreased RD ex vivo compared to the RM + Veh group, in accordance with the evidence of remyelination by IHC. In conclusion, the DTI technology used in the present study can identify some changes in myelination and is a valuable translational tool for evaluating MS pathophysiology and therapeutic efficacy.

PIMD: 31197511

Psychiatric disorders in multiple sclerosis.

Multiple sclerosis (MS) is characterized by a large spectrum of symptoms, involving all functional systems. Psychiatric symptoms are common in people with MS (pwMS) having an important impact on quality of life and on some features of MS (fatigue, sleep, disability, adherence to disease-modifying drugs). The main psychiatric disturbances in MS are depressive, bipolar, anxiety, schizophrenic and obsessive-compulsive syndromes.Literature search for original articles and review in the databases, including PubMed and Scopus from 1959 to 2019.Studies answering the aim of this review were selected and reported. Epidemiological and clinical aspects of psychiatric syndromes (PS) in MS as well as self-report diagnostic scales and radiological correlates of PS in MS are described. Moreover, some radiological studies about primary psychiatric disorders (PD) are reported to underline how gray matter atrophy, white matter abnormalities and corpus callosum involvement in these diseases, as features in common with MS, may explain the more frequent occurrence of PD in MS than in the general population.

PIMD: 31186441

Central nervous system targeted autoimmunity causes regional atrophy: a 9.4T MRI study of the EAE mouse model of Multiple Sclerosis.

Atrophy has become a clinically relevant marker of progressive neurodegeneration in multiple sclerosis (MS). To better understand atrophy, mouse models that feature atrophy along with other aspects of MS are needed. The experimental autoimmune encephalomyelitis (EAE) mouse model of MS was used to determine the extent of atrophy in a model of inflammation-associated central nervous system pathology. High-resolution magnetic resonance imaging (MRI) and atlas-based volumetric analysis were performed to measure brain regional volumes in EAE mice. EAE brains were larger at peak clinical disease (days 14-16) compared to controls, with affected regions including the cerebellum, hippocampus, and corpus callosum. Following peak clinical disease, EAE mice exhibited significant loss of volume at chronic long-term disease duration (day 66+). Atrophy was identified in both white and grey matter regions including the cerebral cortex, cerebellum, hippocampus, corpus callosum, basal forebrain, midbrain, optic tract, and colliculus. Histological analysis of the atrophied cortex, cerebellum, and hippocampus showed demyelination, and axonal/neuronal loss. We hypothesize this atrophy could be a result of inflammatory associated neurodegenerative processes, which may also be involved in MS. Using MRI and atlas-based volumetrics, EAE has the potential to be a test bed for treatments aimed at reducing progressive neurological deterioration in MS.

PIMD: 31184779

BRCA1/BRCA2-containing complex subunit 3 controls oligodendrocyte differentiation by dynamically regulating lysine 63-linked ubiquitination.

Oligodendrocytes (OLs) provide the myelin sheath surrounding axons that propagates action potentials in the central nervous system (CNS). The metabolism of myelinated membranes and proteins is strictly regulated in the OLs and is closely associated with OL differentiation and maturation. The ubiquitination-associated proteasome and endosomal system have not yet been well studied during OL differentiation and maturation. Here, we determined the functions of the Lys63-linked ubiquitination (K63Ub) and K63-specific deubiquitination (DUB) systems regulated by BRCA1/BRCA2-containing complex subunit 3 (BRCC3) during OL differentiation. The competitive inhibition of K63Ub by overexpression of mutant ubiquitin (K63R) in oligodendrocyte precursor cells (OPCs) indicated that the two major CNS myelin proteins, myelin basic protein (MBP) and proteolipid protein (PLP), were upregulated in OLs derived from K63R OPCs. In contrast, the knockdown of BRCC3 (BRCC3-KD) through the application of lentivirus-mediated shRNA delivery system into OPCs suppressed OL differentiation by decreasing MBP expression and PLP production. Further immunoprecipitation assays revealed higher levels of sphingolipid GalC, MBP, and PLP, which were associated with K63Ub-immunoprecipitants and detected in endosome/lysosomal compartments, in BRCC3-KD OLs than those in OLs transfected with the scrambled shRNA (scramble OLs). The differentiation of OLs from BRCC3-KD OPCs was impaired in the demyelinating corpus callosum of rats receiving a cuprizone-containing diet. In the demyelinating tissues from human patients suffering from multiple sclerosis, we detected a decreased number of BRCC3-expressing OLs at the lesion site, accompanied by a greater number of OLs expressing EEA1 and K63Ub at high levels. Altogether, the counterbalance of the K63Ub machinery and BRCC3-triggered DUB machinery are important for the cellular trafficking of myelin proteins and OL differentiation.

PIMD: 31168611

Demyelination-Remyelination in the Central Nervous System: Ligand-Dependent Participation of the Notch Signaling Pathway.

Multiple sclerosis (MS) is an immune-mediated CNS disease mostly affecting young people. MS and other neurodegenerative and white matter disorders involve oligodendrocyte (OL) damage and demyelination. Therefore, elucidating the signaling pathways involved in the remyelination process through the maturation of OL progenitor cells (OPCs) may contribute to the development of new therapeutic approaches. In this context, this paper further characterizes toxic cuprizone (CPZ)-induced demyelination and spontaneous remyelination in rats and investigates the role of ligand-dependent Notch signaling activation along demyelination/remyelination both in vivo and in vitro. Toxic treatment generated an inflammatory response characterized by both microgliosis and astrogliosis. Interestingly, early demyelination revealed an increase in the proportion of Jagged1+/GFAP+ cells, which correlated with an increase in Jagged1 transcript and concomitant Jagged1-driven Notch signaling activation, particularly in NG2+ OPCs, in both the corpus callosum (CC) and subventricular zone (SVZ). The onset of remyelination then exhibited an increase in the proportion of F3/contactin+/NG2+ cells, which correlated with an increase in F3/contactin transcript during ongoing remyelination in the CC. Moreover, neurosphere cultures revealed that neural progenitor cells (NPCs) present in the brain SVZ of CPZ-treated rats recapitulate in vitro the mechanisms underlying the response to toxic injury observed in vivo, compensating for mature OL loss. Altogether, the present results offer strong evidence of cell-type and ligand-specific Notch signaling activation and its time- and area-dependent participation in toxic demyelination and spontaneous remyelination.

PIMD: 31163175

Multiple functional therapeutic effects of DL-3-n-butylphthalide in the cuprizone model of demyelination.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). The disease mechanisms driving progressive MS remain unresolved. Without this information, current therapeutic strategies are unsatisfactory in preventing disease progression. Our previous work revealed that DL-3-n-butylphthalide (NBP) treatment reduced demyelination in an ethidium bromide mouse model of demyelination. Here, we examine the effect of NBP in the cuprizone model of demyelination by evaluating the pathologic, functional, and behavioral consequences of treatment with NBP.Forty mice were divided randomly into 4 groups: a normal diet group, a cuprizone diet group, and two NBP groups (10 and 20 mg/kg). CNS infiltration by microglia, axon health and myelination were assessed using immunohistochemistry and electron microscopy, and the levels of cytoplasmic complexes were assessed by Western blotting.The results showed the neuroprotective effects of the NBP included suppressing the microglia activation through inhibition of nuclear factor-κB (NF-κB) expression, thus decreasing activation of the NF-κB signaling pathway. In particular, myelin density was increased due to an increased mean number of mature oligodendrocytes (OLs) in the high-dose NBP (20 mg/kg) subgroup through reduced oligodendrocyte apoptosis. Meanwhile, increased expression of myelin sheath proteins, including proteolipid protein (PLP) and myelin basic protein (MBP), was observed in the same subgroup.These data suggest that NBP may not only have anti-inflammatory properties but also promote the survival of OLs in a mouse cuprizone model of demyelination. NBP may have a potential role in the treatment of MS.

PIMD: 31139686

Corpus callosum axon diameter relates to cognitive impairment in multiple sclerosis.

To evaluate alterations in apparent axon diameter and axon density obtained by high-gradient diffusion MRI in the corpus callosum of MS patients and the relationship of these advanced diffusion MRI metrics to neurologic disability and cognitive impairment in MS.Thirty people with MS (23 relapsing-remitting MS [RRMS], 7 progressive MS [PMS]) and 23 healthy controls were scanned on a human 3-tesla (3T) MRI scanner equipped with 300 mT/m maximum gradient strength using a comprehensive multishell diffusion MRI protocol. Data were fitted to a three-compartment geometric model of white matter to estimate apparent axon diameter and axon density in the midline corpus callosum. Neurologic disability and cognitive function were measured using the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), and Minimal Assessment of Cognitive Function in MS battery.Apparent axon diameter was significantly larger and axon density reduced in the normal-appearing corpus callosum (NACC) of MS patients compared to healthy controls, with similar trends seen in PMS compared to RRMS. Larger apparent axon diameter in the NACC of MS patients correlated with greater disability as measured by the EDSS (= 0.555, = 0.007) and poorer performance on the Symbol Digits Modalities Test (= -0.593, = 0.008) and Brief Visuospatial Memory Test-Revised (= -0.632, < 0.01), tests of interhemispheric processing speed and new learning and memory, respectively.Apparent axon diameter in the corpus callosum obtained from high-gradient diffusion MRI is a potential imaging biomarker that may be used to understand the development and progression of cognitive impairment in MS.

PIMD: 31138656

Neural Stem Cells of the Subventricular Zone Contribute to Neuroprotection of the Corpus Callosum after Cuprizone-Induced Demyelination.

Myelin loss occurring in demyelinating diseases, including multiple sclerosis, is the leading cause of long-lasting neurological disability in adults. While endogenous remyelination, driven by resident oligodendrocyte precursor cells (OPCs), might partially compensate myelin loss in the early phases of demyelinating disorders, this spontaneous reparative potential fails at later stages. To investigate the cellular mechanisms sustaining endogenous remyelination in demyelinating disorders, we focused our attention on endogenous neural precursor cells (eNPCs) located within the subventricular zone (SVZ) since this latter area is considered one of the primary sources of new OPCs in the adult forebrain. First, we fate mapped SVZ-eNPCs in cuprizone-induced demyelination and found that SVZ endogenous neural stem/precursor cells are recruited during the remyelination phase to the corpus callosum (CC) and are capable of forming new oligodendrocytes. When we ablated SVZ-derived eNPCs during cuprizone-induced demyelination in female mice, the animals displayed reduced numbers of oligodendrocytes within the lesioned CC. Although this reduction in oligodendrocytes did not impact the ensuing remyelination, eNPC-ablated mice experienced increased axonal loss. Our results indicate that, in toxic models of demyelination, SVZ-derived eNPCs contribute to support axonal survival. One of the significant challenges in MS research is to understand the detrimental mechanisms leading to the failure of CNS tissue regeneration during disease progression. One possible explanation is the inability of recruited oligodendrocyte precursor cells (OPCs) to complete remyelination and to sustain axonal survival. The contribution of endogenous neural precursor cells (eNPCs) located in the subventricular zone (SVZ) to generate new OPCs in the lesion site has been debated. Using transgenic mice to fate map and to selectively kill SVZ-derived eNPCs in the cuprizone demyelination model, we observed migration of SVZ-eNPCs after injury and their contribution to oligodendrogenesis and axonal survival. We found that eNPCs are dispensable for remyelination but protect partially from increased axonal loss.

PIMD: 31100354

Voluntary running wheel attenuates motor deterioration and brain damage in cuprizone-induced demyelination.

Growing data from human and animal studies indicate the beneficial effects of exercise on several clinical outcomes in patients with multiple sclerosis (MS), an autoimmune, demyelinating disease, suggesting that it may slow down the disease progression, by reducing brain damage. However, the mechanisms involved are still elusive. Aim of this study was to address the effects of voluntary running wheel in a toxic-demyelinating model of MS, in which demyelination and brain inflammation occur in response to cuprizone (CPZ) treatment. Mice were housed in standard or wheel-equipped cages starting from the day of CPZ or normal chow feeding for three or six weeks and evaluated for weight changes, locomotor skills and neuromuscular functions over the course of the experimental design. Biochemical, molecular biology and immunohistochemical analyses were performed. Exercise prevented early weight loss caused by CPZ, indicating improved wellness in these mice. Both neuromuscular function and motor coordination were significantly enhanced by exercise in CPZ-treated mice. Moreover, exercise induced an early protection against axonal damage and the loss of the myelin associated proteins, myelin basic protein (MBP) and 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase), in the striatum and the corpus callosum, in coincidence of a strongly attenuated microglia activation in both brain areas. Further, during the late phase of the treatment, exercise in CPZ mice reduced the recruitment of new OLs compared to sedentary CPZ mice, likely due to the precocious protection against myelin damage. Overall, these results suggest that life-style interventions can be effective against the demyelinating-inflammatory processes occurring in the brains of MS patients.

PIMD: 31067791

Relationship of Iron Metabolism and Short-Term Cuprizone Treatment of C57BL/6 Mice.

One of the models to investigate the distinct mechanisms contributing to neurodegeneration in multiple sclerosis is based on cuprizone (CZ) intoxication. CZ is toxic to mature oligodendrocytes and produces demyelination within the central nervous system but does not cause direct neuronal damage. The CZ model is suitable for better understanding the molecular mechanism of de- and remyelination processes of oligodendrocytes. CZ is a copper chelating agent and it also affects the iron metabolism in brain and liver tissues. To determine the early effect of CZ treatment on iron homeostasis regulation, cytosolic and mitochondrial iron storage, as well as some lipid metabolism genes, we investigated the expression of respective iron homeostasis and lipid metabolism genes of the corpus callosum (CC) and the liver after short-term CZ administration. In the present study C57BL/6 male mice aged four weeks were fed with standard rodent food premixed with 0.2 w/w% CZ for two or eight days. The major findings of our experiments are that short-term CZ treatment causes significant changes in iron metabolism regulation as well as in the expression of myelin and lipid synthesis-related genes, even before apparent demyelination occurs. Both in the CC and the liver the iron uptake, utilization and storage are modified, though not always the same way or to the same extent in the two organs. Understanding the role of iron in short-term and long-term CZ intoxication could provide a partial explanation of the discrepant signs of acute and chronic MS. These could contribute to understanding the development of multiple sclerosis and might provide a possible drug target.

PIMD: 31040210

Gene expression in oligodendrocytes during remyelination reveals cholesterol homeostasis as a therapeutic target in multiple sclerosis.

Regional differences in neurons, astrocytes, oligodendrocytes, and microglia exist in the brain during health, and regional differences in the transcriptome may occur for each cell type during neurodegeneration. Multiple sclerosis (MS) is multifocal, and regional differences in the astrocyte transcriptome occur in experimental autoimmune encephalomyelitis (EAE), an MS model. MS and EAE are characterized by inflammation, demyelination, and axonal damage, with minimal remyelination. Here, RNA-sequencing analysis of MS tissues from six brain regions suggested a focus on oligodendrocyte lineage cells (OLCs) in corpus callosum. Olig1-RiboTag mice were used to determine the translatome of OLCs in vivo in corpus callosum during the remyelination phase of a chronic cuprizone model with axonal damage. Cholesterol-synthesis gene pathways dominated as the top up-regulated pathways in OLCs during remyelination. In EAE, remyelination was induced with estrogen receptor-β (ERβ) ligand treatment, and up-regulation of cholesterol-synthesis gene expression was again observed in OLCs. ERβ-ligand treatment in the cuprizone model further increased cholesterol synthesis gene expression and enhanced remyelination. Conditional KOs of ERβ in OLCs demonstrated that increased cholesterol-synthesis gene expression in OLCs was mediated by direct effects in both models. To address this direct effect, ChIP assays showed binding of ERβ to the putative estrogen-response element of a key cholesterol-synthesis gene (Fdps). As fetal OLCs are exposed in utero to high levels of estrogens in maternal blood, we discuss how remyelinating properties of estrogen treatment in adults during injury may recapitulate normal developmental myelination through targeting cholesterol homeostasis in OLCs.

PIMD: 31037121

{'sup': '18', '#text': 'Molecular Imaging of Immune Cell Dynamics During De- and Remyelination in the Cuprizone Model of Multiple Sclerosis by [F]DPA-714 PET and MRI.'}

: Activation and dysregulation of innate, adaptive and resident immune cells in response to damage determine the pathophysiology of demyelinating disorders. Among the plethora of involved cells, microglia/macrophages and astrocytes play an important role in the pathogenesis of demyelinating disorders. The in-depth investigation of the spatio-temporal profile of these cell types may inform about the exact disease state and localization as well as may allow to monitor therapeutic modulation of the components of the neuroinflammatory response during the course of multiple sclerosis (MS). In this study, we aimed to non-invasively decipher the degree and temporal profile of neuroinflammation (TSPO - [F]DPA-714 PET) in relation to selected magnetic resonance imaging (MRI) parameters (T maps) in the cuprizone (CPZ)-induced model of demyelination. Methods: C57Bl6 () mice were fed with a standard chow mixed with 0.2% (w/w) CPZ for 4 (; demyelination) and 6 weeks (; spontaneous remyelination). The degree of neuroinflammation at de- and remyelination was assessed by [F]DPA-714 PET, multi-echo T MRI, autoradiography and immunohistochemistry. : CPZ-induced brain alterations were confirmed by increase of T relaxation times in both white and grey matter after 3 and 5 weeks of CPZ. Peak [F]DPA-714 was found in the corpus callosum (CC, white matter), the hippocampus (HC, grey matter) and thalamus (grey matter) after 4 weeks of CPZ treatment and declined after 6 weeks of CPZ. autoradiography and dedicated immunofluorescence showed demyelination/remyelination with corresponding increased/decreased TSPO levels in the CC and hippocampus, confirming the spatial distribution of [F]DPA-714 . The expression of TSPO microglia and astrocytes is time-dependent in this model. Microglia predominantly express TSPO at demyelination, while the majority of astrocytes express TSPO during remyelination. The combination of PET- and MRI-based imaging biomarkers demonstrated the regional and temporal development of the CPZ model-associated neuroinflammatory response in grey and white matter regions. : The combination of [F]DPA-714 PET and T mapping may allow to further elucidate the regional and temporal profile of inflammatory signals depending on the myelination status, although the underlying inflammatory microenvironment changes. A combination of the described imaging biomarkers may facilitate the development of patient-tailored strategies for immunomodulatory and neuro-restorative therapies in MS.

PIMD: 31033006

Curcumin ameliorates experimental autoimmune encephalomyelitis in a C57BL/6 mouse model.

Multiple sclerosis (MS) is a common inflammatory disease of the central nervous system. Although the exact etiology of the disease is largely unknown, it is identified that cytokines may play an important role in the pathogenesis of MS. In this study, the effects of curcumin has been investigated on the expression levels of selected cytokine coding genes as well as the extent of demyelination in the corpus callosum of C57BL/6 experimental autoimmune encephalomyelitis (EAE) model of MS. Gene expression analyses revealed that treatment with curcumin could lead to a significant reduction in the expression levels of pro-inflammatory cytokine coding genes including IL-6 ($p = 0.001$), IL-17 ($p = 0.001$), tumor necrosis factor (TNF)-α ($p = 0.008$), and interferon (IFN)-γ ($p = 0.033$) as well as a significant increase in the expression level of transforming growth factor (TGF)-β ($p = 0.006$) as an anti-inflammatory cytokine. Moreover, the expression of glutathione peroxidase (GPX)-1 gene and the activity of anti-oxidant enzymes were significantly higher ($p < 0.001$) in curcumin-treated mice. Luxol fast blue staining also confirmed a significant reduction in the extent of demyelination in the curcumin-treated group ($p < 0.001$). Our results have confirmed that curcumin is an effective therapeutic agent that could ameliorate the severity of EAE.

PIMD: 31030018

Callosal lesions on magnetic resonance imaging with multiple sclerosis, neuromyelitis optica spectrum disorder and acute disseminated encephalomyelitis.

To clarify the features of callosal lesions on magnetic resonance imaging (MRI) in Multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), and acute disseminated encephalomyelitis (ADEM).Chinese patients diagnosed with MS (n=33), NMOSD (n=31), and ADEM (n=18) were enrolled. Characteristics of lesions in corpus callosum were evaluated with 1.5 Tesla MRI scanners. Chi-squared test (Fisher's exact test) was used to analyze the data.In corpus callosum, NMOSD and ADEM lesions tend to have a diffuse distribution (p=0.006, p=0.033) and blurred margins ($p < 0.001$, p=0.017), when compared with MS; lesions in NMOSD were less ovoid (p=0.006), while fewer lesions in ADEM existed in the rostrum and genu (p=0.002). NMOSD has the most heterogeneous intensity on post-enhancement sequences (p=0.016, p=0.001). Radial-like lesions were more common in MS and NMOSD (p=0.019, $p < 0.001$).MS lesions were most likely focally-localized with clear margins. Radial callosal lesions are characteristic of MS and NMOSD but rarely seen in ADEM. The signal intensities of the lesion were the most heterogeneous in NMOSD. Therefore, the lesion patterns in corpus callosum may serve as a useful clue for correct diagnosis, facilitating early treatment.

PIMD: 31018126

PAD2-Mediated Citrullination Contributes to Efficient Oligodendrocyte Differentiation and Myelination.

Citrullination, the deimination of peptidylarginine residues into peptidylcitrulline, has been implicated in the etiology of several diseases. In multiple sclerosis, citrullination is thought to be a major driver of pathology through hypercitrullination and destabilization of myelin. As such, inhibition of citrullination has been suggested as a therapeutic strategy for MS. Here, in contrast, we show that citrullination by peptidylarginine deiminase 2 (PAD2) contributes to normal oligodendrocyte differentiation, myelination, and motor function. We identify several targets for PAD2, including myelin and chromatin-related proteins, implicating PAD2 in epigenomic regulation. Accordingly, we observe that PAD2 inhibition and its knockdown affect chromatin accessibility and prevent the upregulation of oligodendrocyte differentiation genes. Moreover, mice lacking PAD2 display motor dysfunction and a decreased number of myelinated axons in the corpus callosum. We conclude that citrullination contributes to proper oligodendrocyte lineage progression and myelination.

PIMD: 31016544

Oligoprotective effect of metformin through the AMPK-dependent on restoration of mitochondrial hemostasis in the cuprizone-induced multiple sclerosis model.

Oxidative stress with mitochondrial defects has a central role in the development and deterioration of Multiple sclerosis (MS). According to new findings of the effects of metformin on mitochondrial function, has attracted a lot of attention. Furthermore, it is suggested that metformin exerts its beneficial influence through AMP-activated protein kinase (AMPK) pathway. In the current study, we investigated the possible protective effects of metformin on oxidative stress and mitochondrial function by activating the AMPK pathway in the cuprizone-induced demyelination. Mice were fed with cuprizone for 6 weeks. Animals simultaneously received metformin. After sacrificing animals, myelinations, and gliosis, changes in transcription factor and biochemical analysis were assessed. Transmission electron microscopy and luxol fast blue staining revealed that the myelinated axons within corpus callosum of cuprizone-induced demyelination animals increased after administration of metformin. Metformin also upregulated the expression of mitochondrial biogenesis genes. Furthermore, the biochemical analysis demonstrated that metformin ameliorated the oxidative stress induced by cuprizone. Immunohistochemistry analysis showed that astrogliosis and microgliosis were decreased after metformin administration while it enhanced the number of oligodendrocytes. Our data implicated that metformin exerts its therapeutic effects on MS by AMPK signaling improved mitochondrial homeostasis and protected oligodendrocytes.

PIMD: 31012202

Probing demyelination and remyelination of the cuprizone mouse model using multimodality MRI.

Various studies by MRI exhibit that the corpus callosum (CC) is the most vulnerable to cuprizone administration, detecting the demyelination and remyelination process using different MRI parameters are, however, lacking.To investigate the sensitivity of multiparametric MRI both in vivo and ex vivo for demyelination and remyelination.Prospective.A cuprizone mice model with an age-matched control group (n = 5), 4-week cuprizone exposure group followed by 9-week on a normal diet (n = 6), and a 13-week cuprizone exposure group (n = 6).3D gradient recalled echo, T -weighted, and diffusion tensor imaging (DTI) at 7.0T and 9.4T.Quantification of DTI metrics, quantitative susceptibility mapping (QSM), and T -weighted imaging intensity in major white matter bundles.Nonparametric permutation tests were used with a cluster-forming threshold as 3.09 (equivalent to P = 0.001), and the significant level as P = 0.05 with family-wise correction.In vivo susceptibility values increased from -11.7 to -0.7 ppb (P < 0.001) in CC and from -13.7 to -5.1 ppb (P < 0.001) in the anterior commissure (AC) after the 13-week cuprizone exposure. Ex vivo susceptibility values increased from -25.4 to 7.4 ppb (P < 0.001) in CC and from -41.6 to -15.8 ppb (P < 0.001) in AC. Susceptibility values showed high variations to demyelination for in vivo studies (94.0% in CC, 62.8% in AC). Susceptibility values exhibited higher variations than radial diffusivity for ex vivo studies (129.1% vs. 28.3% in CC, 62.0% vs. 25.0% in AC). In addition to the differential susceptibility variations in different white matter tracts, intraregional demyelination variation was also present not only in CC but also in the AC area by voxel-based analysis.QSM is sensitive to the demyelination process of cuprizone exposure, which can be a complementary technique to conventional T -weighted images and DTI metrics.2 Technical Efficacy Stage: 2 J. Magn. Reson. Imaging 2019;50:1852-1865.

PIMD: 30968379

[Susac Syndrome: A Diagnostic Chameleon].

Susac's syndrome (SuS) is a rare, probably autoimmune endotheliopathy of the central nervous system, retina and inner ear. It is characterized by a clinical triad of encephalopathy, branch retinal artery occlusions (BRAOs) and sensorineural hearing loss. To date, more than 300 cases of SuS have been reported in the literature. However, SuS remains an under- and misdiagnosed entity in the clinical setting. This report presents an exemplary case of a patient, who was initially misdiagnosed with relapsing-remitting multiple sclerosis. At initial presentation, the patient did not demonstrate the complete clinical triad, and the interval between symptom onset and diagnosis was 4 months. Typical diagnostic features, which enabled the diagnosis of SuS were: a) MRI findings with T2-hyperintense snowball-like lesions of the corpus callosum and subcortical white matter and hyperintense lesions in diffusionweighted imaging with reduced apparent diffusion coefficient; b) BRAOs and vessel wall hyperfluorescence in fluorescein angiography and a significant thickness reduction of the inner retinal layers in optical coherence tomography; c) bilateral sensorineural hearing loss. The patient was aggressively treated with cyclophosphamide, rituximab, glucocorticoids and acetylsalicylic acid with a good response to therapy. This report draws attention to the need to take SuS into consideration in the differential diagnosis at the interface of neurological, psychiatric, ophthalmological and otorhinolaryngological disorders. As SuS may result in severe and persistent neurological deficits, an interdisciplinary collaboration is fundamental for the prompt diagnosis and initiation of adequate immunosuppressive treatment.

PIMD: 30957304

Magnetic resonance elastography of brain: Comparison between anisotropic and isotropic stiffness and its correlation to age.

Noninvasive measurement of mechanical properties of brain tissue using magnetic resonance elastography (MRE) has been a promising method for investigating neurologic disorders such as multiple sclerosis, hydrocephalus, and Alzheimer's. However, because of the regional and directional dependency of brain stiffness, estimating anisotropic stiffness is important. This study investigates isotropic and anisotropic stiffness as a function of age as well as the correlation between isotropic and anisotropic stiffness.MRE and diffusion tensor imaging (DTI) were performed on 28 healthy subjects with age ranges between 18-62 y. Isotropic and anisotropic stiffness was measured and compared with age for different regions of interest such as the thalamus, corpus callosum, gray matter, white matter, and whole brain.Isotropic stiffness in gray matter ($r = -0.57$; $P = 0.001$) showed a significant decrease with age. Anisotropic stiffness in gray matter showed a significant decrease with age in C through C and in the thalamus, only in C . Between anisotropic and isotropic stiffness, gray matter showed a significant positive correlation in C through C , C and C showed a significant negative correlation in the thalamus and whole brain, and C showed a negative correlation in the corpus callosum. No significant difference between genders was observed in any measurements.This study demonstrated a change in isotropic and anisotropic stiffness with age in different regions of the brain along with a correlation of anisotropic stiffness to isotropic stiffness.

PIMD: 30940543

Pathological changes in mice with long term cuprizone administration.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). In MS, a long disease duration is known to be a strong risk factor for converting the clinical course of the disease from relapse remitting MS to secondary progressing MS. There is a hypothesis that long sustained demyelination may exhaust neurons, however, pathological changes induced in neurons following demyelination remain unknown. Cuprizone administration can induce and sustain demyelination in the mouse CNS. We examined pathological changes in mice following long sustained demyelination caused by up to 34-week cuprizone administration. Twelve-week cuprizone administration induced severe demyelination in the cerebral cortex, corpus callosum and deep cerebellar nuclei. Demyelination persisted up to 34 weeks, as shown by myelin basic protein immunohistochemistry. In contrast, cuprizone administration developed demyelination in the striatum by week 34. In these demyelinated regions, no neuronal loss was observed. However, in the striatum and deep cerebellar nuclei, cuprizone-induced demyelination changed the intracellular distribution of parvalbumin (PV). Furthermore, in the striatum, there was an increase in PV in the demyelinated axons and most PV immunoreactivity did not co-localize with SMI32 immunoreactivity in mice with 34-week cuprizone administration. Further, mice with 34-week cuprizone administration showed motor coordination dysfunction in the balance beam test. However, 12-week withdrawal from the cuprizone diet induced remyelination in the regions and motor coordination dysfunction recovered. These results indicate that 34-week cuprizone administration induces and sustains demyelination and results in reversible motor coordination dysfunction. The change of intracellular PV distribution suggests that PV may protect demyelinated axons by Ca buffering. This model may be useful to investigate pathological and behavioral changes following demyelination in the CNS.

PIMD: 30901701

Discriminative clinical and neuroimaging features of motor-predominant hereditary diffuse leukoencephalopathy with axonal spheroids and primary progressive multiple sclerosis: A preliminary cross-sectional study.

Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) is a rare autosomal-dominant white matter disease, typically characterized by juvenile cognitive decline and frontoparietal white matter lesions. A portion of HDLS patients exhibit preferential motor dysfunctions as their initial symptoms, mimicking multiple sclerosis (MS). However, there is no study comparing this phenotype of HDLS and primary progressive multiple sclerosis (PPMS), which greatly resemble each other. This is the first preliminary study to clarify the clinical and neuroimaging features of motor-predominant HDLS, and compare it with PPMS, using cases whose colony stimulating factor 1 receptor (CSF1R) were sequenced.Clinical and radiological data from Japanese patients at the Department of Neurology, Kyushu University Hospital, Fukuoka, Japan, were evaluated retrospectively and cross-sectionally. Twenty-nine brain and 18 spinal cord magnetic resonance imaging (MRI) scans from four motor-predominant HDLS patients with CSF1R mutations and 15 PPMS patients without CSF1R mutations, were evaluated using an HDLS MRI scoring system.Two patients with HDLS were initially diagnosed with MS and received immunotherapy. Clinically, motor-predominant HDLS and PPMS patients resembled each other in onset age and disability. However, motor-predominant HDLS patients had a significantly higher frequency of frontal release signs, lower positivity rates of oligoclonal IgG bands (OCB), and lower IgG index values. Total HDLS MRI scores, total white matter lesions (WMLs), and brain atrophy were similar between the diseases. However, motor-predominant HDLS patients had more marked atrophy of the corpus callosum (CC) body, more WMLs in the deep and subcortical regions of the frontoparietal lobes, fewer WMLs in the occipitotemporal periventricular regions, and more restricted diffusivity lesions on MRI than PPMS patients. There was a stronger association between disease duration and CC index in HDLS, suggesting more rapid progression compared with PPMS.Motor-predominant HDLS has characteristic frequent frontal release signs, normal findings for OCB and the IgG index, severe CC body atrophy, abundant deep and subcortical WMLs in the frontoparietal lobes, subtle occipitotemporal lobe periventricular WMLs, and more restricted diffusivity lesions on MRI. Although the present study was limited by the small number of HDLS cases, we propose that immunotherapy should be avoided in such cases.

PIMD: 30901089

Differential effect on myelination through abolition of activity-dependent synaptic vesicle release or reduction of overall electrical activity of selected cortical projections in the mouse.

Myelination of axons by oligodendrocytes in the central nervous system is crucial for fast, saltatory conduction of action potentials. As myelination is central for brain development and plasticity, and deficits are implicated in several neural disorders such as multiple sclerosis, major depressive disorder, bipolar disorder and schizophrenia, it is important to elucidate the underlying mechanisms regulating myelination. Numerous mechanisms have been proposed by which the communication between oligodendrocytes and active axons may regulate the onset and maintenance of activity-dependent myelination. We compared two models of 'silencing' layer V and/or VI cortical projection neurons from early stages by either decreasing their excitability through Kir2.1 expression, an inward rectifying potassium channel, introduced through in utero electroporation at embryonic day (E)13.5, or inhibiting regulated vesicular release through Cre-dependent knock-out of synaptosomal associated protein 25 kDA (SNAP25). SNAP25 is a component of the soluble N-ethylmaleimide fusion protein attachment protein receptor (SNARE) complex, which, among others, is needed for calcium-dependent regulated vesicle release from synapses. In layer VI cortical projection neurons in the Ntsr1-Cre;Ai14;Snap25 mouse, we found that inhibiting regulated vesicular release significantly decreased the amount of myelin basic protein (MBP, used as marker for myelination) and the amount of myelinated projections at postnatal day (P)14 without affecting the initial timing of onset of myelination in the brain (at P7/P8). Additionally, overall oligodendrocyte maturation appears to be affected. A strong trend towards reduced node of Ranvier (NoR) length was also observed in Ntsr1-Cre;Ai14;Snap25 corpus callosum. An equally strong trend towards reduced NoR length was observed in Rbp4-Cre;Ai14;Snap25 corpus callosum at P14, and the g-ratio in the spinal cord dorsal column was reduced at P18. However, no measurable differences in levels of MBP were detected in the striatum when comparing Rbp4-Cre;Ai14;Snap25 and control brains. Conversely, Kir2.1 in utero electroporation at E13.5 did not significantly affect the amount of MBP or number of myelinated callosal axons at P14 but did significantly decrease the NoR length measured in the corpus callosum. It therefore seems likely that the excitability of the neuron can potentially perform a modulating function of myelin characteristics, whereas regulated vesicular release has the potential to have a more pronounced effect on overall myelination, but in a cell-type specific manner.

PIMD: 30896448

Neuronal activity in vivo enhances functional myelin repair.

In demyelinating diseases such as Multiple Sclerosis (MS), demyelination of neuronal fibers impairs impulse conduction and causes axon degeneration. While neuronal activity stimulates oligodendrocyte production and myelination in normal conditions, it remains unclear whether the activity of demyelinated axons restores their loss-of-function in a harmful environment. To investigate this question, we established a model to induce a moderate optogenetic stimulation of demyelinated axons in the corpus callosum at the level of the motor cortex in which cortical circuit activation and locomotor effects were reduced in adult freely moving mice. We demonstrate that a moderate activation of demyelinated axons enhances the differentiation of oligodendrocyte precursor cells onto mature oligodendrocytes, but only under a repeated stimulation paradigm. This activity-dependent increase in the oligodendrocyte pool promotes an extensive remyelination and functional restoration of conduction, as revealed by ultrastructural analyses and compound action potential recordings. Our findings reveal the need of preserving an appropriate neuronal activity in the damaged tissue to promote oligodendrocyte differentiation and remyelination, likely by enhancing axon-oligodendroglia interactions. Our results provide new perspectives for translational research using neuromodulation in demyelinating diseases.

PIMD: 30864249

Plant polyprenols reduce demyelination and recover impaired oligodendrogenesis and neurogenesis in the cuprizone murine model of multiple sclerosis.

Recent studies showed hepatoprotective, neuroprotective, and immunomodulatory properties of polyprenols isolated from the green verdure of Picea abies (L.) Karst. This study aimed to investigate effects of polyprenols on oligodendrogenesis, neurogenesis, and myelin content in the cuprizone demyelination model. Demyelination was induced by 0.5% cuprizone in CD-1 mice during 10 weeks. Nine cuprizone-treated animals received daily injections of polyprenols intraperitoneally at a dose of 12-mg/kg body weight during Weeks 6-10. Nine control animals and other nine cuprizone-treated received sham oil injections. At Week 10, brain sections were stained for myelin basic protein, neuro-glial antigen-2, and doublecortin to evaluate demyelination, oligodendrogenesis, and neurogenesis. Cuprizone administration caused a decrease in myelin basic protein in the corpus callosum, cortex, hippocampus, and the caudate putamen compared with the controls. Oligodendrogenesis was increased, and neurogenesis in the subventricular zone and the dentate gyrus of the hippocampus was decreased in the cuprizone-treated group compared with the controls. Mice treated with cuprizone and polyprenols did not show significant demyelination and differences in oligodendrogenesis and neurogenesis as compared with the controls. Our results suggest that polyprenols can halt demyelination, restore impaired neurogenesis, and mitigate reactive overproduction of oligodendrocytes caused by cuprizone neurotoxicity.

PIMD: 30855715

[Appraisal of cerebral atrophy in multiple sclerosis by means of the corpus callosum index. Reply].

PIMD: 30855714

[Appraisal of cerebral atrophy in multiple sclerosis by means of the corpus callosum index].

PIMD: 30811744

Therapeutic effect of oligomeric proanthocyanidin in cuprizone-induced demyelination.

What is the central question of this study? Oligomeric proanthocyanidin has the capacity to alleviate abnormalities in neurological functioning. However, whether oligomeric proanthocyanidin can reduce the progression of demyelination or promote remyelination in demyelinating diseases remains unknown. What is the main finding and its importance? Oligomeric proanthocyanidin can improve cuprizone-induced demyelination by inhibiting immune cell infiltration, reversing overactivated microglia, decreasing the inflammatory cytokines secreted by inflammatory cells and decreasing the production of myelin oligodendrocyte glycoprotein -specific antibody in the brain.Demyelinating diseases of the CNS, including multiple sclerosis, neuromyelitis optica and acute disseminated encephalomylitis, are characterized by recurrent primary demyelination-remyelination and progressive neurodegeneration. In the present study, we investigated the therapeutic effect of oligomeric proanthocyanidin (OPC), the most effective component of grape seed extract, in cuprizone-fed C57BL/6 mice, a classic demyelination-remyelination model. Our results showed that OPC attenuated abnormal behaviour, reduced demyelination and increased expression of myelin basic protein and expression of O4 oligodendrocytes in the corpus callosum. Oligomeric proanthocyanidin also reduced the numbers of B and T cells, activated microglia in the corpus callosum and inhibited secretion of inflammatory factors. Furthermore, concentrations of myelin oligodendrocyte glycoprotein-specific antibodies were significantly reduced in serum and brain homogenates after OPC treatment. Together, these results demonstrate a potent therapeutic effect for OPC in cuprizone-mediated demyelination and clearly highlight multiple effects of this natural product in attenuating myelin-specific autoantibodies and the inflammatory microenvironment in the brain.

PIMD: 30802808

Cognitive speed and white matter integrity in secondary progressive multiple sclerosis.

Processing speed (PS) deficits have been consistently observed in secondary progressive multiple sclerosis (SPMS). However, the underlying neural correlates have not been clarified yet. The present study aimed to investigate the relationship between macrostructural and microstructural white matter (WM) integrity and performance on different cognitive measures with prominent PS load.Thirty-one patients with SPMS were recruited and underwent neurological, neuropsychological, and MRI assessments. The associations between a composite index of PS abilities and scores on various tests with prominent PS load and T1-weighted and diffusion tensor image parameters were tested. Analyses were carried out using voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS).VBM results showed that only the semantic fluency task correlated with grey matter (GM) volume in a range of cortical and subcortical areas bilaterally as well as the corpus callosum and the superior longitudinal fasciculus. TBSS analysis revealed consistent results across all the cognitive measures investigated, showing a prominent role of commissural and frontal associative WM tracts in supporting PS-demanding cognitive operations.In patients with SPMS, PS abilities are mainly dependent on the degree of both macrostructural and microstructural WM integrity. Preservation of associative WM tracts that support information integration seems crucial to sustain performance in tasks requiring fast cognitive processes.

PIMD: 30761708

Axonal water fraction as marker of white matter injury in primary-progressive multiple sclerosis: a longitudinal study.

Diffuse white matter (WM) injury is prominent in primary-progressive multiple sclerosis (PP-MS) pathology and is a potential biomarker of disease progression. Diffusion kurtosis imaging allows the quantification of non-Gaussian water diffusion, providing metrics with high WM pathological specificity. The aim of this study was to characterize the pathological changes occurring in the normal-appearing WM of patients with PP-MS at baseline and at 1-year follow-up and to assess their impact on disability and short-term disease progression.A total of 26 patients with PP-MS and 20 healthy controls were prospectively enrolled. Diffusion kurtosis imaging single-shot echo-planar imaging (EPI) was acquired on a 3-T scanner (Philips Achieva, Best, The Netherlands) (voxel size, $2 \times 2 \times 2$ mm , 30 directions for each b-value = 1000, 2000 s/mm and one b = 0 s/mm). A two-compartment biophysical model of WM tract integrity was used to derive spatial maps of axonal water fraction (AWF), intra-axonal diffusivity, extra-axonal axial and radial diffusivities (D , D) and tortuosity from the following WM tracts: corpus callosum (CC), corticospinal tract (CST) and posterior thalamic radiation (PTR).At baseline, patients with PP-MS showed a widespread decrease of AWF, tortuosity and D and an increase of D in CC, CST and PTR (P ranging from 0.001 to 0.036). At 1-year follow-up, a significant AWF decrease was detected in the body of CC (P = 0.048), PTR (P = 0.008) and CST (P = 0.044). Baseline AWF values in CST significantly discriminated progressed from non-progressed patients (P = 0.021; area under the curve, 0.854).Based on its change over time and its relationship with disease progression, among the analyzed metrics, AWF seems the most sensitive metric of WM tissue damage in PP-MS and therefore it could be considered as a marker for monitoring disease progression.

PIMD: 30697184

Predictors of Evolution Into Multiple Sclerosis After a First Acute Demyelinating Syndrome in Children and Adolescents.

The aim of the study was to estimate the rate of evolution or for multiple sclerosis (MS), after a first acute demyelinating event (ADE) in pediatric patients, and to investigate the variables that predict this evolution. We retrospectively evaluated the clinical and neuroradiological features of children who presented a first ADE between January 2005 and April 2017. All patients included underwent a baseline MRI, a cerebrospinal fluid and blood analysis, including virological examinations. The evolution into MS was determined by the 2013 International Pediatric Multiple Sclerosis Study Group (IPMSSG) criteria. Clinical and radiological features predictive of MS were determined using multivariate analyses. Ninety-one patients were selected (mean age at onset: 10.11 ± 4.6). After a mean follow-up of 5.6 ± 2.3 years, 35% of patients' conditions evolved to MS. In the logistic multivariate analysis of clinical and laboratory data, the best predictors of evolution into MS were: the presence of oligoclonal bands in CSF (< 0.001), past infection with EBV (< 0.001), periventricular lesions (< 0.001), hypointense lesions on T1 (< 0.001), and lesions of the corpus callosum (< 0.001) including Dawson fingers (< 0.001). Our findings suggest that a pattern of neuroimaging and laboratory findings may help to distinguish between, at clinical onset, children with a monophasic syndrome (clinically isolated syndrome or acute disseminated encephalomyelitis) from those who will develop MS.

PIMD: 30696113

Expression of Translocator Protein and [18F]-GE180 Ligand Uptake in Multiple Sclerosis Animal Models.

Positron emission tomography (PET) ligands targeting the translocator protein (TSPO) represent promising tools to visualize neuroinflammation in multiple sclerosis (MS). Although it is known that TSPO is expressed in the outer mitochondria membrane, its cellular localization in the central nervous system under physiological and pathological conditions is not entirely clear. The purpose of this study was to assess the feasibility of utilizing PET imaging with the TSPO tracer, [18F]-GE180, to detect histopathological changes during experimental demyelination, and to determine which cell types express TSPO. C57BL/6 mice were fed with cuprizone for up to 5 weeks to induce demyelination. Groups of mice were investigated by [18F]-GE180 PET imaging at week 5. Recruitment of peripheral immune cells was triggered by combining cuprizone intoxication with MOG immunization (i.e., Cup/EAE). Immunofluorescence double-labelling and transgene mice were used to determine which cell types express TSPO. [18F]-GE180-PET reliably detected the cuprizone-induced pathology in various white and grey matter regions, including the corpus callosum, cortex, hippocampus, thalamus and caudoputamen. Cuprizone-induced demyelination was paralleled by an increase in TSPO expression, glia activation and axonal injury. Most of the microglia and around one-third of the astrocytes expressed TSPO. TSPO expression induction was more severe in the white matter corpus callosum compared to the grey matter cortex. Although mitochondria accumulate at sites of focal axonal injury, these mitochondria do not express TSPO. In Cup/EAE mice, both microglia and recruited monocytes contribute to the TSPO expressing cell populations. These findings support the notion that TSPO is a valuable marker for the in vivo visualization and quantification of neuropathological changes in the MS brain. The pathological substrate of an increase in TSPO-ligand binding might be diverse including microglia activation, peripheral monocyte recruitment, or astrocytosis, but not axonal injury.

PIMD: 30679747

Analogues of ERβ ligand chloroindazole exert immunomodulatory and remyelinating effects in a mouse model of multiple sclerosis.

Pharmaceutical agents currently approved for the treatment of multiple sclerosis reduce relapse rates, but do not reverse or prevent neurodegeneration nor initiate myelin repair. The highly selective estrogen receptor (ER) β ligand chloroindazole (IndCl) shows particular promise promoting both remyelination while reducing inflammatory cytokines in the central nervous system of mice with experimental autoimmune encephalomyelitis. To optimize these benefits, we developed and screened seven novel IndCl analogues for their efficacy in promoting primary oligodendrocyte (OL) progenitor cell survival, proliferation, and differentiation in vitro by immunohistochemistry. Two analogues, IndCl-o-chloro and IndCl-o-methyl, induced proliferation and differentiation equivalent to IndCl and were selected for subsequent in vivo evaluation for their impact on clinical disease course, white matter pathology, and inflammation. Both compounds ameliorated disease severity, increased mature OLs, and improved overall myelination in the corpus callosum and white matter tracts of the spinal cord. These effects were accompanied by reduced production of the OL toxic molecules interferon-γ and chemokine (C-X-C motif) ligand, CXCL10 by splenocytes with no discernable effect on central nervous system-infiltrating leukocyte numbers, while IndCl-o-methyl also reduced peripheral interleukin (IL)-17. In addition, expression of the chemokine CXCL1, which is associated with developmental oligodendrogenesis, was upregulated by IndCl and both analogues. Furthermore, callosal compound action potential recordings from analogue-treated mice demonstrated a larger N1 component amplitude compared to vehicle, suggesting more functionally myelinated fibers. Thus, the o-Methyl and o-Chloro IndCl analogues represent a class of ERβ ligands that offer significant remyelination and neuroprotection as well as modulation of the immune system; hence, they appear appropriate to consider further for therapeutic development in multiple sclerosis and other demyelinating diseases.

PIMD: 30660624

Hydroxyfasudil alleviates demyelination through the inhibition of MOG antibody and microglia activation in cuprizone mouse model.

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system characterized by oligodendrocyte loss and progressive neurodegeneration. The cuprizone (CPZ)-induced demyelination is widely used to investigate the demyelination/remyelination. Here, we explored the therapeutic effects of Hydroxyfasudil (HF), an active metabolite of Fasudil, in CPZ model. HF improved behavioral abnormality and reduced myelin damage in the corpus callosum. Splenic atrophy and myelin oligodendrocyte glycoprotein (MOG) antibody were observed in CPZ model, which were partially restored and obviously inhibited by HF, therefore reducing pathogenic binding of MOG antibody to oligodendrocytes. HF inhibited the percentages of CD4IL-17 T cells from splenocytes and infiltration of CD4 T cells and CD68 macrophages in the brain. HF also declined microglia-mediated neuroinflammation, and promoted the production of astrocyte-derived brain derived neurotrophic factor (BDNF) and regeneration of NG2 oligodendrocyte precursor cells. These results provide potent evidence for the therapeutic effects of HF in CPZ-induced demyelination.

PIMD: 30652255

Astrocyte ablation induced by La-aminoadipate (L-AAA) potentiates remyelination in a cuprizone demyelinating mouse model.

Chronic demyelination in the central nervous system (CNS) is accompanied by an increase in the number of reactive astrocytes and astrogliosis. There are controversial issues regarding astrocytes and their roles in demyelinating diseases in particular for multiple sclerosis (MS). We aimed to evaluate possible roles for pharmacologic astrocyte ablation strategy using La-aminoadipate (L-AAA) on remyelination in a cuprizone model of demyelination. Male C57BL/6 mice were fed with 0.2% cuprizone for 12 weeks followed by 2-week administration of L-AAA through a cannula inserted 1 mm above the corpus callosum. Rotarod test showed a significant decrease in the range of motor coordination deficits after ablation of astrocytes in mice receiving cuprizone. Results of Luxol fast blue (LFB) and transmission electron microscopy (TEM) for evaluation of myelin content within the corpus callosum revealed a noticeable rise in the percentage of myelinated areas and in the number of myelinated fibers after L-AAA administration in the animals. Astrocyte ablation reduced protein expressions for GFAP (an astrocyte marker) and Iba-1 (a microglial marker), but increased expression of Olig2 (an oligodendrocyte marker) assessed by immunofluorescence. Finally, expression of genes related to recruitment of microglia (astrocyte chemokines CXCL10 and CXCL12) and suppression of oligodendrocyte progenitor cell (OPC) differentiation (astrocyte peptides ET-1 and EDNRB) showed a considerable decrease after administration of L-AAA (for all $p < 0.05$). These results are indicative of improved remyelination after ablation of astrocytes possibly through hampering microgliosis and astrogliosis and a further rise in the number of matured Olig2 cells.

PIMD: 30631981

Oral Delivery of Methylthioadenosine to the Brain Employing Solid Lipid Nanoparticles: Pharmacokinetic, Behavioral, and Histopathological Evidences.

The present study aimed to orally deliver methylthioadenosine (MTA) to the brain employing solid lipid nanoparticles (SLNs) for the management of neurological conditions like multiple sclerosis. The stearic acid-based SLNs were below 100 nm with almost neutral zeta potential and offered higher drug entrapment and drug loading. Cuprizone-induced demyelination model in mice was employed to mimic the multiple sclerosis-like conditions. It was observed that the MTA-loaded SLNs were able to maintain the normal metabolism, locomotor activity, motor coordination, balancing, and grip strength of the rodents in substantially superior ways vis-à-vis plain MTA. Histopathological studies of the corpus callosum and its subsequent staining with myelin staining dye luxol fast blue proved the potential of MTA-loaded SLNs in the remyelination of neurons. The pharmacokinetic studies provided the evidences for improved bioavailability and enhanced bioresidence supporting the pharmacodynamic findings. The studies proved that SLN-encapsulated MTA can be substantially delivered to the brain and can effectively remyelinate the neurons. It can reverse the multiple sclerosis-like symptoms in a safer and effective manner, that too by oral route.

PIMD: 30628737

Effect of the CSF1R inhibitor PLX3397 on remyelination of corpus callosum in a cuprizone-induced demyelination mouse model.

Multiple sclerosis (MS) is a chronic inflammatory disease affecting the central nervous system (CNS). Despite introducing multiple immunomodulatory approaches for MS, there are still major concerns about possible ways for improving remyelination in this disease. Microglia exert essential roles in regulation of myelination processes, and interaction between colony-stimulating factor 1 (CSF1) with its receptor CSF1R is considered as a key regulator of microglial differentiation and survival. The aim of this study was to investigate possible roles for a CSF1R inhibitor PLX3397 in recovery of central myelination processes. Chronic demyelination was induced in mice by addition of 0.2% cuprizone to the chow for 12 weeks. Next, animals were undergoing a diet containing 290 mg/kg PLX3397 to induce microglial ablation. The PLX3397 treatment caused a significant decrease in the rate of expression for the CSF1/CSF1R axis, and a reduction in the protein expressions for the microglial marker Iba-1 and for the oligodendrocyte marker Olig-2. Findings from Luxol fast blue (LFB) staining and transmission electron microscopy (TEM) showed an increase in the rate of myelination for the mice receiving PLX3397. The rate of destruction in the nerve fibers and the extent of the gaps formed between layers of myelin sheaths was also reduced after the treatment with PLX3397. In addition, animals experienced an improvement in recovery of motor deficit after receiving PLX3397 (for all $P < 0.05$). It could be concluded that PLX3397 could retain myelination in the MS model possibly through regulation of the myelin environment.

PIMD: 30620337

Loss of the sphingolipid desaturase DEGS1 causes hypomyelinating leukodystrophy.

Sphingolipid imbalance is the culprit in a variety of neurological diseases, some affecting the myelin sheath. We have used whole-exome sequencing in patients with undetermined leukoencephalopathies to uncover the endoplasmic reticulum lipid desaturase DEGS1 as the causative gene in 19 patients from 13 unrelated families. Shared features among the cases include severe motor arrest, early nystagmus, dystonia, spasticity, and profound failure to thrive. MRI showed hypomyelination, thinning of the corpus callosum, and progressive thalamic and cerebellar atrophy, suggesting a critical role of DEGS1 in myelin development and maintenance. This enzyme converts dihydroceramide (DhCer) into ceramide (Cer) in the final step of the de novo biosynthesis pathway. We detected a marked increase of the substrate DhCer and DhCer/Cer ratios in patients' fibroblasts and muscle. Further, we used a knockdown approach for disease modeling in Danio rerio, followed by a preclinical test with the first-line treatment for multiple sclerosis, fingolimod (FTY720, Gilenya). The enzymatic inhibition of Cer synthase by fingolimod, 1 step prior to DEGS1 in the pathway, reduced the critical DhCer/Cer imbalance and the severe locomotor disability, increasing the number of myelinating oligodendrocytes in a zebrafish model. These proof-of-concept results pave the way to clinical translation.

PIMD: 30607821

Evaluation strategy to determine reliable demyelination in the cuprizone model.

In multiple sclerosis patients, chronic clinical deficits are known to result from axonal degeneration which is triggered by inadequate remyelination. The underlying molecular mechanisms of remyelination and its failure remain currently unclear. In vivo models, among the cuprizone model, are valuable tools to study underlying mechanisms of remyelination and its failure. Since complete and reproducible demyelination of the analyzed brain region is an indispensable prerequisite for efficient remyelination experiments, in this study we systematically addressed which part of the corpus callosum is reliably and consistently demyelinated after acute cuprizone-induced demyelination. Following a novel evaluation strategy, we can show that at the level of the rostral hippocampus, the most medial sectors of the corpus callosum (spanning 500 µm in the horizontal plane) are consistently demyelinated, whereas more lateral sectors show inconsistent and incomplete demyelination. These results precisely define a part of the corpus callosum which should be used as a region of interest during remyelination experiments.

PIMD: 30606727

"Ears of the Lynx" MRI Sign Is Associated with SPG11 and SPG15 Hereditary Spastic Paraplegia.

The "ears of the lynx" MR imaging sign has been described in case reports of hereditary spastic paraplegia with a thin corpus callosum, mostly associated with mutations in the gene, causing Spastic Paraplegia type 11 (SPG11). This sign corresponds to long T1 and T2 values in the forceps minor of the corpus callosum, which appears hyperintense on FLAIR and hypointense on T1-weighted images. Our purpose was to determine the sensitivity and specificity of the ears of the lynx MR imaging sign for genetic cases compared with common potential mimics.Four independent raters, blinded to the diagnosis, determined whether the ears of the lynx sign was present in each of a set of 204 single anonymized FLAIR and T1-weighted MR images from 34 patients with causal mutations associated with SPG11 or Spastic Paraplegia type 15 (SPG15). 34 healthy controls, and 34 patients with multiple sclerosis.The interrater reliability for FLAIR images was substantial (Cohen κ, 0.66-0.77). For these images, the sensitivity of the ears of the lynx sign across raters ranged from 78.8 to 97.0 and the specificity ranged from 90.9 to 100. The accuracy of the sign, measured by area under the receiver operating characteristic curve, ranged from very good (87.1) to excellent (93.9).The ears of the lynx sign on FLAIR MR imaging is highly specific for the most common genetic subtypes of hereditary spastic paraplegia with a thin corpus callosum. When this sign is present, there is a high likelihood of a genetic mutation, particularly associated with SPG11 or SPG15, even in the absence of a family history.

PIMD: 30588771

Diffusion tensor imaging and disability progression in multiple sclerosis: A 4-year follow-up study.

Diffusion tensor imaging (DTI) is sensitive technique to detect widespread changes in water diffusivity in the normal-appearing white matter (NAWM) that appears unaffected in conventional magnetic resonance imaging. We aimed to investigate the prognostic value and stability of DTI indices in the NAWM of the brain in an assessment of disability progression in patients with a relapsing-onset multiple sclerosis (MS).Forty-six MS patients were studied for DTI indices (fractional anisotropy (FA), mean diffusivity (MD), radial (RD), and axial (AD) diffusivity) in the NAWM of the corpus callosum (CC) and the internal capsule at baseline and at 1 year after. DTI analysis for 10 healthy controls was also performed at baseline. Simultaneously, focal brain lesion volume and atrophy measurements were done at baseline for MS patients. Associations between DTI indices, volumetric measurements, and disability progression over 4 years were studied by multivariate logistic regression analysis.At baseline, most DTI metrics differed significantly between MS patients and healthy controls. There was tendency for associations between baseline DTI indices in the CC and disability progression ($p < 0.05$). Changes in DTI indices over 1 year were observed only in the CC ($p < 0.008$), and those changes were not found to predict clinical worsening over 4 years. Clear-cut association with disability progression was not detected for baseline volumetric measurements.Aberrant diffusivity measures in the NAWM of the CC may provide additional information for individual disability progression over 4 years in MS with the relapsing-onset disease. CC may be a good target for DTI measurements in monitoring disease activity in MS, and more studies are needed to assess the related prognostic potential.

PIMD: 30588379

The neural basis of fatigue in multiple sclerosis: A multimodal MRI approach.

Fatigue is a frequent disabling symptom in multiple sclerosis (MS), but its pathophysiology remains incompletely understood. This study aimed to explore the underlying neural basis of fatigue in patients with MS.We enrolled 60 consecutive patients with MS and 60 healthy controls (HC) matched on age, sex, and education. Fatigue was assessed using the Portuguese version of the Modified Fatigue Impact Scale (MFIS). All participants underwent 3T brain MRI (conventional and diffusion tensor imaging [DTI] sequences). White matter (WM) focal lesions were identified and T1/T2 lesion volumes were computed. Tract-based spatial statistics were applied for voxel-wise analysis of DTI metrics fractional anisotropy and mean diffusivity (MD) on normal-appearing WM (NAWM). Using Freesurfer software, total and regional volumes of cortical and subcortical gray matter (GM) were calculated.Compared to HC, patients with MS scored significantly higher on MFIS (33.8 ± 19.7 vs 16.5 ± 15.1, < 0.001). MFIS scores were not significantly correlated with T1/T2 lesion volumes, total GM volume, or any regional volume of cortical and subcortical GM. Significant correlations were found between global scores of MFIS and MD increase of the NAWM skeleton, including corona radiata, internal capsule, external capsule, corticospinal tract, cingulum, corpus callosum, fornix, superior longitudinal fasciculus, superior fronto-occipital fasciculus, sagittal stratum, posterior thalamic radiation, cerebral peduncle, and uncinate fasciculus.In this study, fatigue was associated with widespread NAWM damage but not with lesion load or GM atrophy. Functional disconnection, caused by diffuse microstructural WM damage, might be the main neural basis of fatigue in MS.

PIMD: 30582962

The endocannabinoid 2-AG enhances spontaneous remyelination by targeting microglia.

Remyelination is an endogenous process by which functional recovery of damaged neurons is achieved by reinstating the myelin sheath around axons. Remyelination has been documented in multiple sclerosis (MS) lesions and experimental models, although it is often incomplete or fails to affect the integrity of the axon, thereby leading to progressive disability. Microglia play a crucial role in the clearance of the myelin debris produced by demyelination and in inflammation-dependent OPC activation, two processes necessary for remyelination to occur. We show here that following corpus callosum demyelination in the TMEV-IDD viral murine model of MS, there is spontaneous and partial remyelination that involves a temporal discordance between OPC mobilization and microglia activation. Pharmacological treatment with the endocannabinoid 2-AG enhances the clearance of myelin debris by microglia and OPC differentiation, resulting in complete remyelination and a thickening of the myelin sheath. These results highlight the importance of targeting microglia during the repair processes in order to enhance remyelination.

PIMD: 30576361

Gray matter atrophy in multiple sclerosis despite clinical and lesion stability during natalizumab treatment.

Brain volume loss is an important surrogate marker for assessing disability in MS; however, contribution of gray and white matter to the whole brain volume loss needs further examination in the context of specific MS treatment.To examine whole and segmented gray, white, thalamic, and corpus callosum volume loss in stable patients receiving natalizumab for 2-5 years.This was a retrospective study of 20 patients undergoing treatment with natalizumab for 24-68 months. Whole brain volume loss was determined with SIENA. Gray and white matter segmentation was done using FAST. Thalamic and corpus callosum volumes were determined using Freesurfer. T1 relaxation values of chronic hypointense lesions (black holes) were determined using a quantitative, in-house developed method to assess lesion evolution.Over a mean of 36.6 months, median percent brain volume change (PBVC) was -2.0% (IQR 0.99-2.99). There was decline in gray ($p = 0.001$) but not white matter ($p = 0.6$), and thalamic ($p = 0.01$) but not corpus callosum volume ($p = 0.09$). Gray matter loss correlated with PBVC (Spearman's $r = 0.64$, $p = 0.003$) but not white matter (Spearman's $r = 0.42$, $p = 0.07$). Age significantly influenced whole brain volume loss ($p = 0.010$, multivariate regression), but disease duration and baseline T2 lesion volume did not. There was no change in T1 relaxation values of lesions or T2 lesion volume over time. All patients remained clinically stable.These results demonstrate that brain volume loss in MS is primarily driven by gray matter changes and may be independent of clinically effective treatment.

PIMD: 30572821

Structural MRI correlates of PASAT performance in multiple sclerosis.

The Paced Auditory Serial Addition Test (PASAT) is a useful cognitive test in patients with multiple sclerosis (MS), assessing sustained attention and information processing speed. However, the neural underpinnings of performance in the test are controversial. We aimed to study the neural basis of PASAT performance by using structural magnetic resonance imaging (MRI) in a series of 242 patients with MS.PASAT (3-s) was administered together with a comprehensive neuropsychological battery. Global brain volumes and total T2-weighted lesion volumes were estimated. Voxel-based morphometry and lesion symptom mapping analyses were performed.Mean PASAT score was 42.98 ± 10.44; results indicated impairment in 75 cases (31.0%). PASAT score was correlated with several clusters involving the following regions: bilateral precuneus and posterior cingulate, bilateral caudate and putamen, and bilateral cerebellum. Voxel-based lesion symptom mapping showed no significant clusters. Region of interest-based analysis restricted to white matter regions revealed a correlation with the left cingulum, corpus callosum, bilateral corticospinal tracts, and right arcuate fasciculus. Correlations between PASAT scores and global volumes were weak.PASAT score was associated with regional volumes of the posterior cingulate/precuneus and several subcortical structures, specifically the caudate, putamen, and cerebellum. This emphasises the role of both cortical and subcortical structures in cognitive functioning and information processing speed in patients with MS.

PIMD: 30568702

Fingolimod Enhances Oligodendrocyte Differentiation of Transplanted Human Induced Pluripotent Stem Cell-Derived Neural Progenitors.

Multiple sclerosis (MS) is an autoimmune disease which affects myelin in the central nervous system (CNS) and leads to serious disability. Currently available treatments for MS mainly suppress the immune system. Regenerative medicine-based approaches attempt to increase myelin repair by targeting endogenous progenitors or transplanting stem cells or their derivatives. Fingolimod exerts anti-inflammatory effects and directly affects neural cells. In this study we assessed the effect of fingolimod on transplanted human induced pluripotent stem cell derived neural progenitors (hiPSC-NPs). hiPSC-NPs were labeled by green fluorescence protein (GFP) and transplanted into the corpus callosum of mice which were chronically demyelinated after cuprizone (CPZ) feedings for 10 weeks. The animals received fingolimod from 1 day prior to NPs transplantation via gavage as well as daily intraperitoneal cyclosporine A from 2 days before cell transplantation until the time of sampling. At either 7 or 21 days after NPs transplantation, the animals were sacrificed and their brains were histologically evaluated for the number of transplanted cells and their fate. In the animals treated with fingolimod, we observed higher numbers of NPs within the injection site compared to the animals who did not receive fingolimod showing that hiPSC- NPs were more efficiently differentiated to the oligodendrocyte lineage. These data have suggested that repetitive treatment with fingolimod, beside its anti-inflammatory effect, may enhance the survival and differentiation of transplanted NPs to oligodendrocyte lineage cells to participate in myelin repair.

PIMD: 30539784

The protective effect of rifampicin on behavioral deficits, biochemical, and neuropathological changes in a cuprizone model of demyelination.

Multiple sclerosis (MS) is a disease of the central nervous system (CNS) in which both neuroinflammation and neurodegeneration play critical roles in the pathogenesis of the disease. A growing body of evidence indicates that some antibiotics have anti-inflammatory and neuroprotective properties. Rifampicin, commonly used for the treatment of mycobacteria, has been shown to exert neuroprotective activities in neurodegenerative diseases. In this study, we examined the efficacy of rifampicin on demyelination, gliosis, apoptosis, inflammation, behavioral dysfunction, and biochemical alterations in the cuprizone model of demyelination. For this aim, male C57BL/6J mice were fed a chow containing 0.2% cuprizone (w/w) for 6 weeks to induce reversible demyelination in the corpus callosum. Mice intraperitoneally received serial doses of rifampicin (10, 20, or 40 mg/kg body weight) in the last 7 days of a 6-week period of cuprizone treatment. The results showed that the administration of rifampicin led to the improvement in motor behavioral deficits. In line with this, rifampicin decreased the number of apoptotic cells in the corpus callosum thereby diminishing the expression of cleaved caspase-3 and Bax, as well as increasing Bcl-2. Moreover, rifampicin significantly lowered the levels of interleukin-6, interleukin-1β, caspase-12 activity, heme oxygenase-1(HO-1), nitric oxide (NO), and malondialdehyde (MDA) in mice treated with cuprizone. Conversely, the activity of glutathione peroxidase (GPx) and the level of ferric reducing ability of plasma (FRAP) were increased in response to the treatment with rifampicin. Histopathological findings demonstrated that rifampicin statistically promoted remyelination and mitigated microgliosis and astrogliosis. It seems that rifampicin is able to be added to the armamentarium of therapies for multiple sclerosis.

PIMD: 30519158

Inter-Vendor Reproducibility of Myelin Water Imaging Using a 3D Gradient and Spin Echo Sequence.

Myelin water imaging can be achieved using multicomponent T relaxation analysis to quantify measurement of myelin content, termed the myelin water fraction (MWF). Therefore, myelin water imaging can be a valuable tool to better understand the underlying white matter pathology in demyelinating diseases, such as multiple sclerosis. To apply myelin water imaging in multisite studies and clinical applications, it must be acquired in a clinically feasible scan time (less than 15 min) and be reproducible across sites and scanner vendors. Here, we assessed the reproducibility of MWF measurements in regional and global white matter in 10 healthy human brains across two sites with two different 3 T magnetic resonance imaging scanner vendors (Philips and Siemens), using a 32-echo gradient and spin echo (GRASE) sequence. A strong correlation was found between the MWF measurements in the global white matter (Pearson's = 0.91; < 0.001) for all participants across the two sites. The mean intersite MWF coefficient of variation across participants was 2.77% in the global white matter and ranged from 4.47% (splenium of the corpus callosum) to 17.89% (genu of the corpus callosum) in white matter regions of interest. Bland-Altman analysis showed a good agreement in MWF measurements between the two sites with small bias of 0.002. Overall, MWF estimates were in good agreement across the two sites and scanner vendors. Our findings support the use of quantitative multi-echo T relaxation metrics, such as the MWF, in multicenter studies and clinical trials to gain deeper understanding about the pathological processes resulting from the underlying disease progression in neurodegenerative diseases.

PIMD: 30484274

[Appraisal of cerebral atrophy in multiple sclerosis by means of the corpus callosum index].

The course of multiple sclerosis is characterised by the development of cerebral atrophy. It is of interest to monitor it in order to evaluate the treatment response, and the preferred technique consists in performing brain volume analyses, which are currently restricted to the field of research.To analyse the corpus callosum index (CCI) as a possible alternative to the methods based on brain segmentation.Our sample was made up of 109 patients with recently diagnosed demyelinating diseases (90 relapsing-remitting multiple sclerosis, 7 primary progressive forms and 12 isolated demyelinating syndromes), and the CCI was calculated in their first magnetic resonance brain scan, together with 101 healthy controls. The sequences of the patients were submitted to a volumetric analysis using the software package MSmetrix.The mean value of the CCI was 0.377 in patients and 0.411 in the controls, and the difference was statistically significant ($p < 0.001$). The CCI also showed a statistically significant correlation with the brain volume ($p < 0.001$; $r = 0.444$) and with the lesional volume in the FLAIR sequence ($p < 0.001$; $r = -0.521$), while no association was observed with the volume of grey matter ($p = 0.058$).The CCI is related to the overall brain volume obtained by volumetric techniques and may reflect the presence of atrophy in the initial stages of demyelinating diseases, which makes it a fast and easy to calculate alternative.

PIMD: 30447856

MRI findings in pediatric neuromyelitis optica spectrum disorder with MOG antibody: Four cases and review of the literature.

Myelin oligodendrocyte glycoprotein antibodies (MOG Abs) are frequently detected in pediatric acquired demyelinating syndrome (ADS), and MOG-Ab-positive ADS differs from multiple sclerosis (MS) and aquaporin-4 (AQP4)-Ab-positive neuromyelitis optica spectrum disorder (NMOSD) in terms of age distribution, therapeutic response, and prognosis.Based on medical records, we retrospectively evaluated patients with MOG-Ab-positive NMOSD treated in the acute phase who were followed up in the chronic phase at our hospital from January 2011 to December 2017.The patients comprised two boys and two girls aged 3-12 (median, 8) years. Peak MOG-Ab titers were 1:2048 to 1:32768 (median, 1:10240), and the relapse rate ranged from 0 to 1.25 times/year (median, 0.59 times/year); no sequelae were observed in any cases. Lesions other than those of optic neuritis were distributed at the cortex in one patient, subcortical white matter in four, deep white matter in three, and brainstem in one, all of which were disseminated lesions. No lesions were found in the corpus callosum, periventricular white matter, diencephalon, and regions adjacent to the third and fourth ventricles. The lesions tended to be asymptomatic, and two patients aged >5 years had well-demarcated lesions.All the patients showed disseminated lesions in the subcortical region to deep white matter, which were different from those found in MS and AQP4-Ab-positive NMOSD and were consistent with the characteristics of brain lesions in MOG-Ab-positive ADS, including other disease types.

PIMD: 30445309

Protective and therapeutic role of Bilobalide in cuprizone-induced demyelination.

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system characterized by recurrent and progressive demyelination, neuroinflammation and oligodendrocyte loss. The cuprizone (CPZ) model is characterized by primary and reversible demyelination, accompanied by oligodendrocyte loss and neuroinflammation. In the current study, we explored the efficiency of Bilobalide in the demyelination and remyelination. The results demonstrate that Bilobalide improved behavioral abnormality and promoted remyelination in the corpus callosum by using Luxol Fast Blue, Black Gold II and myelin basic protein (MBP) staining. We for the first time found that CPZ caused the splenic atrophy and induced the formation of myelin oligodendrocyte glycoprotein (MOG) antibody, which was attenuated by Bilobalide. Thus, Bilobalide decreased the loss of O4+ oligodendrocytes possibly through MOG antibody-dependent cell cytotoxicity. Bilobalide also prevented the infiltration of CD4 T cells, CD68 macrophages and B220 B cells within the brain, and reduced the inflammatory microenvironment mediated with Iba1iNOS and Iba1NF-kB microglia after CPZ challenge, accompanied by the inhibition of IL-1β and IL-6 in the brain. These results identify a potent therapeutic efficiency for Bilobalide and highlight clear pleiotropic effects of the compound beyond specific autoantibody and inflammatory microenvironment in CPZ-mediated demyelination.

PIMD: 30365980

Clinical spectrum of inflammatory central nervous system demyelinating disorders associated with antibodies against myelin oligodendrocyte glycoprotein.

Immunoglobulin G (IgG) antibodies against myelin oligodendrocyte glycoprotein (MOG) are detected in the serum of some patients with demyelinating diseases. These patients are known to show repeated clinical episodes of inflammatory demyelinating attacks in the central nervous system. Although the associated pathogenicity and mechanism of inflammatory demyelination remains inconclusive, it is known that patients with MOG-IgG antibodies have a different clinical spectrum from those with other demyelinating diseases, such as multiple sclerosis. Based on our database of 85 MOG-IgG positive (+) cases, the most frequently associated clinical episodes were isolated optic neuritis (67.5%), encephalitis (26.5%), and myelitis (19.3%). Optic neuritis in MOG-IgG (+) disease usually involves the long segment of optic nerves and sometimes happens bilaterally, but visual acuity usually recovers with proper treatment in the acute phase. Brain and brainstem lesions usually present vague and focal appearances with irregular margins, typically in subcortical or brainstem regions, but occasionally in the cortex or corpus callosum. Due to these characteristics, MOG-IgG (+) cases with brain or brainstem lesions are sometimes diagnosed with acute disseminated encephalomyelitis, meningitis, or symptomatic epilepsy. The myelitis in MOG-IgG (+) typically shows longitudinally extensive lesions as seen in neuromyelitis optica spectrum disorders. Acute treatment to reduce attack-related disability is recommended in MOG-IgG (+) disease, and long-term immunosuppression may be considered in patients with a high frequency of relapses and/or high risk of neurological disability.

PIMD: 30303567

Changes in neurosteroidogenesis during demyelination and remyelination in cuprizone-treated mice.

Changes of neurosteroids may be involved in the pathophysiology of multiple sclerosis (MS). The present study investigated whether changes of neurosteroidogenesis also occurred in the grey and white matter regions of the brain in mice subjected to cuprizone-induced demyelination. Accordingly, we compared the expression of neurosteroidogenic proteins, including steroidogenic acute regulatory protein (StAR), voltage-dependent anion channel (VDAC) and 18 kDa translocator protein (TSPO), as well as neurosteroidogenic enzymes, including the side chain cleavage enzyme (P450scc), 3β-hydroxysteroid dehydrogenase/isomerase and 5α-reductase (5α-R), during the demyelination and remyelination periods. Using immunohistochemistry and a quantitative polymerase chain reaction, we demonstrated a decreased expression of StAR, P450scc and 5α-R with respect to an increase astrocytic and microglial reaction and elevated levels of tumor necrosis factor (TNF)α during the cuprizone demyelination period in the hippocampus, cortex and corpus callosum. These parameters, as well as the glial reaction, were normalised after 2 weeks of spontaneous remyelination in regions containing grey matter. Conversely, persistent elevated levels of TNFα and low levels of StAR and P450scc were observed during remyelination in corpus callosum white matter. We conclude that neurosteroidogenesis/myelination status and glial reactivity are inversely related in the hippocampus and neocortex. Establishing a cause and effect relationship for the measured variables remains a future challenge for understanding the pathophysiology of MS.

PIMD: 30297998

Age Influences Microglial Activation After Cuprizone-Induced Demyelination.

Multiple sclerosis (MS) is a chronic inflammatory CNS disease, which causes demyelinated lesions and damages white and gray matter regions. Aging is a significant factor in the progression of MS, and microglia, the immune cells of the CNS tissue, play an important role in all disease stages. During aging, microglia are functionally altered. These age-related changes probably already begin early and might influence the progression of CNS pathologies. The aim of the present study was to investigate whether microglia in the middle-aged CNS already react differently to demyelination. For this purpose, several microglia markers (ionized calcium binding adaptor molecule 1 (Iba-1), P2RY12, F4/80, CD68, major histocompatibility complex II (MHCII), macrophage receptor with collagenous structure (Marco), Translocator protein 18 kD (TSPO), CD206, and CD163) were analyzed in the acute cuprizone demyelination model in young (2-month-old) and middle-aged (10-month-old) mice. In addition, microglial proliferation was quantified using double-labeling with proliferating cell nuclear antigen (PCNA) and bromodeoxyuridine (BrdU), which was injected with the onset of remyelination. To compare age-related microglial changes during de- and remyelination in both gray and white matter, the hilus of the dorsal hippocampal dentate gyrus (DG) and the splenium of the corpus callosum (CC) were analyzed in parallel. Age-related changes in microglia of healthy controls were more pronounced in the analyzed gray matter region (higher levels of F4/80 and Marco as well as lower expression of CD68 in middle-aged mice). During de- and remyelination, a stronger increase of the microglial markers Iba-1, CD68 and TSPO was observed in the splenium of the younger groups. There was a significant reduction of P2RY12 during demyelination, however, this was age- and region-dependent. The induction of the anti-inflammatory markers CD206 and CD163 was stronger in the middle-aged group, but also differed between the two analyzed regions. De- and remyelination led to a significant increase in PCNA microglia only in young groups within the white matter region. The number of BrdU microglia was not changed during de- or remyelination. These results clearly show that microglia are already altered during middle-age and also react differently to CNS demyelination, however, this is highly region-dependent.

PIMD: 30294609

Balo's concentric sclerosis in a patient with spontaneous remission based on magnetic resonance imaging: A case report and review of literature.

Balo's concentric sclerosis (BCS) is a rare monophasic demyelinating disease known as multiple sclerosis subtype and seen as a round lesion with variable hyper and hypo-detoxification layers. Characteristic appearance can be seen as "bulb eye" or "onion bulb". The initial terminology for this neurological disorder was leukoencephalitis periaxialis concentrica; this is defined as a disease in which the white matter of the brain is destroyed in concentric layers in such a way as to leave the axial cylinders intact. This report presents a case of BCS with spontaneous healing of the patient and a mass lesion with concentric rings adjacent to the left lateral ventricle and the posterior portion of the corpus callosum with peripheral vasogenic edema. The neurological lesion of the patient was similar to the magnetic resonance imaging and clinical findings of the BCS.

PIMD: 30277321

Absence of infratentorial lesions in Fabry disease contributes to differential diagnosis with multiple sclerosis.

Multiple Sclerosis (MS) has been proposed as a possible differential diagnosis with Fabry Disease (FD). We evaluated the incidence of infratentorial lesions in FD patients, investigating whether their presence could help in differentiating these two conditions. We explored the diagnostic accuracy of this sign alone and in combination to the involvement of corpus callosum (CC).White Matter lesions were retrospectively evaluated on FLAIR images available from 136 MS and 144 FD patients. Infratentorial involvement was assessed considering the whole cerebellum, and the part of the brainstem included between the occipital foramen and the upper edge of the red nucleus. Furthermore, the presence of callosal lesions was also recorded, evaluating the portion of CC included between the two external walls of the lateral ventricles.Infratentorial involvement was detectable in 119/136 (87.5%) MS patients, while it was present in only 17/144 (11.8%) FD patients. When the diagnostic performance of a positive infratentorial involvement was evaluated in combination with the presence of CC lesions, a specificity of 97%, with a positive predictive value of 96% was reached.We concluded that the absence of infratentorial lesions, especially when combined to the evaluation of other typical imaging features, can help in the differential diagnosis between MS and FD.

PIMD: 30268035

Exploring mania-associated white matter injury by comparison with multiple sclerosis: a diffusion tensor imaging study.

Bipolar disorder (BD), especially in its active phases, has shown some neuroimaging and immunological similarities with multiple sclerosis (MS). The objective of this study was to compare white matter (WM) alterations in BD patients in manic phase (M-BD) and MS patients at early stage of disease and with low lesion burden. We compared diffusion tensor imaging (DTI)-derived fractional anisotropy (FA), mean diffusivity (MD) and radial diffusivity (RD) in a priori selected WM regions (i.e., corpus callosum and cingulum) betwixt 23 M-BD, 23 MS patients and 46 healthy controls. Both M-BD and MS showed WM changes in the corpus callosum, which, however, showed a greater impairment in MS patients. However, considering the different sub-regions of corpus callosum separately (i.e., genu, body, splenium), M-BD and MS presented an opposite pattern in spatial distribution of WM microstructure alterations, with a greater impairment in the anterior region in M-BD and in the posterior region in MS. Common features as well as divergent patterns in DTI changes are detected in M-BD and early MS, prompting a deeper investigation of analogies and differences in WM and immunological alterations of these disorders.

PIMD: 30243236

The Bayesian risk estimate at onset (BREMSO) correlates with cognitive and physical disability in patients with early multiple sclerosis.

Prevention of long-term disability is the goal of therapeutic intervention in Relapsing Remitting MS (RRMS). The Bayesian Risk Estimate for MS at Onset (BREMSO) gives an individual risk score predicting disease evolution into Secondary Progressive MS (SPMS). We investigated whether BREMSO correlates with physical disability, cognitive dysfunction, and regional brain atrophy early in MS.One hundred RRMS patients with at least two years of follow-up were enrolled. BREMSO score as well as Symbol Digit Modalities Test (SDMT) and Multiple Sclerosis Severity Score (MSSS), Timed 25-Foot Walk Test (T25-FW) and 9-Hole Peg Test (9-HPT), were assessed. Intracranial volume (ICV), subcortical gray matter structures and corpus callosum (CC) were automatically segmented on MRI images and their volumes measured.BREMSO score correlated negatively with SDMT at visit1 (β=-0.33, p=0.019), visit2 (β=-0.34, p=0.017) and visit3 (β=-0.34, p=0.014), and positively with MSSS at visit1 (r=0.38, p=0.006), visit2 (r=0.47, p<0.0001) and visit3 (r=0.42, p=0.002), but not with T25-FW and 9-HPT. BREMSO negatively correlated with CC volume at baseline (p<0.03). No correlations were found with ICV and subcortical gray matter.BREMSO score at onset correlated with physical disability (MSSS), cognitive function (SDMT) and CC volume measurements in patients with early MS.

PIMD: 30238390

Visualization of the Breakdown of the Axonal Transport Machinery: a Comparative Ultrastructural and Immunohistochemical Approach.

Axonal damage is a major factor contributing to disease progression in multiple sclerosis (MS) patients. On the histological level, acute axonal injury is most frequently analyzed by anti-amyloid precursor protein immunohistochemistry. To what extent this method truly detects axonal injury, and whether other proteins and organelles are as well subjected to axonal transport deficits in demyelinated tissues is not known. The aim of this study was to correlate ultrastructural morphology with the immunohistochemical appearance of acute axonal injury in a model of toxin-induced oligodendrocyte degeneration. C57BL/6J mice were intoxicated with 0.25% cuprizone to induce demyelination. The corpus callosum was investigated by serial block-face scanning electron microscopy (i.e., 3D EM), immunohistochemistry, and immunofluorescence microscopy. Brain tissues of progressive MS patients were included to test the relevance of our findings in mice for MS. Volumes of axonal swellings, determined by 3D EM, were comparable to volumes of axonal spheroids, determined by anti-APP immunofluorescence stains. Axonal swellings were present at myelinated and non-myelinated axonal internodes. Densities of amyloid precursor protein (APP) spheroids were highest during active demyelination. Besides APP, vesicular glutamate transporter 1 and mitochondrial proteins accumulated at sites of axonal spheroids. Such accumulations were found as well in lesions of progressive MS patients. In this correlative ultrastructural-immunohistochemical study, we provide strong evidence that breakdown of the axonal transport machinery results in focal accumulations of mitochondria and different synaptic proteins. We provide new marker proteins to visualize acute axonal injury, which helps to further understand the complex nature of axonal damage in progressive MS.

PIMD: 30232810

Teriflunomide's Effect on Glia in Experimental Demyelinating Disease: A Neuroimaging and Histologic Study.

Teriflunomide reduces disability progression and brain atrophy in multiple sclerosis patients. The exact mechanism of action by which teriflunomide exerts these effects is currently unknown. We assessed the effect of teriflunomide on brain glial cells in the Theiler's murine encephalomyelitis virus (TMEV) by using a histological approach in combination with neuroimaging.Forty-eight SJL female mice received an intracerebral injection of TMEV at 6-8 weeks of age and were then treated with teriflunomide (n = 24) or placebo (n = 24) for 9 months. They were examined with MRI and behavioral testing at 2, 6, and 9 months postinduction (mPI). Of those, 18 teriflunomide-treated and 17 controls mice were analyzed histologically at 9 mPI to sample from different brain regions for myelination status, microglial density, and oligodendroglial lineage. The histological and MRI outcomes were correlated.Corpus callosum microglial density was numerically lower in the teriflunomide-treated mice compared to the control group (141.1 ± 21.7 SEM vs. 214.74 ± 34.79 SEM, Iba1 cells/mm , P = .087). Basal ganglia (BG) microglial density in the teriflunomide group exhibited a negative correlation with fractional anisotropy (P = .021) and a positive correlation with mean diffusivity (P = .034), indicating less inflammation and axonal damage. Oligodendroglial lineage cell and myelin density were not significantly different between treatment groups. However, a significant positive correlation between BG oligodendrocytes and BG volume (P = .027), and with N-acetyl aspartate concentration (P = .008), was found in the teriflunomide group, indicating less axonal loss.Teriflunomide altered microglia density and oligodendrocytes differentiation, which was associated with less evident microstructural damage on MRI.

PIMD: 30232349

N-Phenylquinazolin-2-amine Yhhu4952 as a novel promotor for oligodendrocyte differentiation and myelination.

Oligodendrocytes are a type of glial cells that ensheath multiple neuronal axons and form myelin. Under pathological conditions, such as multiple sclerosis (MS), inflammatory damage to myelin and oligodendrocytes leads to demyelination. Although the demyelinated regions can partially resolve functional deficits through remyelination, however, as the disease progresses, remyelination typically becomes incomplete and ultimately fails. One possible explanation for this failure is the activation of the Notch pathway in MS lesions, which impedes oligodendrocyte precursor cells (OPCs) at maturation. This leads to a potential target for remyelination. Here, we have identified a compound Yhhu4952 that promoted the maturation of cultured OPCs in a dose-dependent and time-dependent manner. Neonatal rats showed a significant increase in the expression of myelin basic protein (MBP) and the prevalence of mature oligodendrocytes in the corpus callosum after Yhhu4952 treatment. The compound was also effective in promoting remyelination in cuprizone-induced demyelination model and improving severity scores in experimental autoimmune encephalomyelitis (EAE) model. Mechanism studies revealed that Yhhu4952 promotes OPC differentiation through the inhibition of the Jagged1-Notch1 pathway. These findings suggest Yhhu4952 is potentially useful for proceeding oligodendrocyte differentiation and remyelination.

PIMD: 30230638

{'sub': '1', '#text': 'Multicenter Measurements of T Relaxation and Diffusion Tensor Imaging: Intra and Intersite Reproducibility.'}

Quantitative T and diffusion tensor imaging (DTI) may provide information about pathological changes underlying disability and progression in diseases like multiple sclerosis (MS). Imaging the corpus callosum (CC), a primary site of damage in MS with a critical role in interhemispheric connectivity, may be useful for assessing overall brain health, prognosis, and therapy efficacy. We assessed the feasibility of multisite clinical trials using advanced MRI by examining the intra and intersite reproducibility of T and DTI measurements in the CC and segmented white matter (WM).Five healthy volunteers were scanned twice within 24 hours at six 3T sites. Coefficients of variation (COVs) and intraclass correlation coefficients (ICCs) for CC and WM T , fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (D), and radial diffusivity (D) assessed intrasite and intersite reliability.CC and WM T showed excellent intrasite reproducibility with low COVs (mean = .90% and .89%, respectively) and good ICCs (CC = .78, WM = .90). T also demonstrated intersite reliability (low COVs: CC = 2.4%, WM = 1.8%; moderate ICCs: CC = .43, WM = .69). DTI had low intrasite COVs (CC: FA = 1.3%, MD = 1.5%, D = 1.4%, D = 2.2%; WM: FA = .9%, MD = .9%, D = .7%, D = 1.2%) and high intrasite ICCs (CC: FA = .95, MD = .97, D = .94, D = .97; CC: FA = .9, MD = .66, D = .88, D = .63), indicating excellent intrasite reproducibility. DTI also showed excellent intersite reliability with low COVs (CC: FA = 2.1%, MD = 4.1%, D = 3.4%, D = 5.3%, WM: FA = 1.3%, MD = 1.9%, D = 1.8%, D = 2.1%,) and good ICCs (CC: FA = .90, MD = .84, D = .72, D = .90; WM: FA = .83, MD = .34, D = .62, D = .41).T and DTI measures are reproducible using equivalent MRI scanners and sequence protocols. Using a similar MR system, it is feasible to carry out multicenter studies using T and DTI to evaluate changes within the CC and WM.

PIMD: 30208252

The TAM receptor TYRO3 is a critical regulator of myelin thickness in the central nervous system.

Multiple sclerosis (MS) is an autoimmune, demyelinating disease of the central nervous system (CNS). Major deficits arise in MS patients due to an inability to repair damaged myelin sheaths following CNS insult, resulting in prolonged axonal exposure and neurodegeneration. The TAM receptors (Tyro3, Axl, and Mertk) have been implicated in MS susceptibility, demyelination and remyelination. Previously, we have shown that Tyro3 regulates developmental myelination and myelin thickness within the optic nerve and rostral region of the corpus callosum (CC) of adult mice. In this study we have verified and extended our previous findings via a comprehensive analysis of axonal ensheathment and myelin thickness in the CC of unchallenged mice, following demyelination and during myelin repair. We show that the loss of the Tyro3 receptor correlates with significantly thinner myelin sheaths in both unchallenged mice and during remyelination, particularly in larger caliber axons. The hypomyelinated phenotype observed in the absence of Tyro3 occurs independently of any influence upon oligodendrocyte precursor cell (OPC) maturation, or density of oligodendrocytes (OLs) or microglia. Rather, the primary effect of Tyro3 is upon the radial expansion of myelin. The loss of Tyro3 leads to a reduction in the number of myelin lamellae on axons, and is therefore most likely a key component of the regulatory mechanism by which oligodendrocytes match myelin production to axonal diameter.

PIMD: 30196252

X linked Charcot-Marie-Tooth disease and multiple sclerosis: emerging evidence for an association.

X linked Charcot-Marie-Tooth disease (CMTX) is a hereditary neuropathy caused by mutations in coding for connexin-32, a gap junction protein expressed in Schwann cells, but also found in oligodendrocytes. Four patients with CMTX developing central nervous system (CNS) demyelination compatible with multiple sclerosis (MS) have been individually published. We presently sought to systematically investigate the relationship between CMTX and MS.Over 20 years, 70 consecutive patients (36 men) with mutations were identified at our Neurogenetics Unit, Athens, Greece, and assessed for clinical features suggestive of MS. Additionally, 18 patients with CMTX without CNS symptoms and 18 matched controls underwent brain MRI to investigate incidental findings. Serum from patients with CMTX and MS was tested for CNS immunoreactivity.We identified three patients with CMTX who developed clinical features suggestive of inflammatory CNS demyelination fulfilling MS diagnostic criteria. The resulting 20-year MS incidence (4.3%) differed significantly from the highest background 20-year MS incidence ever reported from Greece (p=0.00039). The search for incidental brain MRI findings identified two CMTX cases (11%) with lesions suggestive of focal demyelination compared with 0 control. Moreover, 10 cases in the CMTX cohort had hyperintensity in the splenium of the corpus callosum compared with 0 control (p=0.0002). No specific CNS-reactive humoral factors were identified in patients with CMTX and MS.We have demonstrated a higher than expected frequency of MS in patients with CMTX and identified incidental focal demyelinating lesions on brain MRI in patients with CMTX without CNS symptoms. This provides circumstantial evidence for mutations acting as a possible MS risk factor.

PIMD: 30143908

Microglia polarization by methylprednizolone acetate accelerates cuprizone induced demyelination.

Glucocorticoids (GC) are known as inflammatory drugs, which are used in neuroinflammatory diseases. Unlike the classic picture, recent studies have revealed that some GC drugs exacerbate inflammatory responses in their acute and prolonged administration. Multiple sclerosis (MS) is a demyelinating inflammatory disorder, in which reactive M1 microglia phenotype play a central role. Since methylprednisolone (MP), as a synthetic GC, are commonly used by MS patients, in this study, we evaluated the effect of long-term administration of MP on microglia polarization in cuprizone (CPZ)-induced MS model. The immunostaining results showed that chronic exposure to MP in the CPZ treated mice increased the number of Iba-1 positive microglia, which significantly expressed IP10 as M1 marker than arginase as M2 marker. MP treatment induced significant amplification in the transcript levels of iNOS and TNF-α (M1-related markers) in the corpus callosum of the MS mice, whereas no change detected in the expression of IL-10 (M2-related marker) between the groups. In addition, evaluation of myelin by luxol fast blue staining and transmission electron microscopy revealed that prolonged MP administration increased demyelination in comparison to the CPZ group. In conclusion, our results show that chronic MP therapy in the CPZ-induced demyelination model of MS polarized microglia to M1 pro-inflammatory phenotype.

PIMD: 30114292

Orthologous proteins of experimental de- and remyelination are differentially regulated in the CSF proteome of multiple sclerosis subtypes.

Here, we applied a multi-omics approach (i) to examine molecular pathways related to de- and remyelination in multiple sclerosis (MS) lesions; and (ii) to translate these findings to the CSF proteome in order to identify molecules that are differentially expressed among MS subtypes.To relate differentially expressed genes in MS lesions to de- and remyelination, we compared transcriptome of MS lesions to transcriptome of cuprizone (CPZ)-induced de- and remyelination. Protein products of the overlapping orthologous genes were measured within the CSF by quantitative proteomics, parallel reaction monitoring (PRM). Differentially regulated proteins were correlated with molecular markers of inflammation by using MesoScale multiplex immunoassay. Expression kinetics of differentially regulated orthologous genes and proteins were examined in the CPZ model.In the demyelinated and remyelinated corpus callosum, we detected 1239 differentially expressed genes; 91 orthologues were also differentially expressed in MS lesions. Pathway analysis of these orthologues suggested that the TYROBP (DAP12)-TREM2 pathway, TNF-receptor 1, CYBA and the proteasome subunit PSMB9 were related to de- and remyelination. We designed 129 peptides representing 51 orthologous proteins, measured them by PRM in 97 individual CSF, and compared their levels between relapsing (n = 40) and progressive MS (n = 57). Four proteins were differentially regulated among relapsing and progressive MS: tyrosine protein kinase receptor UFO (UFO), TIMP-1, apolipoprotein C-II (APOC2), and beta-2-microglobulin (B2M). The orthologous genes/proteins in the mouse brain peaked during acute remyelination. UFO, TIMP-1 and B2M levels correlated inversely with inflammation in the CSF (IL-6, MCP-1/CCL2, TARC/CCL17). APOC2 showed positive correlation with IL-2, IL-16 and eotaxin-3/CCL26.Pathology-based multi-omics identified four CSF markers that were differentially expressed in MS subtypes. Upregulated TIMP-1, UFO and B2M orthologues in relapsing MS were associated with reduced inflammation and reflected reparatory processes, in contrast to the upregulated orthologue APOC2 in progressive MS that reflected changes in lipid metabolism associated with increased inflammation.

PIMD: 30103962

Diffusion tensor imaging findings in the multiple sclerosis patients and their relationships to various aspects of disability.

The aim of the study was to assess microstructural changes within strategic brain regions in multiple sclerosis (MS) patients, using diffusion tensor imaging (DTI), with regard to various aspects of disability.The study comprised 50 patients with relapsing-remitting MS (37 women, 13 men, mean age 36.4 yrs) and 27 age- and sex-matched controls. Using DTI, fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were obtained within corpus callosum (CC), both thalami (TH) and middle cerebellar peduncles (MCP). Disability was assessed using Expanded Disability Status Scale (EDSS), MS Functional Composite (MSFC), Symbol Digit Modalities Test (SDMT) and Fatigue Severity Scale (FSS). DTI indices were compared between the patients and controls and in the MS group - referred to disability measures.Significant decrease in FA and increase in ADC within CC and both TH were found in MS patients compared to the controls. DTI indices within CC and TH correlated significantly with SDMT score, and within TH and MCP - with MSFC manual dexterity measure.Changes in DTI measures in normal appearing white and grey matter in the MS patients indicate subtle alterations of the tissue integrity. An occult damage to the strategic brain regions may contribute to various aspects of disability due to MS.

PIMD: 30091739

Moringa oleifera Ameliorates Histomorphological Changes Associated with Cuprizone Neurotoxicity in the Hippocampal Cornu ammonis (CA) 3 Region.

Cuprizone-induced neurotoxicity has severally been used to study demyelinating diseases like multiple sclerosis(MS), adversely affecting both the white and grey matters of the brain. Lesions have been observed in different regions ofthe brain including, corpus callosum, neocortex and the hippocampal formation. The current study explored the role ofMoringa oleifera leaf extract in restoring the resultant histomorphological changes in cuprizone-induced hippocampaldamage in Wistar rats. Twenty adult female Wistar rats with average weight of 163.74 ± 3.59 g were grouped into A: Control,administered with 1 ml of normal saline, B: received 0.4% cuprizone diet, C: received 1.875 mg/ml/day of Moringa extract,and D: received a combination of cuprizone and Moringa in similar doses. Administration was oral for 5 weeks. The weightsof animals were assessed during treatment, and at the termination of experiment, the rats were euthanized and the brainswere fixed in 4% paraformaldehyde. The tissue was processed for histological and histochemical examinations using theHaematoxylin and Eosin stain and cresyl fast violet stain to assess the general microarchitecture and neuronal cellsrespectively of hippocampal cornu ammonis (CA) 3 region. The body weight of cuprizone-treated rats was reduced and thiswas ameliorated significantly in animals that were co-administered with Moringa. Similarly, there were histologicalalterations in the CA3 region of the hippocampus with the presence of pyknotic pyramidal cells organized in clusters andCA3 cells with degenerative changes, but administration of Moringa led to a better organised and fairly intact histologicalappearance. Pharmaceutical development of Moringa oleifera into appropriate therapeutic formulations could offer somerelief to patients of demyelinating conditions that have clinical features of neurological deficits.

PIMD: 30073779

MRI in predicting conversion to multiple sclerosis within 1 year.

Most patients diagnosed with multiple sclerosis (MS) present with a clinically isolated syndrome (CIS). We aimed to verify previously reported imaging and clinical findings, and to identify new MRI findings that might serve as prognostic factors for a second clinical episode or a change in the MRI scan during the first year following a CIS.We identified from our medical records, 46 individuals who presented with an episode of CIS, which was followed clinically and with imaging studies. A neuroradiologist blinded to the clinical data reviewed the images and recorded the number of lesions, lesion location, and the largest longitudinal diameter of the lesion.One year after the first MRI, 25 (54%) patients had progressed to MS. The clinical presentation of those who were and were not diagnosed with MS was predominantly motor or sensory deficit. Patients with lesions that were temporal, occipital, or perpendicular to the corpus callosum at the first episode were more likely to have recurrence. Individuals with a combination of more than 13 lesions, with maximal lesion length greater than 0.75 cm, and a lesion perpendicular to the corpus callosum, had a 19 times higher chance of conversion MS during the following year.Assessment of the number of lesions, lesion location, and maximal lesion size can predict the risk to develop another clinical episode or a new lesion/new enhancement in MRI during the year after CIS. For patients with a higher risk of recurrence, we recommend closer follow-up.

PIMD: 30051273

Multimodal assessment of normal-appearing corpus callosum is a useful marker of disability in relapsing-remitting multiple sclerosis: an MRI cluster analysis study.

Corpus callosum (CC) is frequently involved in relapsing-remitting multiple sclerosis (RRMS). Magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) allow to study CC macrostructural and microstructural tissue integrity. Here, we applied a data-driven approach to MRI and DTI data of normal-appearing CC in RRMS subjects, and subsequently evaluated if differences in tissue integrity corresponded to different levels of physical disability and cognitive impairment.74 RRMS patients and 20 healthy controls (HC) underwent 3 T MRI and DTI. Thickness and fractional anisotropy (FA) along midsagittal CC were extracted, and values from RRMS patients were fed to a hierarchical clustering algorithm. We then used ANOVA to test for differences in clinical and cognitive variables across the imaging-based clusters and HC.We found three distinct MRI-based subgroups of RRMS patients with increasing severity of CC damage. The first subgroup showed callosal integrity similar to HC (Cluster 1); Cluster 2 had milder callosal damage; a third subgroup showed the most severe callosal damage (Cluster 3). Cluster 3 included patients with longer disease duration and worst scores in Expanded Disability Status Scale. Cognitive domains of verbal memory, executive functions and processing speed were impaired in Cluster 3 and Cluster 2 compared to Cluster 1 and HC.Within the same homogeneous cohort of patients, we could identify three neuroimaging RRMS clusters characterized by different involvement of normal-appearing CC. Interestingly, these corresponded to three distinct levels of clinical and cognitive disability.

PIMD: 30018535

mCSF-Induced Microglial Activation Prevents Myelin Loss and Promotes Its Repair in a Mouse Model of Multiple Sclerosis.

A pathological hallmark of multiple sclerosis (MS) is myelin loss in brain white matter accompanied by compromised remyelination. Demyelinated lesions are deeply associated with oligodendrocyte apoptosis and a robust inflammatory response. Although various studies point towards a noxious role of inflammation in MS, others emphasize a positive role for the innate immune cells in disease progression. A cytokine well-known to stimulate cell survival, proliferation and differentiation of myeloid cells, macrophage colony-stimulating factor (mCSF), was administered to mice during a 5 week-long cuprizone diet. Treated mice exhibited reduced myelin loss during the demyelination phase, together with an increased number of microglia and oligodendrocyte precursor cells in lesion sites. Tamoxifen-induced conditional deletion of the mCSF receptor in microglia from cuprizone-fed mice caused aberrant myelin debris accumulation in the corpus callosum and reduced microglial phagocytic response. mCSF therefore plays a key role in stimulating myelin clearance by the brain innate immune cells, which is a prerequisite for proper remyelination and myelin repair processes.

PIMD: 30010211

Effect of Notch1 gene on remyelination in multiple sclerosis in mouse models of acute demyelination.

This study aims to explore the effects of Notch1 gene on remyelination in multiple sclerosis (MS). A mouse model of acute demyelination was successfully established and the model mice were grouped as cuprizone (CPZ) group, CPZ + small interfering RNA (siRNA)-Notch1 (siNotch1) group, and CPZ + siRNA negative control (NC) group. Meanwhile, another 3 groups (control, control + siNotch1, and control + siRNA NC) were established in normal mice. The changes of weight and maintenance time in rotating drum of mice were observed. Western blot analysis for the protein expressions related to Notch signaling pathway and oligodendrocyte (OL) differentiation in the corpus callosum of the mice. After model establishment, the weight of CPZ-induced demyelinated mice was decreased. During the repair period, the balance ability and movement of the mice was recovered, especially for those injected with siNotch1 plasmid. After model establishment, the number of myelinated axons was decreased. In comparison with the CPZ and CPZ siRNA NC groups, the CPZ + siNotch1 group had a decrease in the number of premature OLs, but increase in mature OLs, and a decrease in oligodendrocyte precursor cells and astrocytes. The expressions of proteins related to Notch signaling pathway, such as HES, Jagged-1 were decreased in the CPZ + siNotch1 group in contrast to the CPZ and CPZ + siRNA groups, but the OL-related transcription factor Sox10 was increased in the CPZ + siNotch1 group than in the CPZ + siRNA NC and CPZ groups, and Id2 was decreased. Our study provided evidence that the inhibition of Notch1 gene could accelerate remyelination in MS.

PIMD: 29950159

Distinct regional brain atrophy pattern in multiple sclerosis and neuropsychiatric systemic lupus erythematosus patients.

Differentiation of systemic lupus erythematosus (SLE) from multiple sclerosis (MS) can be challenging, especially when neuropsychiatric (NP) symptoms are accompanied by white matter lesions in the brain. Given the lack of discriminative power of currently applied tools for their differentiation, there is an unmet need for other measures that can aid in distinguishing between the two autoimmune disorders. In this study we aimed at exploring whether brain atrophy measures could serve as markers differentiating MS and SLE. Thirty-seven relapsing-remitting MS and 38 SLE patients with nervous system manifestations, matched according to age and disease duration, underwent 1.5 Tesla magnetic resonance imaging (MRI), including volumetric sequences, and clinical assessment. Voxelwise analysis was performed using ANTS-SyN elastic registration protocol, FSL Randomise and Gamma methods. Cortical and subcortical segmentation was performed with Freesurfer 5.3 pipeline using T1-weighted MPRAGE sequence data. Using MRI volumetric markers of general and subcortical gray matter atrophy and clinical variables, we built a stepwise multivariable logistic diagnostic model to identify MRI parameters that best differentiate MS and SLE patients. We found that the best volumetric predictors to distinguish them were: fourth ventricle volume (sensitivity 0.86, specificity 0.57, area under the curve, AUC 0.77), posterior corpus callosum (sensitivity 0.81, specificity 0.57, AUC 0.68), and third ventricle to thalamus ratio (sensitivity 0.42, specificity 0.84, AUC 0.65). The same classifiers were identified in a subgroup analysis that included patients with a short disease duration. In MS brain atrophy and lesion load correlated with clinical disability, while in SLE age was the main determinant of brain volume. This study proposes new imaging parameters for differential diagnosis of MS and SLE with central nervous system involvement. We show there is a different pattern of atrophy in MS and SLE, and the key structural volumes that are differentially affected include fourth ventricle and posterior section of corpus callosum, followed by third ventricle to thalamus ratio. Different correlation patterns between volumetric and clinical data may suggest that while in MS atrophy is driven mainly by disease activity, in SLE it is mostly associated with age. However, these results need further replication in a larger cohort.

PIMD: 29877125

Brain Lesion Load and Anatomic Distribution in Patients With Juvenile Clinically Isolated Syndrome Predicts Rapidly Advanced to Multiple Sclerosis.

The aim was to assess brain lesion load and anatomical distribution in patients with juvenile clinically isolated syndrome and define magnetic resonance imaging (MRI) variables associated with rapidly advancing to multiple sclerosis. Patients were followed for one year after disease onset. Patients who experienced a second relapse were defined as those who rapidly advanced to multiple sclerosis. In all, 46 juvenile patients with a clinical presentation suggestive of multiple sclerosis were evaluated; 21 with gadolinium-enhancing lesions on initial brain MRI were excluded as they had already fulfilled the diagnosis criteria for multiple sclerosis. A total of 25 patients, 10 males and 15 females (mean ± SE age at onset 15.6 ± 0.6 years), met the definition of clinically isolated syndrome. The presence of a corpus callosum lesion at onset significantly differentiated between sustained clinically isolated syndrome and patients who rapidly advanced to multiple sclerosis.

PIMD: 29873041

G-Protein-Coupled Receptor Gpr17 Expression in Two Multiple Sclerosis Remyelination Models.

In multiple sclerosis patients, demyelination is prominent in both the white and gray matter. Chronic clinical deficits are known to result from acute or chronic injury to the myelin sheath and inadequate remyelination. The underlying molecular mechanisms of remyelination and its failure remain currently unclear. Recent studies have recognized G protein-coupled receptor 17 (GPR17) as an important regulator of oligodendrocyte development and remyelination. So far, the relevance of GPR17 for myelin repair was mainly tested in remyelinating white matter lesions. The relevance of GPR17 for gray matter remyelination as well as remyelination of chronic white matter lesions was not addressed so far. Here, we provide a detailed characterization of GPR17 expression during experimental de- and remyelination. Experimental lesions with robust and limited endogenous remyelination capacity were established by either acute or chronic cuprizone-induced demyelination. Furthermore, remyelinating lesions were induced by the focal injection of lysophosphatidylcholine (LPC) into the corpus callosum. GPR17 expression was analyzed by complementary techniques including immunohistochemistry, in situ hybridization, and real-time PCR. In control animals, GPR17 cells were evenly distributed in the corpus callosum and cortex and displayed a highly ramified morphology. Virtually all GPR17 cells also expressed the oligodendrocyte-specific transcription factor OLIG2. After acute cuprizone-induced demyelination, robust endogenous remyelination was evident in the white matter corpus callosum but not in the gray matter cortex. Endogenous callosal remyelination was paralleled by a robust induction of GPR17 expression which was absent in the gray matter cortex. Higher numbers of GPR17 cells were as well observed after LPC-induced focal white matter demyelination. In contrast, densities of GPR17 cells were comparable to control animals after chronic cuprizone-induced demyelination indicating quiescence of this cell population. Our findings demonstrate that GPR17 expression induction correlates with acute demyelination and sufficient endogenous remyelination. This strengthens the view that manipulation of this receptor might be a therapeutic opportunity to support endogenous remyelination.

PIMD: 29859880

A stable and easily reproducible model of focal white matter demyelination.

Demyelination is the end product of numerous pathological processes, and also is one of the main causes of neurological disability in Multiple sclerosis (MS). Research into the pathogenesis of MS is hampered by the conventional rodent models' inability to produce stable demyelination.Focal demyelinating lesions were stereotactically targeted to the corpus callosum with a two-point injection of lysophosphatidylcholine (LPC-2) in mice. Three groups were analyzed (n = 8, each) and water maze, sensorimotor test, and compound action potential were included in functional tests. Electron microscopy was used for morphological analyses while western blot and immunohistochemistry were included for molecular detection.Ten days after the LPC-2 injection, the expression of myelin basic protein (MBP) was reduced, while non-phosphorylated neurofilament (SMI-32) was increased. The amplitude of the N1 segment decreased and less well-defined myelin sheaths was found. Behavioral tests showed increased latency to escape and reduced time spent in target quadrant. Four weeks later, MBP expression still reduced, SMI-32 expression was increased, both spatial learning (D24-D27) and spatial memory (D28) were still significantly impaired in LPC-2 injection mice.Compared with the classic single-point LPC-injection model, our studies showed that the two-point LPC-injection not only could induce demyelination in a short-term manner, but also could cause demyelination in a long-term manner with little remyelination in the mouse corpus callosum.We established a simple, reliable, and inexpensive model of demyelination in the corpus callosum in mice, with functional and morphological reproducibility, and good validity.

PIMD: 29801894

Migraine as possible red flag of PFO presence in suspected demyelinating disease.

To investigate a possible association between isolated white matter lesions suggestive of demyelinating disease in magnetic resonance imaging (MRI) and patent foramen ovale (PFO) evidence in migraine patients, with or without aura.31 migraine patients, 28 females and 3 males, with MRI evidence of white matter lesions suggestive of demyelinating disease according to the Barkhof Criteria. All patients underwent further diagnostics including lumbar puncture, autoimmunity panel and cardiological evaluation to detect the presence of PFO. The mean duration of follow-up was 3.46 years and MIPAV software was used to analyze MRI imaging.14 of the 31 patients (45%) had PFO. A significant association was found between PFO and migraine with visual aura ($p < 0.001$). No difference in lesion number, volume or area between patients with and without PFO was found, but the distribution was mainly occipital ($p < 0.001$) in patients with PFO. The follow-up showed a stationary lesion load in all PFO patients; no infratentorial or spinal cord lesion and no enhancement or corpus callosum lesion was ever detected. At the end of follow-up four patients developed multiple sclerosis: younger age at first MRI and oligoclonal bands were associated risk factors.Migraine is often one of the main symptoms leading to MRI, and in many cases white matter lesions of unspecific significance are discovered, thus placing demyelinating diseases in the differential diagnosis. Our study underlines the potential pathogenetic role of PFO in generating white matter lesions in migraine patients (45%), particularly those with visual aura and occipital lesions. For this reason, we affirm that PFO represents a cardinal point in the differential diagnosis of suspected demyelinating disease.

PIMD: 29775564

The antibody rHIgM22 facilitates hippocampal remyelination and ameliorates memory deficits in the cuprizone mouse model of demyelination.

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating disease of the CNS. In addition to motor, sensory and visual deficits, MS is also characterized by hippocampal demyelination and memory impairment. We recently demonstrated that a recombinant human-derived monoclonal IgM antibody, which is designated rHIgM22 and currently in clinical development for people with MS, accelerates remyelination of the corpus callosum in the brains of cuprizone-treated mice. Here, we investigated the effects of rHIgM22 in the hippocampus and on hippocampal-dependent learning and memory in the same mouse model of cuprizone-induced demyelination and spontaneous remyelination. The degree of hippocampal myelination of cuprizone-fed mice treated with a single dose of rHIgM22 (10 mg/kg of body weight) was examined immediately after the end of the cuprizone diet as well as at different time points during the recovery period with regular food, and compared with that of cuprizone-fed animals treated with either vehicle or human IgM isotype control antibody. Mice fed only regular food were used as controls. Four or five mice per treatment group were examined for each time point. We demonstrate that treatment with rHIgM22 accelerated remyelination of the demyelinated hippocampus. Using two additional cohorts of mice and eight animals per treatment group for each cohort, we also demonstrate that the enhancing effects of rHIgM22 on hippocampal remyelination were accompanied by improved performance in the Morris water maze and amelioration of the memory deficits induced by cuprizone. These results further confirm the remyelination-promoting capabilities of rHIgM22 and support additional investigation of its therapeutic potential in MS.

PIMD: 29754967

White matter microstructural alterations in clinically isolated syndrome and multiple sclerosis.

This study aims to determine whether and how diffusion alteration occurs in the earliest stage of multiple sclerosis (MS) and the differences in diffusion metrics between CIS and MS by using the tract-based spatial statistics (TBSS) method based on diffusion tensor imaging (DTI). Thirty-six CIS patients (mean age ± SD: 34.0 years ± 12.6), 36 relapsing-remitting multiple sclerosis (RRMS) patients (mean age ± SD: 35.0 years ± 9.4) and 36 age- and gender-matched normal controls (NCs) were included in this study. Voxel-wise analyses were performed with TBSS using multiple diffusion metrics, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (λ) and radial diffusivity (λ). In the CIS patients, TBSS analyses revealed diffusion alterations in a few white matter (WM) regions including the anterior thalamic radiation, corticospinal tract, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, body and splenium of the corpus callosum, internal capsule, external capsule, and cerebral peduncle. MS patients showed more widespread diffusion changes (decreased FA, increased λ, λ and MD) than CIS. Exploratory analyses also revealed the possible associations between WM diffusion metrics and clinical variables (Expanded Disability Status Scale and disease duration) in the patients. This study provided imaging evidence for DTI abnormalities in CIS and MS and suggested that DTI can improve our knowledge of the path physiology of CIS and MS and clinical progression.

PIMD: 29754046

Brain stiffens post mortem.

Alterations in brain rheology are increasingly recognized as a diagnostic marker for various neurological conditions. Magnetic resonance elastography now allows us to assess brain rheology repeatably, reproducibly, and non-invasively in vivo. Recent elastography studies suggest that brain stiffness decreases one percent per year during normal aging, and is significantly reduced in Alzheimer's disease and multiple sclerosis. While existing studies successfully compare brain stiffnesses across different populations, they fail to provide insight into changes within the same brain. Here we characterize rheological alterations in one and the same brain under extreme metabolic changes: alive and dead. Strikingly, the storage and loss moduli of the cerebrum increased by 26% and 60% within only three minutes post mortem and continued to increase by 40% and 103% within 45 minutes. Immediate post mortem stiffening displayed pronounced regional variations; it was largest in the corpus callosum and smallest in the brainstem. We postulate that post mortem stiffening is a manifestation of alterations in polarization, oxidation, perfusion, and metabolism immediately after death. Our results suggest that the stiffness of our brain-unlike any other organ-is a dynamic property that is highly sensitive to the metabolic environment. Our findings emphasize the importance of characterizing brain tissue in vivo and question the relevance of ex vivo brain tissue testing as a whole. Knowing the true stiffness of the living brain has important consequences in diagnosing neurological conditions, planning neurosurgical procedures, and modeling the brain's response to high impact loading.

PIMD: 29680798

Corpus callosum demyelination associated with acquired stuttering.

Compared with developmental stuttering, adult onset acquired stuttering is rare. However, several case reports describe acquired stuttering and an association with callosal pathology. Interestingly, these cases share a neuroanatomical localisation also demonstrated in developmental stuttering. We present a case of adult onset acquired stuttering associated with inflammatory demyelination within the corpus callosum. This patient's disfluency improved after the initiation of immunomodulatory therapy.

PIMD: 29675082

Susac's Syndrome (Retinocochleocerebral Vasculopathy): Follow-up of a Pediatric Patient.

Susac's syndrome (SS) is a triad of encephalopathy, branch retinal artery occlusion (BRAO), and sensorineural hearing loss as a result of microvascular occlusions of the brain, retina, and inner ear. It is also a disorder of autoimmune endotheliopathy. SS usually affects young women between the age of 20 and 40 years. SS can be misdiagnosed as multiple sclerosis (MS) or acute disseminated encephalomyelitis (ADEM) because of similar findings. A 15-year-old girl presented in June 2015 with vomiting and severe headache. Cerebral magnetic resonance imaging revealed multiple lesions in the corpus callosum. Cerebrospinal fluid findings gave normal results. The initial diagnosis was MS and steroid (1000 mg/day) was given. She started to describe hallucinations and became paraplegic. She then underwent plasmapheresis five times without response. Her electroencephalogram was diffusely slow with 2-3 Hz delta rhythm at the frontal regions. Audiological examination showed that she had sensorineural hearing loss in her left ear. Ophthalmologic evaluation revealed BRAO in both eyes. On the basis of these findings, she was diagnosed with SS and treated with intravenous immunoglobulin (IVIG) and aspirin. After monthly treatment with IVIG for 6 months, the patient has almost fully recovered. SS should be kept in mind in the differential diagnosis of MS and ADEM.

PIMD: 29671688

A guide to identification and selection of axial planes in magnetic resonance imaging of the brain.

For brain magnetic resonance (MR) examination, three-dimensional imaging is commonly performed. Radiologists need to know the appropriate imaging angle for viewing. We present six imaging angles for the axial images. Each angle is determined by the reference line. The landmarks on the midsagittal MR image to determine the angle of the reference lines are as follows: the supraorbito-meatal line (the center of the mammillary body and the fastigium of the fourth ventricle), the orbito-meatal (OM) line (the center of the mammillary body and the most posterior point of the cerebellar tentorium), the Talairach anterior commissure (AC)-posterior commissure (PC) line (the superior edge of the AC and the inferior edge of the PC), the Schaltenbrand AC-PC line (the center of the AC and the center of the PC), the subcallosal line (the inferior border of the genu and the inferior border of the splenium of the corpus callosum), Reid's baseline (the center of the pituitary gland and the most posterior point of the cerebellar tentorium) and the brainstem vertical line (the line perpendicular to the posterior border of the brainstem). The AC-PC line is most commonly used in MR examination. The OM line is most commonly used in computed tomography examination. The supraorbito-meatal line is recommended for avoiding irradiation to the orbit. In cases of multiple sclerosis, the subcallosal line is recommended in the guidelines. For lesions in the orbital cavity, paranasal cavity or skull base, Reid's baseline is useful. For cases of brainstem lesions, the brainstem vertical line is useful.

PIMD: 29668401

Phase II Randomized Controlled Trial of Constraint-Induced Movement Therapy in Multiple Sclerosis. Part 2: Effect on White Matter Integrity.

Constraint-induced movement therapy (CIMT) is a method of physical rehabilitation that has demonstrated clinical efficacy in patients with chronic stroke, cerebral palsy, and multiple sclerosis (MS).This pilot randomized controlled trial tested whether CIMT can also induce increases in white matter integrity in patients with MS.Twenty adults with chronic hemiparetic MS were randomized to receive either CIMT or complementary and alternative medicine (CAM) treatment (reported in the first article of this pair). Structural white matter change was assessed by tract-based spatial statistics (TBSS); measures included fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD).CIMT and CAM groups did not differ in pretreatment disability or expectancy to benefit. As noted in the companion paper, the motor activity log (MAL) improved more after CIMT than CAM ($P < .001$); the within-group effect size for CIMT was 3.7 (large d' = 0.57), while for CAM it was just 0.7. Improvements in white matter integrity followed CIMT and were observed in the contralateral corpus callosum (FA, $P < .05$), ipsilateral superior occipital gyrus (AD, $P < .05$), ipsilateral superior temporal gyrus (FA, $P < .05$), and contralateral corticospinal tract (MD and RD, $P < .05$).CIMT produced a very large improvement in real-world limb use and induced white matter changes in patients with hemiparetic MS when compared with CAM. The findings suggest in preliminary fashion that the adverse changes in white matter integrity induced by MS might be reversed by CIMT.ClinicalTrials.gov (NCT01081275).

PIMD: 29663845

A 24-month advanced magnetic resonance imaging study of multiple sclerosis patients treated with alemtuzumab.

Tissue damage in both multiple sclerosis (MS) lesions and normal-appearing white matter (NAWM) are important contributors to disability and progression. Specific aspects of MS pathology can be measured using advanced imaging. Alemtuzumab is a humanised monoclonal antibody targeting CD52 developed for MS treatment.To investigate changes over 2 years of advanced magnetic resonance (MR) metrics in lesions and NAWM of MS patients treated with alemtuzumab.A total of 42 relapsing-remitting alemtuzumab-treated MS subjects were scanned for 2 years at 3 T. T relaxation, T relaxation, diffusion tensor, MR spectroscopy and volumetric sequences were performed. Mean T and myelin water fraction (MWF) were determined for stable lesions, new lesions and NAWM. Fractional anisotropy was calculated for the corpus callosum (CC) and N-acetylaspartate (NAA) concentration was determined from a large NAWM voxel. Brain parenchymal fraction (BPF), cortical thickness and CC area were also calculated.No change in any MR measurement was found in lesions or NAWM over 24 months. BPF, cortical thickness and CC area all showed decreases in the first year followed by stability in the second year.Advanced MR biomarkers of myelin (MWF) and neuron/axons (NAA) show no change in NAWM over 24 months in alemtuzumab-treated MS participants.

PIMD: 29627579

Genetic detection of Sonic hedgehog (Shh) expression and cellular response in the progression of acute through chronic demyelination and remyelination.

Multiple sclerosis is a demyelinating disease in which neurological deficits result from damage to myelin, axons, and neuron cell bodies. Prolonged or repeated episodes of demyelination impair remyelination. We hypothesized that augmenting Sonic hedgehog (Shh) signaling in chronically demyelinated lesions could enhance oligodendrogenesis and remyelination. Shh regulates oligodendrocyte development during postnatal myelination, and maintains adult neural stem cells. We used genetic approaches to detect Shh expression and Shh responding cells in vivo. Shh or Gli1 mice were crossed to reporter mice for genetic fate-labeling of cells actively transcribing Shh or Gli1, an effective readout of canonical Shh signaling. Tamoxifen induction enabled temporal control of recombination at distinct stages of acute and chronic cuprizone demyelination of the corpus callosum. Gli1 fate-labeled cells were rarely found in the corpus callosum with tamoxifen given during acute demyelination stages to examine activated microglia, reactive astrocytes, or remyelinating cells. Gli1 fate-labeled cells, mainly reactive astrocytes, were observed in the corpus callosum with tamoxifen given after chronic demyelination. However, Shh expressing cells were not detected in the corpus callosum during acute or chronic demyelination. Finally, SAG, an agonist of both canonical and type II non-canonical Hedgehog signaling pathways, was microinjected into the corpus callosum after chronic demyelination. Significantly, SAG delivery increased proliferation and enhanced remyelination. SAG did not increase Gli1 fate-labeled cells in the corpus callosum, which may indicate signaling through the non-canonical Hedgehog pathway. These studies demonstrate that Hedgehog pathway interventions may have therapeutic potential to modulate astrogliosis and to promote remyelination after chronic demyelination.

PIMD: 29627004

Brain connectivity and cognitive processing speed in multiple sclerosis: A systematic review.

Processing speed (PS) decline is the most commonly observed cognitive deficit in people with multiple sclerosis (MS) resulting in a significant impact on quality of life. Despite its importance, knowledge of the underlying neural substrates is lacking.As MS is increasingly recognised as a disconnection syndrome, our aim was to carry out a systematic literature review to clarify the relationship between PS performance and MRI measures of structural and functional brain connectivity in people with MS.A literature search was carried out on PubMed and Web of Science that included publications predating September 2017. Additional articles were added after inspection of the reference lists of all selected papers.All selected papers were categorised in three sections according to the MRI measures investigated, independently or both. Quality assessment was carried out using a customised set of criteria.Thirty-two articles met the inclusion criteria and were included in the review. Microstructural integrity of the anterior corpus callosum and functional connectivity of frontal areas were more consistently found to correlate with PS performance, though high variability of findings was observed across studies. Several methodological flaws emerged from the reviewed literature.Despite the observed trends, no definite conclusions can be drawn on the relationship between brain connectivity and PS decline in MS given the limitations of the current literature. Future investigations may benefit from theoretical and methodological advances to clarify how MS-related brain damage affects patients' cognition.

PIMD: 29625726

Multiple sclerosis: Left advantage for auditory laterality in dichotic tests of central auditory processing and relationship of psychoacoustic tests with the Multiple Sclerosis Disability Scale-EDSS.

To evaluate the central auditory processing disorders in patients with multiple sclerosis, emphasizing auditory laterality by applying psychoacoustic tests and to identify their relationship with the Multiple Sclerosis Disability Scale (EDSS) functions.Depression scales (HADS), EDSS, and 9 psychoacoustic tests to study CAPD were applied to 26 individuals with multiple sclerosis and 26 controls. Correlation tests were performed between the EDSS and psychoacoustic tests.Seven out of 9 psychoacoustic tests were significantly different (P<.05); right or left (14/19 explorations) with respect to control. In dichotic digits there was a left-ear advantage compared to the usual predominance of RDD. There was significant correlation in five psychoacoustic tests and the specific functions of EDSS.The left-ear advantage detected and interpreted as an expression of deficient influences of the corpus callosum and attention in multiple sclerosis should be investigated. There was a correlation between psychoacoustic tests and specific EDSS functions.

PIMD: 29593734

Experimental Demyelination and Axonal Loss Are Reduced in MicroRNA-146a Deficient Mice.

The cuprizone (CPZ) model of multiple sclerosis (MS) was used to identify microRNAs (miRNAs) related to de- and remyelination. We further investigated the role of miR-146a in miR-146a-deficient (KO) mice: this miRNA is differentially expressed in MS lesions and promotes differentiation of oligodendrocyte precursor cells (OPCs) during remyelination, but its role has not been examined during demyelination.MicroRNAs were examined by Agilent Mouse miRNA Microarray in the corpus callosum during CPZ-induced demyelination and remyelination. Demyelination, axonal loss, changes in number of oligodendrocytes, OPCs, and macrophages/microglia was compared by histology/immunohistochemistry between KO and WT mice. Differential expression of target genes and proteins of miR-146a was analyzed in the transcriptome (4 × 44K Agilent Whole Mouse Genome Microarray) and proteome (liquid chromatography tandem mass spectrometry) of CPZ-induced de- and remyelination in WT mice. Levels of proinflammatory molecules in the corpus callosum were compared in WT versus KO mice by Meso Scale Discovery multiplex protein analysis.miR-146a was increasingly upregulated during CPZ-induced de- and remyelination. The absence of miR-146a in KO mice protected against demyelination, axonal loss, body weight loss, and atrophy of thymus and spleen. The number of CNP oligodendrocytes was increased during demyelination in the miR-146a KO mice, while there was a trend of increased number of NG2 OPCs in the WT mice. miR-146a target genes, SNAP25 and SMAD4, were downregulated in the proteome of demyelinating corpus callosum in WT mice. Higher levels of SNAP25 were measured by ELISA in the corpus callosum of miR-146a KO mice, but there was no difference between KO and WT mice during demyelination. Multiplex protein analysis of the corpus callosum lysate revealed upregulated TNF-RI, TNF-RII, and CCL2 in the WT mice in contrast to KO mice. The number of Mac3 and Iba1 macrophages/microglia was reduced in the demyelinating corpus callosum of the KO mice.During demyelination, absence of miR-146a reduced inflammatory responses, demyelination, axonal loss, the number of infiltrating macrophages, and increased the number of myelinating oligodendrocytes. The number of OPCs was slightly higher in the WT mice during remyelination, indicating a complex role of miR-146a during de- and remyelination.

PIMD: 29574981

Phosphatidylcholine 36:1 concentration decreases along with demyelination in the cuprizone animal model and in post-mortem multiple sclerosis brain tissue.

Multiple sclerosis is a demyelinating and inflammatory disease. Myelin is enriched in lipids, and more specifically, oleic acid. The goal of this study was to evaluate the concentration of oleic acid following demyelination and remyelination in the cuprizone model, test if these changes occurred in specific lipid species, and whether differences in the cuprizone model correlate with changes observed in post-mortem human brains. Eight-week-old C57Bl/6 mice were fed a 0.2% cuprizone diet for 5 weeks and some animals allowed to recover for 11 days. Demyelination, inflammation, and lipid concentrations were measured in the corpus callosum. Standard fatty acid techniques and liquid chromatography combined with tandem mass spectrometry were performed to measure concentrations of fatty acids in total brain lipids and a panel of lipid species within the phosphatidylcholine (PC). Similar measurements were conducted in post-mortem brain tissues of multiple sclerosis patients and were compared to healthy controls. Five weeks of cuprizone administration resulted in demyelination followed by significant remyelination after 11 days of recovery. Compared to control, oleic acid was decreased after 5 weeks of cuprizone treatment and increased during the recovery phase. This decrease in oleic acid was associated with a specific decrease in the PC 36:1 pool. Similar results were observed in human post-mortem brains. Decreases in myelin content in the cuprizone model were accompanied by decreases in oleic acid concentration and is associated with PC 36:1 suggesting that specific lipids could be a potential biomarker for myelin degeneration. The biological relevance of oleic acid for disease progression remains to be verified.

PIMD: 29550717

Lesion accumulation is predictive of long-term cognitive decline in multiple sclerosis.

To investigate the long-term progression of cognitive dysfunction and its neuroanatomical correlates and predictors in multiple sclerosis (MS).A cohort of 37 MS patients reflecting five decades of disease duration and all subtypes was followed over 17.5 years. Matched controls were recruited at the last follow-up. Global cognitive functioning was assessed using a principal component cognitive index based on comprehensive neuropsychological testing. During the last 8.5 years of the study, brain MRI was performed to analyze normalized volumetrics of three global tissue compartments (white and gray matter, lesions) and strategic regions (corpus callosum, thalamus, hippocampus).Cognitive decline progressed continuously throughout the study paralleled by atrophy and lesion accumulation. The cognitive index partly correlated with Expanded Disability Status Scale (ρ = -0.47, p < 0.001) and was mainly associated with the lesion fraction (β = -0.48, p < 0.001) and callosal fraction (β = 0.39, p = 0.002) in multiple linear regression analysis. The lesion fraction was an independent predictor of the cognitive performance 8.5 years later (β = -0.35, p = 0.008). Symbol Digit Modalities Test was most frequently abnormal (40%), while Rey-Osterrieth Complex Figure Test was more sensitive to detect cognitive decline.Cognitive impairment progresses continuously in MS, associated with atrophy and lesion accumulation, suggesting that interventions targeting these processes could be beneficial at all disease stages. Widespread cognitive functions are more profoundly affected, associated with lesions and corpus callosal atrophy, supporting the idea of an underlying disconnection mechanism for cognitive decline in MS.

PIMD: 29549794

Corpus callosum atrophy and post-surgical seizures in temporal lobe epilepsy associated with hippocampal sclerosis.

Our aim in this retrospective study was to explore whether corpus callosum atrophy could predict the post-surgical seizure control in patients with temporal lobe epilepsy associated with Hippocampal Sclerosis (HS).We used the Corpus Callosum Index (CCI) obtained from best mid-sagittal T2/FLAIR or T1-weighted MRI at two time-points, more than one year apart. CCI has been mainly used in Multiple Sclerosis (MS), but not in epilepsy, so we tested the validity of our results performing a proof of concept cohort, incorporating MS patients with and without epilepsy. Then, we explored this measurement in a well-characterized and long-term cohort of patients with temporal lobe epilepsy associated with HS.In the proof of concept cohort (MS without epilepsy n:40, and MS with epilepsy, n:15), we found a larger CCI atrophy rate in MS patients with poor epilepsy control vs. MS without epilepsy (p:0.01). Then, in HS patients (n:74), annualized CCI atrophy rate was correlated with the long-term Engel scale (Rho:0.31, p:0.007). In patients with post-surgical seizure recurrence, a larger CCI atrophy rate was found one year before any seizure relapse. Univariate analysis showed an increased risk of seizure recurrence in males, higher pre-surgical seizure frequency, necessity of invasive EEG monitoring, and higher CCI atrophy rate. Two of these variables were independent predictors in the multivariate analysis, male gender (HR:4.87, p:0.002) and CCI atrophy rate (HR:1.21, p:0.001).We demonstrated that atrophy of the corpus callosum, using the CCI, is related with poor seizure control in two different neurological disorders presenting with epilepsy, which might suggest that corpus callosum atrophy obtained in early post-surgical follow-up, could be a biomarker for predicting recurrences and guiding treatment plans.

PIMD: 29464444

Cuprizone Administration Alters the Iron Metabolism in the Mouse Model of Multiple Sclerosis.

Cuprizone (CZ) is a widely used copper chelating agent to develop non-autoimmune animal model of multiple sclerosis, characterized by demyelination of the corpus callosum (CC) and other brain regions. The exact mechanisms of CZ action are still arguable, but it seems that the only affected cells are the mature oligodendrocytes, possibly via metabolic disturbances caused by copper deficiency. During the pathogenesis of multiple sclerosis, high amount of deposited iron can be found throughout the demyelinated areas of the brain in the form of extracellular iron deposits and intracellularly accumulated iron in microglia. In the present study, we used the accepted experimental model of 0.2% CZ-containing diet with standard iron concentration to induce demyelination in the brain of C57BL/6 mice. Our aim was to examine the changes of iron homeostasis in the CC and as a part of the systemic iron regulation, in the liver. Our data showed that CZ treatment changed the iron metabolism of both tissues; however, it had more impact on the liver. Besides the alterations in the expressions of iron storage and import proteins, we detected reduced serum iron concentration and iron stores in the liver, together with elevated hepcidin levels and feasible disturbances in the Fe-S cluster biosynthesis. Our results revealed that the CZ-containing diet influences the systemic iron metabolism in mice, particularly the iron homeostasis of the liver. This inadequate systemic iron regulation may affect the iron homeostasis of the brain, eventually indicating a relationship among CZ treatment, iron metabolism, and neurodegeneration.

PIMD: 29460173

Changes in the axo-glial junctions of the optic nerves of cuprizone-treated mice.

Demyelination induced by cuprizone in mice has served a useful model system for the study of demyelinating diseases, such as multiple sclerosis. Severity of demyelination by cuprizone, however, varies across different regions of the central nervous system; the corpus callosum is sensitive, while the optic nerves are resistant. Here, we investigated the effects of cuprizone on optic nerves, focusing on the axo-glial junctions. Immunostaining for sodium channels, contactin-associated protein, neurofascins, and potassium channels revealed that there were no massive changes in the density and morphology of the axo-glial junctions in cuprizone-treated optic nerves. However, when we counted the number of incomplete junctional complexes, we observed increased numbers of isolated paranodes. These isolated paranodes were immunopositive for both axonal and glial membrane proteins, indicating that they were the contact sites between axons and glia. These were not associated with sodium channels or potassium channels, suggesting the absence of physiological functions. When teased axons from cuprizone-treated optic nerves were immunostained, the isolated paranodes were found at the internode region of the myelin. From these observations, we conclude that cuprizone induces new contacts between axons and myelins at the internode region.

PIMD: 29448957

Brain region-specific enhancement of remyelination and prevention of demyelination by the CSF1R kinase inhibitor BLZ945.

Multiple sclerosis (MS) is a chronic inflammatory disease affecting the central nervous system (CNS). While multiple effective immunomodulatory therapies for MS exist today, they lack the scope of promoting CNS repair, in particular remyelination. Microglia play a pivotal role in regulating myelination processes, and the colony-stimulating factor 1 (CSF-1) pathway is a key regulator for microglia differentiation and survival. Here, we investigated the effects of the CSF-1 receptor kinase inhibitor, BLZ945, on central myelination processes in the 5-week murine cuprizone model by non-invasive and longitudinal magnetic resonance imaging (MRI) and histology. Therapeutic 2-week BLZ945 treatment caused a brain region-specific enhancement of remyelination in the striatum/cortex, which was absent in the corpus callosum/external capsule. This beneficial effect correlated positively with microglia reduction, increased oligodendrocytes and astrogliosis. Prophylactic BLZ945 treatment prevented excessive demyelination in the corpus callosum by reducing microglia and increasing oligondendrocytes. In the external capsule oligodendrocytes were depleted but not microglia and a buildup of myelin debris and axonal damage was observed. A similar microglial dysfunction in the external capsule with an increase of myelin debris was obvious in triggering receptor expressed on myeloid cells 2 (TREM2) knock-out mice treated with cuprizone. Finally, therapeutic BLZ945 treatment did not change the disease course in experimental autoimmune encephalomyelitis mice, a peripherally driven neuroinflammation model. Taken together, our data suggest that a short-term therapeutic inhibition of the CSF-1 receptor pathway by BLZ945 in the murine cuprizone model enhances central remyelination by modulating neuroinflammation. Thus, microglia-modulating therapies could be considered clinically for promoting myelination in combination with standard-of-care treatments in MS patients.

PIMD: 29414290

Correlation between the corpus callosum index and brain atrophy, lesion load, and cognitive dysfunction in multiple sclerosis.

The corpus callosum index (CCI) can be easily and reliably obtained from conventional magnetic resonance imaging (MRI) and has been proposed as a possible marker of brain atrophy in MS. However, further validation of its correlation with volumetric measurements is still warranted.To assess the correlation of the CCI with the corpus callosum volume (CCV), brain and lesion volumes, and level of disability in MS.Cross-sectional, exploratory study including patients with relapsing-remitting MS. Clinical assessment comprised of physical and cognitive disability scales. MRI parameters included conventional volumetric measurements, the CCI (manual), and the CCV (automated).Twenty-four patients were included. There was a strong correlation between the CCI and CCV. The CCI correlated strongly with the white matter and lesion volumes, and moderately with the whole brain volume and scores on the Paced Auditory Serial Addition Test and MS Functional Composite. There were no correlations between the CCI and either gray matter volume or scores on the Expanded Disability Status Scale, the 9-Hole Peg Test, or the Timed 25-Foot Walk test.The findings support the validity of the CCI as an easy-to-obtain marker of brain atrophy, lesion load, and cognitive dysfunction in patients with MS.

PIMD: 29409686

LPA5 signaling is involved in multiple sclerosis-mediated neuropathic pain in the cuprizone mouse model.

Lysophosphatidic acid (LPA) and LPA1 receptor signaling play a crucial role in the initiation of peripheral nerve injury-induced neuropathic pain through the alternation of pain-related genes/proteins expression and demyelination. However, LPA and its signaling in the brain are still poorly understood. In the present study, we revealed that the LPA5 receptor expression in corpus callosum elevated after the initiation of demyelination, and the hyperalgesia through Aδ-fibers following cuprizone-induced demyelination was mediated by LPA5 signaling. These data suggest that LPA5 signaling may play a key role in the mechanisms underlying neuropathic pain following demyelination in the brain.

PIMD: 29409311

Effect of Multiple Intraperitoneal Injections of Human Bone Marrow Mesenchymal Stem Cells on Cuprizone Model of Multiple Sclerosis

Bone marrow mesenchymal stem cells (BM-MSCs) elicit neuroprotective effects, and their repair ability has been investigated in different experimental models. We aimed to investigate the effect of multiple i.p. BM-MSCs injections in the cuprizone model of multiple sclerosis in mice.Adult male C57BL/6 mice (n = 40) were fed a regular diet or a diet containing cuprizone (0.2% w/w) for 6 six weeks. Bone marrow samples were taken from patients with spinal cord injury. BM-MSCs (2 × 106 in 1 milliliter medium) were administered intraperitoneally for two consecutive weeks at the end of the forth weeks of cuprizone administration. Animals (n = 12) were perfused with 10% paraformaldehyde at the end of sixth week. The brains were sectioned coronally in 6-8-μm thickness (-2.3 to 1.8 mm from bregma). The sections were stained by luxol fast blue-cresyl violet, and images were captured via a microscope. Demyelination ratio was estimated in corpus callosum in a blind manner. A quantitative real-time PCR was used to measure the myelin basic protein gene expression at sixth week.Histologically, cuprizone induced demyelination in the corpus callosum. Demyelinated area was diminished in the corpus callosum of cell-administered group. Cuprizone could decrease myelin-binding protein mRNAs expression in corpus callosum, which was significantly recovered after BM-MSCs injections.Our data indicated a remyelination potency of multiple i.p. BM-MSCs in the cuprizone model of multiple sclerosis in mice.

PIMD: 29380545

Diffusion Kurtosis Imaging Shows Similar Cerebral Axonal Damage in Patients with HIV Infection and Multiple Sclerosis.

In this pilot study, we sought to investigate the pathological changes in the white matter (WM) of medically complex, combination antiretroviral therapy (cART)-treated patients with human immunodeficiency virus (HIV), comparing them to patients with long-standing, secondary progressive multiple sclerosis (SPMS).Using diffusion kurtosis imaging (DKI)-derived WM tract integrity (WMTI) metrics, 15 HIV and 15 age- and sex-matched SPMS patients with similar disease duration underwent magnetic resonance imaging analysis. Maps of WMTI metrics were created. Tract-based spatial statistics analysis of the whole brain and regions of interest analysis of the corpus callosum (CC) and the anterior thalamic radiations (ATRs) were performed and the derived WMTI metrics were compared between the groups of patients.Axonal water fraction, an index of chronic axonal loss, showed similarities between HIV and the chronic MS patients in all regions; in contrast, tortuosity, a measure more sensitive to myelin loss, was regionally variable. In addition, in HIV patients, WMTI metrics of the CC and left ATR were associated with cognitive test scores, suggesting clinical relevance for these measures of WM damage.We conclude that DKI-derived WMTI metrics may be a valuable tool in assessing the WM changes of medically complex HIV-infected individuals. While not powered to examine potential etiologies of WM changes in this pilot sample, regional variations in WMTI metrics were seen. When contrasted with changes consequent to chronic MS of similar duration, HIV and its comorbidities appear to result in similar degrees of axonal damage, but regionally variable amounts of myelin loss and extraxonal abnormality.

PIMD: 29306741

On the role of the amygdala for experiencing fatigue in patients with multiple sclerosis.

Recently, we proposed a model explaining the origin of fatigue in multiple sclerosis (MS) patients. This model assumes that the feeling of fatigue results from inflammation-induced information processing within interoceptive brain areas.To investigate the association between self-reported cognitive fatigue and structural integrity of interoceptive brain areas in MS patients.95 MS patients and 28 healthy controls participated in this study. All participants underwent diffusion tensor MRI and fractional anisotropy data were calculated for the amygdala, the stria terminalis and the corpus callosum, a non-interoceptive brain area. Based on the cognitive fatigue score of the Fatigue Scale for Motor and Cognition, patients were divided into moderately cognitively fatigued (cognitive fatigue score ≥ 28) and cognitively non-fatigued (cognitive fatigue score < 28) MS patients. Healthy controls were recruited as a third group. Repeated measures analyses of covariance, controlling for age, depression and brain atrophy, were performed to investigate whether the factor Group had a significant effect on the fractional anisotropy data.A significant effect of Group was observed for the amygdala ($F = 3.389$, $p = 0.037$). MS patients without cognitive fatigue presented lower values of the amygdala than MS patients with cognitive fatigue and healthy controls. For the stria terminalis and the corpus callosum, no main effect of Group was observed.The structural integrity of the amygdala in non-fatigued MS patients appears to be reduced. According to our model this might indicate that the absence of fatigue in non-fatigued MS patients might result from disturbed inflammation-induced information processing in the amygdala.

PIMD: 29301568

Surfen, a proteoglycan binding agent, reduces inflammation but inhibits remyelination in murine models of Multiple Sclerosis.

Proteoglycans are promising therapeutic targets in Multiple Sclerosis (MS), because they regulate many aspects of the immune response. This was studied using surfen, an agent that binds both heparan sulphate proteoglycans (HSPGs) and chondroitin sulphate proteoglycans (CSPGs). Initial cell culture work on bone marrow derived macrophages (BMDMs) found that surfen reduced concentrations of the chemokines CCL2, CCL4 and CCL5, with reduced messenger (m)RNA expression for Tumor Necrosis Factor, IL-6, IL-1β and inducible nitric oxide synthase. These data were further explored using Experimental Autoimmune Encephalomyelitis (EAE) in mice. Surfen reduced clinical signs during EAE when administered from disease onset, and reduced infiltration by CD4 positive T cells and macrophages into the central nervous system. These mice also showed reduced mRNA expression for the chemokines CCL3 and CCL5, with reduced concentrations of CCL2, CCL3 and CCL5. During EAE, surfen treatment induced a persistent increase in Interleukin (IL)-4 concentrations which may enhance T helper 2 responses. During EAE, surfen treatment reduced mRNA expression for HSPGs (NDST1, agrin, syndecan-4, perlecan, serglycin, syndecan-1) and the CSPG versican. By contrast, surfen increased mRNA expression for the CSPG aggrecan, with no effect on neurocan. During EAE, significant positive correlations were found between mRNA expression and clinical score for syndecan-4, serglycin and syndecan-1 and a significant negative correlation for aggrecan. These correlations were absent in surfen treated mice. Repair in the later stages of MS involves remyelination, which was modeled by injecting lysolecithin (lysophosphatidylcholine, LPC) into mouse corpus callosum to create regions of demyelination. When surfen was injected 2 days after LPC, it delayed remyelination of the lesions, but had no effect when injected 7 days after LPC. The delayed remyelination was associated with local increases in CSPG expression. Therefore surfen suppresses inflammation but inhibits remyelination in these models. A mechanism in common may be increased CSPG expression.

PIMD: 29288338

Toll-Like Receptor 2-Mediated Glial Cell Activation in a Mouse Model of Cuprizone-Induced Demyelination.

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system that is characterized by myelin abnormalities, oligodendrocyte pathology, and concomitant glia activation. The factors triggering gliosis and demyelination are currently not well characterized. New findings suggest an important role of the innate immune response in the initiation and progression of active demyelinating lesions. Especially during progressive disease, aberrant glia activation rather than the invasion of peripheral immune cells is accountable for progressive neuronal injury. The innate immune response can be induced by pathogen-associated or danger-associated molecular patterns, which are identified by pattern recognition receptors (PRRs), including the Toll-like receptors (TLRs). In this study, we used the cuprizone model in mice to investigate the expression of TLR2 during the course of cuprizone-induced demyelination. In addition, we used TLR2-deficient mice to analyze the functional role of TLR2 activation during cuprizone-induced demyelination and reactive gliosis. We show a significantly increased expression of TLR2 in the corpus callosum and hippocampus of cuprizone-intoxicated mice. The absence of receptor signaling in TLR2-deficient mice resulted in less severe reactive astrogliosis in the corpus callosum and cortex. In addition, microglia activation was ameliorated in the corpus callosum of TLR2-deficient mice, but augmented in the cortex compared to wild-type littermates. Extent of demyelination and loss of mature oligodendrocytes was comparable in both genotypes. These results suggest that the TLR2 orchestrates glia activation during gray and white matter demyelination in the presence of an intact blood-brain barrier. Future studies now have to address the underlying mechanisms of the region-specific TLR2-mediated glia activation.

PIMD: 29260029

A structural MRI study of cholinergic pathways and cognition in multiple sclerosis.

White matter hyperintensities (WMH) in the cholinergic pathways are associated with cognitive performance in Alzheimer's disease. This study aimed to evaluate the relationship between the volume reduction of cholinergic pathways and cognitive function in patients with multiple sclerosis (MS).Thirty-two MS patients underwent a brain MRI and cognitive measurements including the Mini-Mental State Examination (MMSE) and the Japanese version of the Montreal Cognitive Assessment (MoCA-J). The extent of WMH within the cholinergic pathways was assessed using the Cholinergic Pathways Hyperintensities Scale (CHIPS). Computerized WMH volumes were also obtained. FreeSurfer was used to measure regional volumes including the cortical and subcortical volumes. The correlations among the CHIPS, the WMH volume, and the clinical data were assessed, in addition to the correlations between the cognitive scores and regional volumes measured by FreeSurfer.The CHIPS score and the WMH volume were strongly positively correlated with each other ($r = 0.87$, $P < 0.001$). The CHIPS score had significantly negative correlations with the MMSE ($r = - 0.49$, $P = 0.003$) and the MoCA-J ($r = - 0.47$, $P = 0.005$) results. The WMH volume had significantly negative correlations with the MMSE ($r = - 0.54$, $P = 0.001$) and the MoCA-J ($r = - 0.57$, $P < 0.001$) results. In the analysis by FreeSurfer, both the MMSE and MoCA-J scores had significant positive correlations only with the volume of the corpus callosum.The CHIPS score tended to be less sensitive to the WMH volume in cognitive function evaluation, although the difference did not reach the level of statistical significance. Thus the CHIPS method may not be as effective in MS patients.

PIMD: 29171579

Common clinical features of pediatric multiple sclerosis in Pakistan - A report of 15 cases.

The aim of this note is to assess the common clinical features of paediatric multiple sclerosis (PMS) in Pakistan. For this purpose, 150 MS patients with the age range of (1-72) years and mean age (34.2±11.09) years were studied during the period 2010 to 2015 from MRI centers of Pakistan. We found 15 paediatric MS cases which had clinical course relapsing-remitting MS (11), secondary-progressive MS (3) and primary-progressive MS (1). Revised McDonald criteria 2010 of MRI was used to disseminate lesions in space and time. Sensory symptoms were found 27% in PMS patients and contributed brain area of corpus callosum, brain stem, periventricle, basal ganglia, white matter and cerebellum. Optic neuritis was the second clinical feature and its prevalence was reported 20% in paediatric patients. In conclusion, Paediatric multiple sclerosis is predicted 10 % with mean age 11.2 years in Pakistan. Sensory and optic neuritis are suggested the common clinical features of paediatric multiple sclerosis in Pakistan.

PIMD: 29143562

Pathological cut-offs of global and regional brain volume loss in multiple sclerosis.

Volumetric MRI surrogate markers of disease progression are lacking.To establish cut-off values of brain volume loss able to discriminate between healthy controls and MS patients.In total, 386 patients after first demyelinating event suggestive of MS (CIS), 964 relapsing-remitting MS (RRMS) patients, 63 secondary-progressive MS (SPMS) patients and 58 healthy controls were included in this longitudinal study. A total of 11,438 MRI scans performed on the same MRI scanner with the same protocol were analysed. Annualised percentage changes of whole brain, grey matter, thalamus and corpus callosum volumes were estimated. We investigated cut-offs able to discriminate between healthy controls and MS patients.At a predefined specificity of 90%, the annualised percentage change cut-off of corpus callosum volume (-0.57%) was able to distinguish between healthy controls and patients with the highest sensitivity (51% in CIS, 48% in RRMS and 42% in SPMS patients). Lower sensitivities (22%-49%) were found for cut-offs of whole brain, grey matter and thalamic volume loss. Among CIS and RRMS patients, cut-offs were associated with greater accumulation of disability.We identified cut-offs of annualised global and regional brain volume loss rates able to discriminate between healthy controls and MS patients.

PIMD: 29142736

Strain differences in cuprizone induced demyelination.

Multiple sclerosis (MS) is a severe neurological disorder, characterized by demyelination of the central nervous system (CNS), and with a prevalence of greater than 2 million people worldwide. In terms of research in MS pathology, the cuprizone toxicity model is widely used. Here we investigated the contribution of genetic differences in response to cuprizone-induced demyelination in two genetically different mouse strains: CD1 and C57BL/6.We demonstrate that exposure to a diet containing 0.2% cuprizone resulted in less severe demyelination in the midline of the corpus callosum over the fornix in CD1 mice than C57BL/6 mice. With continuous cuprizone feeding, demyelination in CD1 mice was not prominent until after 7 weeks, in contrast to C57BL/6 mice, which showed prominent demyelination after 4 weeks of exposure. Concomitantly, immunohistochemical analysis demonstrated more oligodendrocytes, as well as fewer oligodendrocyte progenitor cells, microglia and astrocytes in cuprizone treated CD1 mice. We also analyzed 4-weeks-cuprizone treated corpus callosum tissue samples and found that cuprizone treated CD1 mice showed a smaller reduction of myelin-associated glycoprotein (MAG) and a smaller increase of Iba1 and NG2.These observations suggest that CD1 mice are less vulnerable to cuprizone-induced demyelination than C57BL/6 mice and thus genetic background factors appear to influence the susceptibility to cuprizone-induced demyelination.

PIMD: 29141828

Alternative diagnoses in patients referred to specialized centers for suspected MS.

The aim of this study is to explore the frequency, type, and predictors of alternative diagnoses among patients referred with a recent diagnosis of multiple sclerosis (MS) to two specialized MS centers in the Middle East.This is a retrospective review of a prospectively followed cohort of MS patients at 2 University specialized MS centers. All patients referred for MS were included. The final diagnosis was recorded and demographic, clinical, laboratory, electrophysiological and radiological variables were collected.A total of 554 patients were included in this study of which 431 were referred for diagnostic confirmation. The final diagnosis of MS was confirmed in 300 (70%), while 114 (26%) turned out to have an alternative diagnosis and 15 (3.5%) fulfilled criteria for radiologically isolated syndrome (RIS). The most common alternative diagnoses were psychogenic (16.3%), non-specific MRI white matter lesions (14.7%), NMO (9.5%), migraine (8.6%) and systemic autoimmune disorders (8.6%). The strongest predictors of a final diagnosis of MS were: younger age, presence of oligoclonal bands in the CSF, periventricular, corpus callosum, spinal ($P<0.0001$), or enhancing lesions ($P<0.005$) on MRI.Our study shows that 30% of patients referred for a suspicion of MS end up with a different diagnosis. The most common alternative diagnoses of MS in the Middle East are not different from what has been described in Western countries. Age, MRI and CSF findings can help with the differential diagnosis.

PIMD: 29114096

Fingolimod Protects Against Ischemic White Matter Damage by Modulating Microglia Toward M2 Polarization via STAT3 Pathway.

White matter (WM) ischemic injury, a major neuropathological feature of cerebral small vessel diseases, is an important cause of vascular cognitive impairment in later life. The pathogenesis of demyelination after WM ischemic damage are often accompanied by microglial activation. Fingolimod (FTY720) was approved for the treatment of multiple sclerosis for its immunosuppression property. In this study, we evaluated the neuroprotective potential of FTY720 in a WM ischemia model.Chronic WM ischemic injury model was induced by bilateral carotid artery stenosis. Cognitive function, WM integrity, microglial activation, and potential pathway involved in microglial polarization were assessed after bilateral carotid artery stenosis.Disruption of WM integrity was characterized by demyelination in the corpus callosum and disorganization of Ranvier nodes using Luxol fast blue staining, immunofluorescence staining, and electron microscopy. In addition, radial maze test demonstrated that working memory performance was decreased at 1-month post-bilateral carotid artery stenosis-induced injury. Interestingly, FTY720 could reduce cognitive decline and ameliorate the disruption of WM integrity. Mechanistically, cerebral hypoperfusion induced microglial activation, production of associated proinflammatory cytokines, and priming of microglial polarization toward the M1 phenotype, whereas FTY720 attenuated microglia-mediated neuroinflammation after WM ischemia and promoted oligodendrocytogenesis by shifting microglia toward M2 polarization. FTY720's effect on microglial M2 polarization was largely suppressed by selective signal transducer and activator of transcription 3 (STAT3) blockade in vitro, revealing that FTY720-enabled shift of microglia from M1 to M2 polarization state was possibly mediated by STAT3 signaling.Our study suggested that FTY720 might be a potential therapeutic drug targeting brain inflammation by skewing microglia toward M2 polarization after chronic cerebral hypoperfusion.

PIMD: 29101276

Lesion topographies in multiple sclerosis diagnosis: A reappraisal.

To assess the contributions of cortico-juxtacortical and corpus callosum lesions to multiple sclerosis diagnosis and to compare the value of ≥1 vs ≥3 periventricular lesions in clinically isolated syndromes (CIS).Step 1: We evaluated lesion topography classifications in 657 patients with CIS with stepwise Cox proportional hazards regression models considering second attack as the outcome. Step 2: We established 2 dissemination in space (DIS) versions according to the periventricular lesion cutoffs of ≥1 and ≥3 and assessed their performance at 10 years with second attack as the outcome, first individually and then combined with dissemination in time (DIT) in all cases (n = 326), by age, and by CIS topography.Step 1: The models (hazard ratios [95% confidence interval]) favored ≥1 over ≥3 periventricular lesions (2.5 [1.7-3.6]) and cortico-juxtacortical over juxtacortical lesions (1.4 [1.0-1.8]). Callosal lesions were not selected. Step 2: DIS specificity with ≥1 periventricular lesions was slightly lower than with ≥3 (59.1 vs 61.4) and the same after adding DIT (88.6). Regarding age, ≥3 periventricular lesions improved DIS specificity over ≥1 lesions in the 40-49 years of age bracket (66.7 vs 58.3). This difference disappeared when adding DIT (83.3). Optic neuritis had a similar pattern when evaluating CIS topographies.Our results comply with the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) consensus recommendation of combining cortical and juxtacortical lesions into a single term when possible. Concerning periventricular lesions, maintaining the current ≥1 cutoff in the McDonald criteria does not compromise specificity in typical CIS cases, but attention should be paid to older patients or optic neuritis cases.

PIMD: 29085580

Protective effects of erythropoietin against cuprizone-induced oxidative stress and demyelination in the mouse corpus callosum.

Increasing evidence in both experimental and clinical studies suggests that oxidative stress plays a major role in the pathogenesis of multiple sclerosis. The aim of the present work is to investigate the protective effects of erythropoietin against cuprizone-induced oxidative stress.Adult male C57BL/6J mice were fed a chow containing 0.2 % cuprizone for 6 weeks. After 3 weeks, mice were simultaneously treated with erythropoietin (5,000 IU/kg body weight) by daily intraperitoneal injections.Our results showed that cuprizone induced oxidative stress accompanied with down-regulation of subunits of the respiratory chain complex and demyelination of corpus callosum. Erythropoietin antagonized these effects. Biochemical analysis showed that oxidative stress induced by cuprizone was regulated by erythropoietin. Similarly, erythropoietin induced the expression of subunits of the respiratory chain complex over normal control values reflecting a mechanism to compensate cuprizone-mediated down-regulation of these genes.The data implicate that erythropoietin abolishes destructive cuprizone effects in the corpus callosum by decreasing oxidative stress and restoring mitochondrial respiratory enzyme activity.

PIMD: 29038005

Prednisone alleviates demyelination through regulation of the NLRP3 inflammasome in a C57BL/6 mouse model of cuprizone-induced demyelination.

Myelin abnormalities, oligodendrocyte damage, and concomitant glia activation are common in demyelinating diseases of the central nervous system (CNS). Increasing evidence has demonstrated that the inflammatory response triggers demyelination and gliosis in demyelinating disorders. Numerous clinical interventions, including those used to treat multiple sclerosis (MS), have confirmed prednisone (PDN) as a powerful anti-inflammatory drug that reduces the inflammatory response and promotes tissue repair in multiple inflammation sites. However, the underlying mechanism of PDN in ameliorating myelin damage is not well understood. In our study, a cuprizone (CPZ)-induced demyelinated mouse model was used to explore the mechanism of the protection provided by PDN. Open-field tests showed that CPZ-treated mice exhibited significantly increased anxiety and decreased exploration. However, PDN improved emotional behavior, as evidenced by an increase in the total distance traveled, and central distance traveled as well as the mean amount of time spent in the central area. CPZ-induced demyelination was observed to be alleviated in PDN-treated mice based on luxol fast blue (LFB) staining and myelin basic protein (MBP) expression analyses. In addition, PDN reduced astrocyte and microglia activation in the corpus callosum. Furthermore, we demonstrated that PDN inhibited the Nod-like receptor pyrin domain containing 3 (NLRP3) inflammasome signaling pathway and related inflammatory cytokines and chemokines, including TNF-α, CCL8, CXCL10 and CXCL16. PDN also reduced the serum corticosterone levels in the CPZ-treated mice. Taken together, these results suggest that inhibition of the NLRP3 signaling pathway may be a novel mechanism by which PDN exerts its protective actions in demyelinating diseases.

PIMD: 29023982

MEDI+0: Morphology enabled dipole inversion with automatic uniform cerebrospinal fluid zero reference for quantitative susceptibility mapping.

To develop a quantitative susceptibility mapping (QSM) method with a consistent zero reference using minimal variation in cerebrospinal fluid (CSF) susceptibility.The ventricular CSF was automatically segmented on the R2* map. An L -regularization was used to enforce CSF susceptibility homogeneity within the segmented region, with the averaged CSF susceptibility as the zero reference. This regularization for CSF homogeneity was added to the model used in a prior QSM method (morphology enabled dipole inversion [MEDI]). Therefore, the proposed method was referred to as MEDI+0 and compared with MEDI in a numerical simulation, in multiple sclerosis (MS) lesions, and in a reproducibility study in healthy subjects.In both the numerical simulations and in vivo experiments, MEDI+0 not only decreased the susceptibility variation within the ventricular CSF, but also suppressed the artifact near the lateral ventricles. In the simulation, MEDI+0 also provided more accurate quantification compared to MEDI in the globus pallidus, substantia nigra, corpus callosum, and internal capsule. MEDI+0 measurements of MS lesion susceptibility were in good agreement with those obtained by MEDI. Finally, both MEDI+0 and MEDI showed good and similar intrasubject reproducibility.QSM with a minimal variation in ventricular CSF is viable to provide a consistent zero reference while improving image quality. Magn Reson Med 79:2795-2803, 2018. © 2017 International Society for Magnetic Resonance in Medicine.

PIMD: 29022246

Alpha-lipoic acid mitigates toxic-induced demyelination in the corpus callosum by lessening of oxidative stress and stimulation of polydendrocytes proliferation.

Multiple Sclerosis (MS), is a disease that degenerates myelin in central nervous system (CNS). Reactive oxygen species (ROSs) are toxic metabolites, and accumulating data indicate that ROSs-mediated apoptosis of oligodendrocytes (OLGs) plays a major role in the pathogenesis of MS under oxidative stress conditions. In this study, we investigated the role of endogenous antioxidant alpha-lipoic acid (ALA) as ROSs scavenger in the OLGs loss and myelin degeneration during cuprizone (cup)-induced demyelination in the experimental model of MS. Our results have shown that ALA treatment significantly increased population of mature OLGs (MOG cells), as well as decreased oxidative stress (ROSs, COX-2 and PGE2) and apoptosis mediators (caspase-3 and Bax/Bcl2 ratio) in corpus callosum (CC). Surprisingly, ALA significantly stimulates population of NG2 chondroitin sulfate proteoglycan positive glia (NG2 cells or polydendrocytes), from week 4 afterward. Accordingly ALA could prevents apoptosis, delays demyelination and recruits OLGs survival and regeneration mechanisms in CC. We conclude that ALA has protective effects against toxic demyelination via reduction of redox signaling, and alleviation of polydendrocytes vulnerability to excitotoxic challenge.

PIMD: 28940645

Lineage tracing reveals dynamic changes in oligodendrocyte precursor cells following cuprizone-induced demyelination.

The regeneration of oligodendrocytes is a crucial step in recovery from demyelination, as surviving oligodendrocytes exhibit limited structural plasticity and rarely form additional myelin sheaths. New oligodendrocytes arise through the differentiation of platelet-derived growth factor receptor α (PDGFRα) expressing oligodendrocyte progenitor cells (OPCs) that are widely distributed throughout the CNS. Although there has been detailed investigation of the behavior of these progenitors in white matter, recent studies suggest that disease burden in multiple sclerosis (MS) is more strongly correlated with gray matter atrophy. The timing and efficiency of remyelination in gray matter is distinct from white matter, but the dynamics of OPCs that contribute to these differences have not been defined. Here, we used in vivo genetic fate tracing to determine the behavior of OPCs in gray and white matter regions in response to cuprizone-induced demyelination. Our studies indicate that the temporal dynamics of OPC differentiation varies significantly between white and gray matter. While OPCs rapidly repopulate the corpus callosum and mature into CC1 expressing mature oligodendrocytes, OPC differentiation in the cingulate cortex and hippocampus occurs much more slowly, resulting in a delay in remyelination relative to the corpus callosum. The protracted maturation of OPCs in gray matter may contribute to greater axonal pathology and disease burden in MS.

PIMD: 28929408

Yokukansan Reduces Cuprizone-Induced Demyelination in the Corpus Callosum Through Anti-inflammatory Effects on Microglia.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). The release of inflammatory cytokines and pro-oxidant molecules from microglia has been shown to play a key role in the pathology of MS. Thus, suppression of microglial cell activation is an attractive therapeutic option. Yokukansan, a traditional Japanese herbal medicine, has been shown to suppress microglial activity in the CNS. However, whether or not yokukansan reduces demyelination observed in the CNS during MS remains unknown. In this study, female C57BL/6 mice were fed a diet containing 0.2% cuprizone (bis-cyclohexanone oxaldihydrazone) to induce demyelination in the corpus callosum. We investigated whether or not yokukansan reduces cuprizone-induced demyelination using immunohistochemical analyses. Furthermore, we examined the in vitro anti-inflammatory effects of yokukansan on LPS-stimulated BV2 cells, a murine microglial cell line. Luxol fast blue staining and immunostaining for myelin basic protein demonstrated that yokukansan reduces demyelination of the corpora callosa of cuprizone-fed mice. In addition, yokukansan significantly decreased the number of activated microglial cells in the corpora callosa of cuprizone-fed mice. Furthermore, treatment with 500 μg/ml yokukansan suppressed the expression of interleukin-1β and inducible nitric-oxide synthase mRNA and protein in LPS-stimulated BV2 cells. These findings suggest that yokukansan reduces demyelination owing to anti-inflammatory effects on microglia. As yokukansan has few adverse effects, yokukansan has the potential to be a novel option to treat MS.

PIMD: 28899915

Conditional Deletion of the L-Type Calcium Channel Cav1.2 in NG2-Positive Cells Impairs Remyelination in Mice.

Exploring the molecular mechanisms that drive the maturation of oligodendrocyte progenitor cells (OPCs) during the remyelination process is essential to developing new therapeutic tools to intervene in demyelinating diseases such as multiple sclerosis. To determine whether L-type voltage-gated calcium channels (L-VGCCs) are required for OPC development during remyelination, we generated an inducible conditional knock-out mouse in which the L-VGCC isoform Cav1.2 was deleted in NG2-positive OPCs (Cav1.2). Using the cuprizone (CPZ) model of demyelination and mice of either sex, we establish that Cav1.2 deletion in OPCs leads to less efficient remyelination of the adult brain. Specifically, Cav1.2 OPCs mature slower and produce less myelin than control oligodendrocytes during the recovery period after CPZ intoxication. This reduced remyelination was accompanied by an important decline in the number of myelinating oligodendrocytes and in the rate of OPC proliferation. Furthermore, during the remyelination phase of the CPZ model, the corpus callosum of Cav1.2 animals presented a significant decrease in the percentage of myelinated axons and a substantial increase in the mean g-ratio of myelinated axons compared with controls. In addition, in a mouse line in which the Cav1.2 OPCs were identified by a reporter, we establish that Cav1.2 OPCs display a reduced maturational rate through the entire remyelination process. These results suggest that Ca influx mediated by L-VGCCs in oligodendroglial cells is necessary for normal remyelination and is an essential Ca channel for OPC maturation during the remyelination of the adult brain. Ion channels implicated in oligodendrocyte differentiation and maturation may induce positive signals for myelin recovery. Voltage-gated Ca channels (VGCCs) are important for normal myelination by acting at several critical steps during oligodendrocyte progenitor cell (OPC) development. To determine whether voltage Ca entry is involved in oligodendrocyte differentiation and remyelination, we used a conditional knockout mouse for VGCCs in OPCs. Our results indicate that VGCCs can modulate oligodendrocyte maturation in the demyelinated brain and suggest that voltage-gated Ca influx in OPCs is critical for remyelination. These findings could lead to novel approaches for obtaining a better understanding of the factors that control OPC maturation in order to stimulate this pool of progenitors to replace myelin in demyelinating diseases.

PIMD: 28830026

Progesterone therapy induces an M1 to M2 switch in microglia phenotype and suppresses NLRP3 inflammasome in a cuprizone-induced demyelination mouse model.

Demyelination of the central nervous system (CNS) has been associated to reactive microglia in neurodegenerative disorders, such as multiple sclerosis (MS). The M1 microglia phenotype plays a pro-inflammatory role while M2 is involved in anti-inflammatory processes in the brain. In this study, CPZ-induced demyelination mouse model was used to investigate the effect of progesterone (PRO) therapy on microglia activation and neuro-inflammation. Results showed that progesterone therapy (CPZ+PRO) decreased neurological behavioral deficits, as demonstrated by significantly decreased escape latencies, in comparison to CPZ mice. In addition, CPZ+PRO caused a significant reduction in the mRNA expression levels of M1-markers (iNOS, CD86, MHC-II and TNF-α) in the corpus callosum region, whereas the expression of M2-markers (Trem-2, CD206, Arg-1 and TGF-β) was significantly increased, in comparison to CPZ mice. Moreover, CPZ+PRO resulted in a significant decrease in the number of iNOS and Iba-1/iNOS cells (M1), whereas TREM-2 and Iba-1/TREM-2 cells (M2) significantly increased, in comparison to CPZ group. Furthermore, CPZ+PRO caused a significant decrease in mRNA and protein expression levels of NLRP3 and IL-18 (~2-fold), in comparison to the CPZ group. Finally, CPZ+PRO therapy was accompanied with reduced levels of demyelination, compared to CPZ, as confirmed by immunofluorescence to myelin basic protein (MBP) and Luxol Fast Blue (LFB) staining, as well as transmission electron microscopy (TEM) analysis. In summary, we reported for the first time that PRO therapy causes polarization of M2 microglia, attenuation of M1 phenotype, and suppression of NLRP3 inflammasome in a CPZ-induced demyelination model of MS.

PIMD: 28741711

Diffusion tensor imaging in multiple sclerosis at different final outcomes.

Methods to evaluate the relative contributions of demyelination vs axonal degeneration over the long-term course of MS are urgently needed. We used magnetic resonance diffusion tensor imaging (DTI) to estimate degrees of demyelination and axonal degeneration in the corpus callosum (CC) in cases of MS with different final outcomes.We determined DTI measures mean diffusivity (MD), fractional anisotropy (FA), and axial (AD) and radial (RD) diffusivities in the CC of 31 MS patients, of whom 13 presented a secondary progressive course, 11 a non-progressive course, and seven a monophasic course. The study participants were survivors from an incidence cohort of 254 attack-onset MS patients with 50 years of longitudinal follow-up. As reference, we included five healthy individuals without significant morbidity.In patients with secondary progression, compared to all other groups, the corpus callosum showed increased RD and reduced FA, but no change in AD. None of the parameters exhibited differences among non-progressive and monophasic course groups and controls.Increased RD was observed in secondary progressive MS, indicating significant myelin loss. Normal RD values observed in the clinically isolated syndrome and non-progressive groups confirm their benign nature. AD was not a characterizing parameter for long-term outcome. Demyelination revealed by increased RD is a distinguishing trait for secondary progression.

PIMD: 28718218

Impact of prenatal immune challenge on the demyelination injury during adulthood.

Brain inflammation is associated with several brain diseases such as multiple sclerosis (MS), a disease characterized by demyelination. Whether prenatal immune challenge affects demyelination-induced inflammation in the white matter during adulthood is unclear. In the present study, we used a well-established experimental model of focal demyelination to assess whether prenatal immune challenge affects demyelination-induced inflammation.Pregnant rats were injected with either lipopolysaccharide (100 μg/kg, ip) or pyrogen-free saline. A 2 μL solution of the gliotoxin ethidium bromide (0.04%) was stereotaxically infused into the corpus callosum of adult male offspring. The extent of demyelination lesion was assessed using Luxol fast blue (LFB) staining. Oligodendrocyte precursor cells, mature oligodendrocytes, markers of cellular gliosis, and inflammation were monitored in the vicinity of the demyelination lesion area.Prenatal lipopolysaccharide reduced the size of the demyelination lesion during adulthood. This reduced lesion was associated with enhanced density of mature oligodendrocytes and reduced density of microglial cells in the vicinity of the demyelination lesion. Such reduction in microglial cell density was accompanied by a reduced activation of the nuclear factor κB signaling pathway.These data strongly suggest that prenatal immune challenge dampens the extent of demyelination during adulthood likely by reprogramming the local brain inflammatory response to demyelinating insults.

PIMD: 28714395

Five Decades of Cuprizone, an Updated Model to Replicate Demyelinating Diseases.

Demyelinating diseases of the central nervous system (CNS) comprise a group of neurological disorders characterized by progressive (and eventually irreversible) loss of oligodendrocytes and myelin sheaths in the white matter tracts. Some of myelin disorders include: Multiple sclerosis, Guillain-Barré syndrome, peripheral nerve polyneuropathy and others. To date, the etiology of these disorders is not well known and no effective treatments are currently available against them. Therefore, further research is needed to gain a better understand and treat these patients. To accomplish this goal, it is necessary to have appropriate animal models that closely resemble the pathophysiology and clinical signs of these diseases. Herein, we describe the model of toxic demyelination induced by cuprizone (CPZ), a copper chelator that reduces the cytochrome and monoamine oxidase activity into the brain, produces mitochondrial stress and triggers the local immune response. These biochemical and cellular responses ultimately result in selective loss of oligodendrocytes and microglia accumulation, which conveys to extensive areas of demyelination and gliosis in corpus callosum, superior cerebellar peduncles and cerebral cortex. Remarkably, some aspects of the histological pattern induced by CPZ are similar to those found in multiple sclerosis. CPZ exposure provokes behavioral changes, impairs motor skills and affects mood as that observed in several demyelinating diseases. Upon CPZ removal, the pathological and histological changes gradually revert. Therefore, some authors have postulated that the CPZ model allows to partially mimic the disease relapses observed in some demyelinating diseases.for five decades, the model of CPZ-induced demyelination is a good experimental approach to study demyelinating diseases that has maintained its validity, and is a suitable pharmacological model for reproducing some key features of demyelinating diseases, including multiple sclerosis.

PIMD: 28646890

Influence of type I IFN signaling on anti-MOG antibody-mediated demyelination.

Antibodies with specificity for myelin oligodendrocyte glycoprotein (MOG) are implicated in multiple sclerosis and related diseases. The pathogenic importance of anti-MOG antibody in primary demyelinating pathology remains poorly characterized.The objective of this study is to investigate whether administration of anti-MOG antibody would be sufficient for demyelination and to determine if type I interferon (IFN) signaling plays a similar role in anti-MOG antibody-mediated pathology, as has been shown for neuromyelitis optica-like pathology.Purified IgG2a monoclonal anti-MOG antibody and mouse complement were stereotactically injected into the corpus callosum of wild-type and type I IFN receptor deficient mice (IFNAR1-KO) with and without pre-established experimental autoimmune encephalomyelitis (EAE).Anti-MOG induced complement-dependent demyelination in the corpus callosum of wild-type mice and did not occur in mice that received control IgG2a. Deposition of activated complement coincided with demyelination, and this was significantly reduced in IFNAR1-KO mice. Co-injection of anti-MOG and complement at onset of symptoms of EAE induced similar levels of callosal demyelination in wild-type and IFNAR1-KO mice.Anti-MOG antibody and complement was sufficient to induce callosal demyelination, and pathology was dependent on type I IFN. Induction of EAE in IFNAR1-KO mice overcame the dependence on type I IFN for anti-MOG and complement-mediated demyelination.

PIMD: 28644112

Susac syndrome misdiagnosed as multiple sclerosis with exacerbation by interferon beta therapy.

Susac syndrome is a rare autoimmune disorder characterised by the clinical triad of encephalopathy, retinopathy (branch retinal artery occlusions) and hearing loss. The diagnosis of Susac syndrome may be difficult initially, and it is not uncommon for patients with Susac syndrome to be misdiagnosed with multiple sclerosis. In this case report, we describe a patient who was diagnosed as having multiple sclerosis for three years, with further deterioration after starting treatment with interferon beta-1a. The patient had the triad of encephalopathy, branch retinal artery occlusions and sensorineural hearing loss. She had the classic magnetic resonance imaging appearance, with normal magnetic resonance imaging of the spinal cord and absence of oligoclonal bands in the cerebrospinal fluid. Our patient responded well to treatment with a combination therapy and discontinuation of interferon beta-1a. Our observations raise awareness about the importance of the early and correct diagnosis of Susac syndrome, which usually affects young patients, with an excellent prognosis if treated aggressively at an early stage of the disease. Susac syndrome is underdiagnosed and is not uncommonly misdiagnosed as multiple sclerosis. Susac syndrome is a great mimicker of multiple sclerosis, and establishing diagnostic criteria for this syndrome is very useful. In any patient presenting with a progressive disabling neurological disorder associated with callosal lesions and/or hearing loss, and/or visual loss especially in women, Susac syndrome should be suspected.

PIMD: 28631093

Myelin regulatory factor drives remyelination in multiple sclerosis.

Remyelination is limited in the majority of multiple sclerosis (MS) lesions despite the presence of oligodendrocyte precursor cells (OPCs) in most lesions. This observation has led to the view that a failure of OPCs to fully differentiate underlies remyelination failure. OPC differentiation requires intricate transcriptional regulation, which may be disrupted in chronic MS lesions. The expression of few transcription factors has been differentially compared between remyelinating lesions and lesions refractory to remyelination. In particular, the oligodendrocyte transcription factor myelin regulatory factor (MYRF) is essential for myelination during development, but its role during remyelination and expression in MS lesions is unknown. To understand the role of MYRF during remyelination, we genetically fate mapped OPCs following lysolecithin-induced demyelination of the corpus callosum in mice and determined that MYRF is expressed in new oligodendrocytes. OPC-specific Myrf deletion did not alter recruitment or proliferation of these cells after demyelination, but decreased the density of new glutathione S-transferase π positive oligodendrocytes. Subsequent remyelination in both the spinal cord and corpus callosum is highly impaired following Myrf deletion from OPCs. Individual OPC-derived oligodendrocytes, produced in response to demyelination, showed little capacity to express myelin proteins following Myrf deletion. Collectively, these data demonstrate a crucial role of MYRF in the transition of oligodendrocytes from a premyelinating to a myelinating phenotype during remyelination. In the human brain, we find that MYRF is expressed in NogoA and CNP-positive oligodendrocytes. In MS, there was both a lower density and proportion of oligodendrocyte lineage cells and NogoA+ oligodendrocytes expressing MYRF in chronically demyelinated lesions compared to remyelinated shadow plaques. The relative scarcity of oligodendrocyte lineage cells expressing MYRF in demyelinated MS lesions demonstrates, for the first time, that chronic lesions lack oligodendrocytes that express this necessary transcription factor for remyelination and supports the notion that a failure to fully differentiate underlies remyelination failure.

PIMD: 28616036

Correlation between white matter damage and gray matter lesions in multiple sclerosis patients.

We observed the characteristics of white matter fibers and gray matter in multiple sclerosis patients, to identify changes in diffusion tensor imaging fractional anisotropy values following white matter fiber injury. We analyzed the correlation between fractional anisotropy values and changes in whole-brain gray matter volume. The participants included 20 patients with relapsing-remitting multiple sclerosis and 20 healthy volunteers as controls. All subjects underwent head magnetic resonance imaging and diffusion tensor imaging. Our results revealed that fractional anisotropy values decreased and gray matter volumes were reduced in the genu and splenium of corpus callosum, left anterior thalamic radiation, hippocampus, uncinate fasciculus, right corticospinal tract, bilateral cingulate gyri, and inferior longitudinal fasciculus in multiple sclerosis patients. Gray matter volumes were significantly different between the two groups in the right frontal lobe (superior frontal, middle frontal, precentral, and orbital gyri), right parietal lobe (postcentral and inferior parietal gyri), right temporal lobe (caudate nucleus), right occipital lobe (middle occipital gyrus), right insula, right parahippocampal gyrus, and left cingulate gyrus. The voxel sizes of atrophic gray matter positively correlated with fractional anisotropy values in white matter association fibers in the patient group. These findings suggest that white matter fiber bundles are extensively injured in multiple sclerosis patients. The main areas of gray matter atrophy in multiple sclerosis are the frontal lobe, parietal lobe, caudate nucleus, parahippocampal gyrus, and cingulate gyrus. Gray matter atrophy is strongly associated with white matter injury in multiple sclerosis patients, particularly with injury to association fibers.

PIMD: 28601572

Corpus callosum atrophy as a marker of clinically meaningful cognitive decline in secondary progressive multiple sclerosis. Impact on employment status.

Cognitive impairment in Multiple Sclerosis (MS) is more frequent and pronounced in secondary progressive MS (SPMS). Cognitive decline is an important predictor of employment status in patients with MS. Magnetic Resonance Imaging (MRI) markers have been used to associate tissue damage with cognitive dysfunction. The aim of the study was to designate the MRI marker that predicts cognitive decline in SPMS and explore its effect on employment status. 30 SPMS patients and 30 healthy participants underwent neuropsychological assessment using the Trail Making Test (TMT) parts A and B, semantic and phonological verbal fluency task and a computerized cognitive screening battery (Central Nervous System Vital Signs). Employment status was obtained as a quality of life measure. Brain MRI was performed in all participants. We measured total lesion volume, third ventricle width, thalamic and corpus callosum atrophy. The frequency of cognitive decline for our SPMS patients was 80%. SPMS patients differed significantly from controls in all neuropsychological measures. Corpus callosum area was correlated with cognitive flexibility, processing speed, composite memory, executive functions, psychomotor speed, reaction time and phonological verbal fluency task. Processing speed and composite memory were the most sensitive markers for predicting employment status. Corpus callosum area was the most sensitive MRI marker for memory and processing speed. Corpus callosum atrophy predicts a clinically meaningful cognitive decline, affecting employment status in our SPMS patients.

PIMD: 28576706

rHIgM22 enhances remyelination in the brain of the cuprizone mouse model of demyelination.

Failure of oligodendrocyte precursor cells (OPCs) to differentiate and remyelinate axons is thought to be a major cause of the limited ability of the central nervous system to repair plaques of immune-mediated demyelination in multiple sclerosis (MS). Current therapies for MS aim to lessen the immune response in order to reduce the frequency and severity of attacks, but these existing therapies do not target remyelination or stimulate repair of the damaged tissue. Thus, the promotion of OPC differentiation and remyelination is potentially an important therapeutic goal. Previous studies have shown that a recombinant human-derived monoclonal IgM antibody, designated rHIgM22, promotes remyelination, particularly of the spinal cord in rodent models of demyelination. Here, we examined the effects of rHIgM22 in remyelination in the brain using the mouse model of cuprizone-induced demyelination, which is characterized by spontaneous remyelination. The myelination state of the corpus callosum of cuprizone-fed mice treated with rHIgM22 was examined immediately after the end of the cuprizone diet as well as at different time points during the recovery period with regular food, and compared with that of cuprizone-fed animals treated with either vehicle or human IgM isotype control antibody. Mice fed only regular food were used as controls. We demonstrate that treatment with rHIgM22 accelerated remyelination of the demyelinated corpus callosum. The remyelination-enhancing effects of rHIgM22 were found across different, anatomically distinct regions of the corpus callosum, and followed a spatiotemporal pattern that was similar to that of the spontaneous remyelination process. These enhancing effects were also accompanied by increased differentiation of OPCs into mature oligodendrocytes. Our data indicate strong remyelination-promoting capabilities of rHIgM22 and further support its therapeutic potential in MS.

PIMD: 28566550

Disconnection as a mechanism for social cognition impairment in multiple sclerosis.

To assess the contribution of microstructural normal-appearing white matter (NAWM) damage to social cognition impairment, specifically in the theory of mind (ToM), in multiple sclerosis (MS).We enrolled consecutively 60 patients with MS and 60 healthy controls (HC) matched on age, sex, and education level. All participants underwent ToM testing (Eyes Test, Videos Test) and 3T brain MRI including conventional and diffusion tensor imaging sequences. Tract-based spatial statistics (TBSS) were applied for whole-brain voxel-wise analysis of fractional anisotropy (FA) and mean diffusivity (MD) on NAWM.Patients with MS performed worse on both tasks of ToM compared to HC (Eyes Test 58.7 ± 13.8 vs 81.9 ± 10.4, < 0.001, Hedges g -1.886; Videos Test 75.3 ± 9.3 vs 88.1 ± 7.1, < 0.001, Hedges g -1.537). Performance on ToM tests was correlated with higher values of FA and lower values of MD across widespread white matter tracts. The largest effects (≥90% of voxels with statistical significance) for the Eyes Test were body and genu of corpus callosum, fornix, tapetum, uncinate fasciculus, and left inferior cerebellar peduncle, and for the Videos Test genu and splenium of corpus callosum, fornix, uncinate fasciculus, left tapetum, and right superior fronto-occipital fasciculus.These results indicate that a diffuse pattern of NAWM damage in MS contributes to social cognition impairment in the ToM domain, probably due to a mechanism of disconnection within the social brain network. Gray matter pathology is also expected to have an important role; thus further research is required to clarify the neural basis of social cognition impairment in MS.

PIMD: 28537100

Cerebrospinal fluid neurofilament light levels mark grey matter volume in clinically isolated syndrome suggestive of multiple sclerosis.

Brain atrophy is a known marker of irreversible tissue damage in multiple sclerosis (MS). Cerebrospinal fluid (CSF) osteopontin (OPN) and neurofilament light chain (NF-L) have been proposed as candidate surrogate markers of inflammatory and neurodegenerative processes in MS.To evaluate the relationship between CSF NF-L and OPN levels and brain grey and white matter volumes in patients with clinically isolated syndrome (CIS) suggestive of MS.A total of 41 CIS patients and 30 neurological controls (NCs) were included. CSF NF-L and OPN were measured by commercial ELISA. Measures of brain volume (normalized brain volume (NBV), normalized grey matter volume (NGV), peripheral grey matter volume (PGV), normalized white matter volume (WMV), and ventricular volume) were obtained by SIENAX. Corpus callosum index (CCI) was calculated. Brain volumes were categorized into 'high' and 'low' according to the median value.CSF NF-L and OPN levels were higher in CIS patients in comparison with NCs. CIS patients with 'low' TGV, PGV, and TBV showed higher CSF NF-L levels than CIS patients with 'high' brain volumes. TGV and PGV correlated inversely with NF-L levels, whereas CCI was inversely related to OPN levels. CSF NF-L was the only independent predictor of TGV and PGV.CSF NF-L tracks mainly grey matter damage in patients with CIS suggestive of MS.

PIMD: 28499934

Matrine promotes oligodendrocyte development in CNS autoimmunity through the PI3K/Akt signaling pathway.

Matrine (MAT), a quinolizidine alkaloid derived from the herb Radix Sophorae flavescens, has been recently found to be beneficial in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis, mainly through its anti-inflammatory effect. In the present study, we tested the effect of MAT on ongoing EAE and defined possible mechanisms underlying its effects on myelination and oligodendrocytes.EAE was induced in C57BL/6 mice and MAT treatment was started at disease onset. Clinical scores were monitored daily; spinal cords and the corpus callosum brain region of mice were harvested on day 23 p.i. for inflammatory infiltration and demyelination of the central nervous system. Myelin content and the development of oligodendrocytes and their precursors were determined by immunostaining, and expression of p-Akt, p-mTOR, p-PI3K, and p-P70S6 was determined by Western blot.MAT effectively suppressed EAE severity and increased the expression of proteolipid protein, a myelin protein that is a marker of CNS myelin. MAT treatment largely increased the number of mature oligodendrocytes, and significantly activated the PI3K/Akt/mTOR signaling pathway, which is required for oligodendrocyte survival and axon myelination.These findings demonstrate a beneficial effect of MAT on oligodendrocyte differentiation and myelination during EAE, most likely through activating the PI3K/Akt/mTOR signaling pathway.

PIMD: 28466255

Formyl Peptide Receptor 1-Mediated Glial Cell Activation in a Mouse Model of Cuprizone-Induced Demyelination.

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system that is characterized by myelin abnormalities, oligodendrocyte pathology, and concomitant glia activation. Unclear are the factors triggering gliosis and demyelination. New findings suggest an important role of the innate immune response in the initiation and progression of active demyelinating lesions. The innate immune response is induced by pathogen-associated or danger-associated molecular patterns, which are identified by pattern recognition receptors (PRRs), including the G-protein coupled with formyl peptide receptors (FPRs). Glial cells, the immune cells of the central nervous system, also express the PRRs. In this study, we used the cuprizone mice model to investigate the expression of the FPR1 in the course of cuprizone-induced demyelination In addition, we used FPR1-deficient mice to analyze glial cell activation through immunohistochemistry and real-time RT-PCR in cuprizone model. Our results revealed a significantly increased expression of FPR1 in the cortex of cuprizone-treated mice. FPR1-deficient mice showed a slight but significant decrease of demyelination in the corpus callosum compared to the wild-type mice. Furthermore, FPR1 deficiency resulted in reduced glial cell activation and mRNA expression of microglia/macrophages markers, as well as pro- and anti-inflammatory cytokines in the cortex, compared to wild-type mice after cuprizone-induced demyelination. Combined together, these results suggest that the FPR1 is an important part of the innate immune response in the course of cuprizone-induced demyelination.

PIMD: 28450431

Thalamic Iron Differentiates Primary-Progressive and Relapsing-Remitting Multiple Sclerosis.

Potential differences between primary progressive and relapsing remitting multiple sclerosis are the subject of ongoing controversial discussions. The aim of this work was to determine whether and how primary-progressive and relapsing-remitting multiple sclerosis subtypes differ regarding conventional MR imaging parameters, cerebral iron deposits, and their association with clinical status.We analyzed 24 patients with primary-progressive MS, 80 with relapsing-remitting MS, and 20 healthy controls with 1.5T MR imaging for assessment of the conventional quantitative parameters: T2 lesion load, T1 lesion load, brain parenchymal fraction, and corpus callosum volume. Quantitative susceptibility mapping was performed to estimate iron concentration in the deep gray matter.Decreased susceptibility within the thalamus in relapsing-remitting MS compared with primary-progressive MS was the only significant MR imaging difference between these MS subtypes. In the relapsing-remitting MS subgroup, the Expanded Disability Status Scale score was positively associated with conventional parameters reflecting white matter lesions and brain atrophy and with iron in the putamen and caudate nucleus. A positive association with putaminal iron and the Expanded Disability Status Scale score was found in primary-progressive MS.Susceptibility in the thalamus might provide additional support for the differentiation between primary-progressive and relapsing-remitting MS. That the Expanded Disability Status Scale score was associated with conventional MR imaging parameters and iron concentrations in several deep gray matter regions in relapsing-remitting MS, while only a weak association with putaminal iron was observed in primary-progressive MS suggests different driving forces of disability in these MS subtypes.

PIMD: 28447514

Neuroprotective effects of ellagic acid on cuprizone-induced acute demyelination through limitation of microgliosis, adjustment of CXCL12/IL-17/IL-11 axis and restriction of mature oligodendrocytes apoptosis.

Ellagic acid (EA) is a natural phenol antioxidant with various therapeutic activities. However, the efficacy of EA has not been examined in neuropathologic conditions.In vivo neuroprotective effects of EA on cuprizone (cup)-induced demyelination were evaluated.C57BL/6 J mice were fed with chow containing 0.2% cup for 4 weeks to induce oligodendrocytes (OLGs) depletion predominantly in the corpus callosum (CC). EA was administered at different doses (40 or 80 mg/kg body weight/day/i.p.) from the first day of cup diet. Oligodendrocytes apoptosis [TUNEL assay and myelin oligodendrocyte glycoprotein (MOG)/caspase-3 cells), gliosis (H&E staining, glial fibrillary acidic protein (GFAP) and macrophage-3 (Mac-3) cells) and inflammatory markers (interleukin 17 (IL-17), interleukin 11 (IL-11) and stromal cell-derived factor 1 α (SDF-1α) or CXCL12] during cup intoxication were examined.High dose of EA (EA-80) increased mature oligodendrocytes population (MOG cells, $p < 0.001$), and decreased apoptosis ($p < 0.05$) compared with the cup mice. Treatment with both EA doses did not show any considerable effects on the expression of CXCL12, but significantly down-regulated the expression of IL-17 and up-regulated the expression of IL-11 in mRNA levels compared with the cup mice. Only treatment with EA-80 significantly decreased the population of active macrophage (MAC-3 cells, $p < 0.001$) but not reactive astrocytes (GFAP cells) compared with the cup mice.In this model, EA-80 effectively reduces lesions via reduction of neuroinflammation and toxic effects of cup on mature OLGs. EA is a suitable therapeutic agent for moderate brain damage in neurodegenerative diseases such as multiple sclerosis.

PIMD: 28438714

The effect of morphological and microstructural integrity of the corpus callosum on cognition, fatigue and depression in mildly disabled MS patients.

To assess the value of callosal morphological and microstructural integrity in assessing different cognitive domains, fatigue and depression in mildly disabled multiple sclerosis (MS) patients.We assessed 29 mildly disabled MS patients and 15 healthy controls using 3T magnetic resonance images (T1-weighted, FLAIR and DTI) and neuropsychological tests assessing different cognitive functions, depression and fatigue. We compared the added value of morphological measures (corpus callosum area corrected for total intracranial volume, index, circularity and the more detailed thickness profile) and diffusion features (fractional anisotropy and mean diffusivity) in multilinear models including standard clinical and whole-brain parameters in assessing neuropsychological scores.Even in mildly disabled MS patients, a significant reduction of the corpus callosum ($p<0.001$) was observed in comparison to healthy controls. Callosal area, index and circularity were significantly ($p<0.002$) related to whole-brain white matter volume, T2 lesion load and deep grey matter volume, but not with cortical grey matter. The combination of commonly used imaging and clinical parameters explained between 7% (Fatigue) and 50% (processing speed, verbal memory) of the adjusted variance. Inclusion of the mean diffusivity increased the adjusted R significantly to 69% ($p=0.004$) and 71% ($p=0.002$) for visuospatial and verbal memory respectively.Our results show that callosal features may be used as an alternative to measuring whole-brain volumes. Furthermore, the microstructural integrity of the corpus callosum can help to predict an MS patient's memory performance.

PIMD: 28436460

Histological validation of fast macromolecular proton fraction mapping as a quantitative myelin imaging method in the cuprizone demyelination model.

Cuprizone-induced demyelination in mice is a frequently used model in preclinical multiple sclerosis research. A recent quantitative clinically-targeted MRI method, fast macromolecular proton fraction (MPF) mapping demonstrated a promise as a myelin biomarker in human and animal studies with a particular advantage of sensitivity to both white matter (WM) and gray matter (GM) demyelination. This study aimed to histologically validate the capability of MPF mapping to quantify myelin loss in brain tissues using the cuprizone demyelination model. Whole-brain MPF maps were obtained in vivo on an 11.7T animal MRI scanner from 7 cuprizone-treated and 7 control C57BL/6 mice using the fast single-point synthetic-reference method. Brain sections were histologically stained with Luxol Fast Blue (LFB) for myelin quantification. Significant ($p < 0.05$) demyelination in cuprizone-treated animals was found according to both LFB staining and MPF in all anatomical structures (corpus callosum, anterior commissure, internal capsule, thalamus, caudoputamen, and cortex). MPF strongly correlated with quantitative histology in all animals ($r = 0.95$, $p < 0.001$) as well as in treatment and control groups taken separately ($r = 0.96$, $p = 0.002$ and $r = 0.93$, $p = 0.007$, respectively). Close agreement between histological myelin staining and MPF suggests that fast MPF mapping enables robust and accurate quantitative assessment of demyelination in both WM and GM.

PIMD: 28414816

Fourier transform power spectrum is a potential measure of tissue alignment in standard MRI: A multiple sclerosis study.

Loss of tissue coherency in brain white matter is found in many neurological diseases such as multiple sclerosis (MS). While several approaches have been proposed to evaluate white matter coherency including fractional anisotropy and fiber tracking in diffusion-weighted imaging, few are available for standard magnetic resonance imaging (MRI). Here we present an image post-processing method for this purpose based on Fourier transform (FT) power spectrum. T2-weighted images were collected from 19 patients (10 relapsing-remitting and 9 secondary progressive MS) and 19 age- and gender-matched controls. Image processing steps included: computation, normalization, and thresholding of FT power spectrum; determination of tissue alignment profile and dominant alignment direction; and calculation of alignment complexity using a new measure named angular entropy. To test the validity of this method, we used a highly organized brain white matter structure, corpus callosum. Six regions of interest were examined from the left, central and right aspects of both genu and splenium. We found that the dominant orientation of each ROI derived from our method was significantly correlated with the predicted directions based on anatomy. There was greater angular entropy in patients than controls, and a trend to be greater in secondary progressive MS patients. These findings suggest that it is possible to detect tissue alignment and anisotropy using traditional MRI, which are routinely acquired in clinical practice. Analysis of FT power spectrum may become a new approach for advancing the evaluation and management of patients with MS and similar disorders. Further confirmation is warranted.

PIMD: 28396954

The association between retinal nerve fibre layer thickness and corpus callosum index in different clinical subtypes of multiple sclerosis.

The objective of this paper is to evaluate the association between physical disability in multiple sclerosis (MS) patients, the thickness of the retinal nerve fibre layer (RNFL) and corpus callosum volumes, as expressed by the corpus callosum index (CCI). This study was based on a cohort of 212 MS patients and 52 healthy control subjects, who were age and gender matched. The MS patients included 144 women and 177 relapsing-remitting MS (RRMS) patients. Peripapillary and volumetric optical coherence tomography (OCT) scans of the macula were performed using spectral-domain OCT technology. All magnetic resonance imaging (MRI) scans were performed using 1.5-T systems. CCI and RNFL were lower in MS than healthy control subjects (0.341 versus 0.386, $p < 0.01$ and 92.1 versus 105.0, $p < 0.01$). In addition, CCI correlated with RNFL ($r = 0.464$, $p < 0.01$). This was also true for the subgroup of patients with no history of optic neuritis (ON). There is a correlation between the thickness of the RNFL and CCI values in MS patients with no history of ON, which suggests that OCT might be a suitable marker for neurodegeneration in MS clinical trials.

PIMD: 28394195

Composite MRI measures and short-term disability in patients with clinically isolated syndrome suggestive of MS.

The use of composite magnetic resonance imaging (MRI) measures has been suggested to better explain disability in patients with multiple sclerosis (MS). However, little is known about the utility of composite scores at the earliest stages of the disease.To investigate whether, in patients with clinically isolated syndrome (CIS), a composite MRI measure, rather than the single metrics, would explain conversion to MS and would better correlate with disability at baseline and at 1 year of follow-up.Corticospinal tract (CST), corpus callosum (CC) and optic radiation (OR) volume, fractional anisotropy (FA), and mean diffusivity (MD) values were measured in 27 CIS patients and 24 healthy controls (HCs). Z-scores of FA, MD, and tract volume measures were calculated in patients, based on the corresponding measures obtained from HCs, and then combined in a composite score for each tract. Correlations between Z-scores at baseline and both the Expanded Disability Status Scale (EDSS) at baseline and at follow-up (FU-EDSS) were investigated.Only CST, CC, and OR composite scores as well as the CST volume were significantly associated with FU-EDSS ($p = 0.005$, $p = 0.007$, $p = 0.020$, and $p = 0.010$, respectively).The combination of MRI measures rather than the individual metrics better captured the association between tissue damage in both the CC, OR and CST and short-term follow-up disability.

PIMD: 28386689

Corpus callosum involvement: a useful clue for differentiating Fabry Disease from Multiple Sclerosis.

Multiple sclerosis (MS) has been proposed as a possible differential diagnosis for Fabry disease (FD). The aim of this work was to evaluate the involvement of corpus callosum (CC) on MR images and its possible role as a radiological sign to differentiate between FD and MS.In this multicentric study, we retrospectively evaluated the presence of white matter lesions (WMLs) on the FLAIR images of 104 patients with FD and 117 patients with MS. The incidence of CC-WML was assessed in the two groups and also in a subgroup of 37 FD patients showing neurological symptoms.WMLs were detected in 50 of 104 FD patients (48.1%) and in all MS patients. However, a lesion in the CC was detected in only 3 FD patients (2.9%) and in 106 MS patients (90.6%). In the FD subgroup with neurological symptoms, WMLs were present in 26 of 37 patients (70.3%), with two subjects (5.4%) showing a definite callosal lesion.FD patients have a very low incidence of CC involvement on conventional MR images compared to MS, independently from the clinical presentation and the overall degree of WM involvement. Evaluating the presence of CC lesions on brain MR scans can be used as a radiological sign for a differential diagnosis between MS and FD, rapidly addressing the physician toward a correct diagnosis and subsequent treatment options.

PIMD: 28385127

Retinal nerve fiber layer thickness and neuropsychiatric manifestations in systemic lupus erythematosus.

Background Cognitive impairment is frequent in systemic lupus erythematosus. Atrophy of the corpus callosum and hippocampus have been reported in patients with systemic lupus erythematosus, and diffusion tensor imaging studies have shown impaired white matter integrity, suggesting that white matter damage in systemic lupus erythematosus may underlie the cognitive impairment as well as other neuropsychiatric systemic lupus erythematosus manifestations. Retinal nerve fiber layer thickness, as assessed by optical coherence tomography, has been suggested as a biomarker for white matter damage in neurologic disorders such as multiple sclerosis, Alzheimer's disease and Parkinson's disease. Retinal nerve fiber layer thinning may occur early, even in patients with mild clinical symptoms. Aim The objective of this study was to assess the association of retinal nerve fiber layer thickness, as a biomarker of white matter damage in systemic lupus erythematosus patients, with neuropsychiatric systemic lupus erythematosus manifestations, including cognitive impairment. Methods Twenty-one consecutive patients with systemic lupus erythematosus underwent neuropsychological testing using a validated computerized battery of tests as well as the Rey-Auditory verbal learning test. All 21 patients, as well as 11 healthy, age matched controls, underwent optical coherence tomography testing to assess retinal nerve fiber layer thickness. Correlations between retinal nerve fiber layer thickness and results in eight cognitive domains assessed by the computerized battery of tests as well as the Rey-Auditory verbal learning test were assessed in patients with systemic lupus erythematosus, with and without neuropsychiatric systemic lupus erythematosus, and compared to retinal nerve fiber layer thickness in healthy controls. Results No statistically significant correlation was found between retinal nerve fiber layer thickness in patients with systemic lupus erythematosus as compared to healthy controls. When evaluating by subgroups, no correlation was found between patients with or without neuropsychiatric systemic lupus erythematosus or cognitive impairment and retinal nerve fiber layer thickness. Conclusion Retinal nerve fiber layer thickness of systemic lupus erythematosus patients was not found to be statistically different compared to controls. Within systemic lupus erythematosus patients there was no correlation between retinal nerve fiber layer thickness and cognitive impairment or other neuropsychiatric systemic lupus erythematosus manifestations.

PIMD: 28277551

Comparison of Diffuse Weighted Imaging and Fluid Attenuation Inversion Recovery Sequences of MRI in Brain Multiple Sclerosis Plaques Detection.

Suitable magnetic resonance imaging (MRI) techniques from conventional to new devices can help physicians in diagnosis and follow up of Multiple Sclerosis (MS) patients. The aim of present research was to compare effectiveness of Fluid Attenuation Inversion Recovery (FLAIR) sequence of conventional MRI and Diffuse Weighted Imaging (DWI) sequence as a new technique in detection of brain MS plaques.In this analytic cross sectional study, sample size was assessed as 40 people to detect any significant difference between two sequences with a level of 0.05. DWI and FLAIR sequences of without contrast brain MRI of consecutive MS patients referred to MRI center of Shahid Sadoughi Hospital, Yazd, Iran from January to May 2012, were evaluated.Thirty-two females and 8 males with mean age of 35.20±9.80 yr (range = 11-66 yr) were evaluated and finally 340 plaques including 127(37.2%) in T2WI, 127(37.2%) in FLAIR, 63(18.5%) in DWI and 24(7.1%) in T1WI were detected. FLAIR sequence was more efficient than DWI in detection of brain MS plaques, oval, round, amorphous plaque shapes, frontal and occipital lobes, periventricular, intracapsular, corpus callosum, centrum semiovale, subcortical, basal ganglia plaques and diameter of detected MS plaques in DWI sequence was smaller than in FLAIR.Old lesion can be detected by conventional MRI and new techniques might be more useful in early inflammatory phase of MS and assessment of experimental treatments.

PIMD: 28254088

An effective method for computerized prediction and segmentation of multiple sclerosis lesions in brain MRI.

Multiple sclerosis is one of the major diseases and the progressive MS lesion formation often leads to cognitive decline and physical disability. A quick and perfect method for estimating the number and size of MS lesions in the brain is very important in estimating the progress of the disease and effectiveness of treatments. But, the accurate identification, characterization and quantification of MS lesions in brain magnetic resonance imaging (MRI) is extremely difficult due to the frequent change in location, size, morphology variation, intensity similarity with normal brain tissues, and inter-subject anatomical variation of brain images.This paper presents a method where adaptive background generation and binarization using global threshold are the key steps for MS lesions detection and segmentation. After performing three phase level set, we add third phase segmented region with contour of brain to connect the normal tissues near the boundary. Then remove all lesions except maximum connected area and corpus callosum of the brain to generate adaptive background. The binarization method is used to select threshold based on entropy and standard deviation preceded by non-gamut image enhancement. The background image is then subtracted from binarized image to find out segmented MS lesions.The step of subtraction of background from binarized image does not generate spurious lesions. Binarization steps correctly identify the MS lesions and reduce over or under segmentation. The average Kappa index is 94.88%, Jacard index is 90.43%, correct detection ration is 92.60284%, false detection ratio is 2.55% and relative area error is 5.97% for proposed method. Existing recent methods does not have such accuracy and low value of error rate both mathematically as well as visually due to many spurious lesions generation and over segmentation problems.Proposed method accurately identifies the size and number of lesions as well as location of lesions detection as a radiologist performs. The adaptability of the proposed method creates a number of potential opportunities for use in clinical practice for the detection of MS lesions in MRI. Proposed method gives an improved accuracy and low error compare to existing recent methods.

PIMD: 28239545

{'sub': '2', '#text': 'New rapid, accurate T quantification detects pathology in normal-appearing brain regions of relapsing-remitting MS patients.'}

Quantitative T mapping may provide an objective biomarker for occult nervous tissue pathology in relapsing-remitting multiple sclerosis (RRMS). We applied a novel echo modulation curve (EMC) algorithm to identify T changes in normal-appearing brain regions of subjects with RRMS (N = 27) compared to age-matched controls (N = 38).The EMC algorithm uses Bloch simulations to model T decay curves in multi-spin-echo MRI sequences, independent of scanner, and scan-settings. T values were extracted from normal-appearing white and gray matter brain regions using both expert manual regions-of-interest and user-independent FreeSurfer segmentation.Compared to conventional exponential T modeling, EMC fitting provided more accurate estimations of T with less variance across scans, MRI systems, and healthy individuals. Thalamic T was increased 8.5% in RRMS subjects (< 0.001) and could be used to discriminate RRMS from healthy controls well (AUC = 0.913). Manual segmentation detected both statistically significant increases (corpus callosum & temporal stem) and decreases (posterior limb internal capsule) in T associated with RRMS diagnosis (all < 0.05). In healthy controls, we also observed statistically significant T differences for different white and gray matter structures.The EMC algorithm precisely characterizes T values, and is able to detect subtle T changes in normal-appearing brain regions of RRMS patients. These presumably capture both axon and myelin changes from inflammation and neurodegeneration. Further, T variations between different brain regions of healthy controls may correlate with distinct nervous tissue environments that differ from one another at a mesoscopic length-scale.

PIMD: 28231842

Tissue-type plasminogen activator exerts EGF-like chemokinetic effects on oligodendrocytes in white matter (re)myelination.

The ability of oligodendrocyte progenitor cells (OPCs) to give raise to myelin forming cells during developmental myelination, normal adult physiology and post-lesion remyelination in white matter depends on factors which govern their proliferation, migration and differentiation. Tissue plasminogen activator (tPA) is a serine protease expressed in the central nervous system (CNS), where it regulates cell fate. In particular, tPA has been reported to protect oligodendrocytes from apoptosis and to facilitate the migration of neurons. Here, we investigated whether tPA can also participate in the migration of OPCs during CNS development and during remyelination after focal white matter lesion.OPC migration was estimated by immunohistological analysis in spinal cord and corpus callosum during development in mice embryos (E13 to P0) and after white matter lesion induced by the stereotactic injection of lysolecithin in adult mice (1 to 21 days post injection). Migration was compared in these conditions between wild type and tPA knock-out animals. The action of tPA was further investigated in an in vitro chemokinesis assay.OPC migration along vessels is delayed in tPA knock-out mice during development and during remyelination. tPA enhances OPC migration via an effect dependent on the activation of epidermal growth factor receptor.Endogenous tPA facilitates the migration of OPCs during development and during remyelination after white matter lesion by the virtue of its epidermal growth factor-like domain.

PIMD: 28225274

A Rational Design of a Selective Inhibitor for Kv1.1 Channels Prevalent in Demyelinated Nerves That Improves Their Impaired Axonal Conduction.

K channels containing Kv1.1 α subunits, which become prevalent at internodes in demyelinated axons, may underlie their dysfunctional conduction akin to muscle weakness in multiple sclerosis. Small inhibitors were sought with selectivity for the culpable hyper-polarizing K currents. Modeling of interactions with the extracellular pore in a Kv1.1-deduced structure identified diaryldi(2-pyrrolyl)methane as a suitable scaffold with optimized alkyl ammonium side chains. The resultant synthesized candidate [2,2'-((5,5'(di-p-topyldiaryldi(2-pyrrolyl)methane)bis(2,2'carbonyl)bis(azanediyl)) diethaneamine·2HCl] (8) selectively blocked Kv1.1 channels (IC ≈ 15 μM) recombinantly expressed in mammalian cells, induced a positive shift in the voltage dependency of K current activation, and slowed its kinetics. It preferentially inhibited channels containing two or more Kv1.1 subunits regardless of their positioning in concatenated tetramers. In slices of corpus callosum from mice subjected to a demyelination protocol, this novel inhibitor improved neuronal conduction, highlighting its potential for alleviating symptoms in multiple sclerosis.

PIMD: 28217397

A5 segment aneurysm of the anterior cerebral artery, imbedded into the body of the corpus callosum: A case report.

The A5 segment aneurysms of the anterior cerebral artery are rare, approximately 0.5% of all intracranial aneurysms. They are small with a wide base located in the midline, with the domes mostly projecting upward or backward.The authors describe a unique case of A5 segment aneurysm, with the dome embedded into the body of the corpus callosum. This 41-year-old female was admitted to the neurology department for possible multiple sclerosis investigation. Computed tomography angiogram (CTA) revealed a 4-mm right-sided pericallosal artery aneurysm, with rare configuration, which was caudally projected, embedded into the body of the corpus callosum. Considering the family history, patient underwent a prophylactic ligation surgery. The postoperative CT and CTA showed no complication and successful occlusion of the aneurysm with no ischemia or hemorrhage in the corpus callosum.To the best of our knowledge, this is the first case of an aneurysm with this configuration. Our rare case of A5 segment aneurysm demonstrates the importance of planning of the surgery, choosing the appropriate approach, and knowing the detailed anatomy of the region, as well as the necessity of microsurgical clipping of small unruptured AdistAs.

PIMD: 28192470

Differentiation of oligodendrocyte progenitor cells from dissociated monolayer and feeder-free cultured pluripotent stem cells.

Oligodendrocytes myelinate axons and form myelin sheaths in the central nervous system. The development of therapies for demyelinating diseases, including multiple sclerosis and leukodystrophies, is a challenge because the pathogenic mechanisms of disease remain poorly understood. Primate pluripotent stem cell-derived oligodendrocytes are expected to help elucidate the molecular pathogenesis of these diseases. Oligodendrocytes have been successfully differentiated from human pluripotent stem cells. However, it is challenging to prepare large amounts of oligodendrocytes over a short amount of time because of manipulation difficulties under conventional primate pluripotent stem cell culture methods. We developed a proprietary dissociated monolayer and feeder-free culture system to handle pluripotent stem cell cultures. Because the dissociated monolayer and feeder-free culture system improves the quality and growth of primate pluripotent stem cells, these cells could potentially be differentiated into any desired functional cells and consistently cultured in large-scale conditions. In the current study, oligodendrocyte progenitor cells and mature oligodendrocytes were generated within three months from monkey embryonic stem cells. The embryonic stem cell-derived oligodendrocytes exhibited in vitro myelinogenic potency with rat dorsal root ganglion neurons. Additionally, the transplanted oligodendrocyte progenitor cells differentiated into myelin basic protein-positive mature oligodendrocytes in the mouse corpus callosum. This preparative method was used for human induced pluripotent stem cells, which were also successfully differentiated into oligodendrocyte progenitor cells and mature oligodendrocytes that were capable of myelinating rat dorsal root ganglion neurons. Moreover, it was possible to freeze, thaw, and successfully re-culture the differentiating cells. These results showed that embryonic stem cells and human induced pluripotent stem cells maintained in a dissociated monolayer and feeder-free culture system have the potential to generate oligodendrocyte progenitor cells and mature oligodendrocytes in vitro and in vivo. This culture method could be applied to prepare large amounts of oligodendrocyte progenitor cells and mature oligodendrocytes in a relatively short amount of time.

PIMD: 28188915

Machine learning based compartment models with permeability for white matter microstructure imaging.

Some microstructure parameters, such as permeability, remain elusive because mathematical models that express their relationship to the MR signal accurately are intractable. Here, we propose to use computational models learned from simulations to estimate these parameters. We demonstrate the approach in an example which estimates water residence time in brain white matter. The residence time τ of water inside axons is a potentially important biomarker for white matter pathologies of the human central nervous system, as myelin damage is hypothesised to affect axonal permeability, and thus τ. We construct a computational model using Monte Carlo simulations and machine learning (specifically here a random forest regressor) in order to learn a mapping between features derived from diffusion weighted MR signals and ground truth microstructure parameters, including τ. We test our numerical model using simulated and in vivo human brain data. Simulation results show that estimated parameters have strong correlations with the ground truth parameters (R={0.88,0.95,0.82,0.99}) for volume fraction, residence time, axon radius and diffusivity respectively), and provide a marked improvement over the most widely used Kärger model (R={0.75,0.60,0.11,0.99}). The trained model also estimates sensible microstructure parameters from in vivo human brain data acquired from healthy controls, matching values found in literature, and provides better reproducibility than the Kärger model on both the voxel and ROI level. Finally, we acquire data from two Multiple Sclerosis (MS) patients and compare to the values in healthy subjects. We find that in the splenium of corpus callosum (CC-S) the estimate of the residence time is 0.57±0.05s for the healthy subjects, while in the MS patient with a lesion in CC-S it is 0.33±0.12s in the normal appearing white matter (NAWM) and 0.19±0.11s in the lesion. In the corticospinal tracts (CST) the estimate of the residence time is 0.52±0.09s for the healthy subjects, while in the MS patient with a lesion in CST it is 0.56±0.05s in the NAWM and 0.13±0.09s in the lesion. These results agree with our expectations that the residence time in lesions would be lower than in NAWM because the loss of myelin should increase permeability. Overall, we find parameter estimates in the two MS patients consistent with expectations from the pathology of MS lesions demonstrating the clinical potential of this new technique.

PIMD: 28177496

Synaptophysin Is a Reliable Marker for Axonal Damage.

Synaptophysin is an abundant membrane protein of synaptic vesicles. The objective of this study was to determine the utility of identifying synaptophysin accumulations (spheroids/ovoids/bulbs) in CNS white matter as an immunohistochemical marker of axonal damage in demyelinating and neuroinflammatory conditions. We studied the cuprizone toxicity and Theiler's murine encephalomyelitis virus (TMEV) infection models of demyelination and analyzed CNS tissue from patients with multiple sclerosis (MS). Synaptophysin colocalized with the amyloid precursor protein (APP), a well-known marker of axonal damage. In the cuprizone model, numerous pathological synaptophysin/APP-positive spheroids/ovoids were identified in the corpus callosum at the onset of demyelination; the extent of synaptophysin/APP-positive vesicle aggregates correlated with identified reactive microglia; during late and chronic demyelination, the majority of synaptophysin/APP-positive spheroids/ovoids resolved but a few remained, indicating persistent axonal damage; in the remyelination phase, scattered large synaptophysin/APP-positive bulbs persisted. In the TMEV model, only a few large- to medium-sized synaptophysin/APP-positive bulbs were found in demyelinated areas. In MS patient tissue samples, the bulbs appeared exclusively at the inflammatory edges of lesions. In conclusion, our data suggest that synaptophysin as a reliable marker of axonal damage in the CNS in inflammatory/demyelinating conditions.

PIMD: 28128219

Astrocyte-derived tissue Transglutaminase affects fibronectin deposition, but not aggregation, during cuprizone-induced demyelination.

Astrogliosis as seen in Multiple Sclerosis (MS) develops into astroglial scarring, which is beneficial because it seals off the site of central nervous system (CNS) damage. However, astroglial scarring also forms an obstacle that inhibits axon outgrowth and (re)myelination in brain lesions. This is possibly an important cause for incomplete remyelination in the CNS of early stage MS patients and for failure in remyelination when the disease progresses. In this study we address whether under demyelinating conditions in vivo, tissue Transglutaminase (TG2), a Ca -dependent enzyme that catalyses posttranslational modification of proteins, contributes to extracellular matrix (ECM) deposition and/or aggregation. We used the cuprizone model for de- and remyelination. TG2 immunoreactivity and enzymatic activity time-dependently appeared in astrocytes and ECM, respectively, in the corpus callosum of cuprizone-treated mice. Enhanced presence of soluble monomeric and multimeric fibronectin was detected during demyelination, and fibronectin immunoreactivity was slightly decreased in cuprizone-treated TG2 mice. In vitro TG2 overexpression in astrocytes coincided with more, while knock-down of TG2 with less fibronectin production. TG2 contributes, at least partly, to fibronectin production, and may play a role in fibronectin deposition during cuprizone-induced demyelination. Our observations are of interest in understanding the functional implications of TG2 during astrogliosis.

PIMD: 28124770

The Effect of Stereotactic Injections on Demyelination and Remyelination: a Study in the Cuprizone Model.

Remyelination is the natural repair mechanism in demyelinating disorders of the central nervous system (CNS) such as multiple sclerosis. Several animal models have been used to study demyelination and remyelination. Among toxic animal models, oral administration of the toxin cuprizone leads to white and gray matter demyelination. In contrast, focal demyelination models include the stereotactic application of a toxin such as lysolecithin or ethidium bromide. The injection procedure generates a local disruption of the blood-brain barrier (BBB) and might thus trigger a local inflammatory reaction and consequently may influence demyelination and remyelination. In order to study such consequences, we applied stereotactic injections in the cuprizone model where demyelination and remyelination are mediated independent of this procedure. Immunohistochemistry was performed to detect the presence of lymphocytes and activated glial cells in the injection area. Blood protein stainings were used to assess the integrity of the BBB and myelin staining to evaluate demyelination and remyelination processes. Stereotactic injection led to a local disruption of the BBB as shown by local extravasation of blood proteins. Along the injection canal, T and B lymphocytes could be detected and there was a tendency of a higher microgliosis and astrocytosis. However, these changes did not influence demyelination and remyelination processes at the site of injection, in the corpus callosum, or in the cerebral cortex. Our results suggest that a local stereotactic injection has no major impact on CNS demyelination and remyelination.

PIMD: 28119561

Electroacupuncture Promotes Remyelination after Cuprizone Treatment by Enhancing Myelin Debris Clearance.

Promoting remyelination is crucial for patients with demyelinating diseases including multiple sclerosis. However, it is still a circuitous conundrum finding a practical remyelinating therapy. Electroacupuncture (EA), originating from traditional Chinese medicine (TCM), has been widely used to treat CNS diseases all over the world, but the role of EA in demyelinating diseases is barely known. In this study, we examined the remyelinating properties and mechanisms of EA in cuprizone-induced demyelinating model, a CNS demyelinating murine model of multiple sclerosis. By feeding C57BL/6 mice with chow containing 0.2% cuprizone for 5 weeks, we successfully induce demyelination as proved by weight change, beam test, pole test, histomorphology, and Western Blot. EA treatment significantly improves the neurobehavioral performance at week 7 (2 weeks after withdrawing cuprizone chow). RNA-seq and RT-PCR results reveal up-regulated expression of myelin-related genes, and the expression of myelin associated protein (MBP, CNPase, and O4) are also increased after EA treatment, indicating therapeutic effect of EA on cuprizone model. It is widely acknowledged that microglia exert phagocytic effect on degraded myelin debris and clear these detrimental debris, which is a necessary process for subsequent remyelination. We found the remyelinating effect of EA is associated with enhanced clearance of degraded myelin debris as detected by dMBP staining and red oil O staining. Our further studies suggest that more microglia assemble in demyelinating area (corpus callosum) during the process of EA treatment, and cells inside corpus callosum are mostly in a plump, ameboid, and phagocytic shape, quite different from the ramified cells outside corpus callosum. RNA-seq result also unravels that most genes relating to positive regulation of phagocytosis (GO:0050766) are up-regulated, indicating enhanced phagocytic process after EA treatment. During the process of myelin debris clearance, microglia tend to change their phenotype toward M2 phenotype. Thus, we also probed into the phenotype of microglia in our study. Immuno-staining results show increased expression of CD206 and Arg1, and the ratio of CD206/CD16/32 are also higher in EA group. In conclusion, these results demonstrate for the first time that EA enhances myelin debris removal from activated microglia after demyelination, and promotes remyelination.

PIMD: 28090127

Parametrization of white matter manifold-like structures using principal surfaces.

In this manuscript, we are concerned with data generated from a diffusion tensor imaging (DTI) experiment. The goal is to parameterize manifold-like white matter tracts, such as the corpus callosum, using principal surfaces. The problem is approached by finding a geometrically motivated surface-based representation of the corpus callosum and visualized fractional anisotropy (FA) values projected onto the surface. The method also applies to any other diffusion summary. An algorithm is proposed that 1) constructs the principal surface of a corpus callosum; 2) flattens the surface into a parametric 2D map; 3) projects associated FA values on the map. The algorithm is applied to a longitudinal study containing 466 diffusion tensor images of 176 multiple sclerosis (MS) patients observed at multiple visits. For each subject and visit the study contains a registered DTI scan of the corpus callosum at roughly 20,000 voxels. Extensive simulation studies demonstrate fast convergence and robust performance of the algorithm under a variety of challenging scenarios.

PIMD: 28061362

Developing easy to perform routine MRI measurements as potential surrogates for cognitive impairment in MS.

One of the most frequently disabling symptoms in Multiple Sclerosis (MS) is cognitive impairment which is often insidious in onset and therefore difficult to recognize in the early stages, for both persons with MS and clinicians. A biomarker that would help identify those at risk of cognitive impairment, or with only mild impairment, would be a useful tool for clinicians. Using MRI, already an integral tool in the diagnosis and monitoring of disease activity in MS, would be ideal. Thus, this study aimed to determine if simple measures on routine MRI could serve as potential biomarkers for cognitive impairment in MS.We retrospectively identified 51 persons with MS who had a cognitive assessment and MRI within six months of the MRI. Simple linear measurements of the hippocampi, bifrontral and third ventricular width, bicaudate width and the anterior, mid and posterior corpus callosum were made. Pearson's correlations examined the relationship between these MRI measures and cognitive tests, and MRI measures were compared in persons with MS who were either normal or cognitively impaired on objective cognitive tests using Analysis of Covariance (ANCOVA).Bicaudate span and third ventricular width were both negatively correlated, while corpus callosal measures were positive correlated with cognitive test performance. After controlling for potential confounders, bicaudate span was significant different on measures of immediate recall. Both anterior and posterior corpus collosal measure were significantly different on measures of verbal fluency, immediate recall and higher executive function; while the anterior corpus callosum was also significantly different on processing speed. The middle corpus collosal measure was significantly different on immediate recall and higher executive function.This study presents data demonstrating that simple to apply MRI measures of atrophy may serve as biomarkers for cognitive impairment in persons with MS. Further prospective studies are needed to validate these findings.

PIMD: 28054131

Global and regional annual brain volume loss rates in physiological aging.

The objective is to estimate average global and regional percentage brain volume loss per year (BVL/year) of the physiologically ageing brain. Two independent, cross-sectional single scanner cohorts of healthy subjects were included. The first cohort (n = 248) was acquired at the Medical Prevention Center (MPCH) in Hamburg, Germany. The second cohort (n = 316) was taken from the Open Access Series of Imaging Studies (OASIS). Brain parenchyma (BP), grey matter (GM), white matter (WM), corpus callosum (CC), and thalamus volumes were calculated. A non-parametric technique was applied to fit the resulting age-volume data. For each age, the BVL/year was derived from the age-volume curves. The resulting BVL/year curves were compared between the two cohorts. For the MPCH cohort, the BVL/year curve of the BP was an increasing function starting from 0.20% at the age of 35 years increasing to 0.52% at 70 years (corresponding values for GM ranged from 0.32 to 0.55%, WM from 0.02 to 0.47%, CC from 0.07 to 0.48%, and thalamus from 0.25 to 0.54%). Mean absolute difference between BVL/year trajectories across the age range of 35-70 years was 0.02% for BP, 0.04% for GM, 0.04% for WM, 0.11% for CC, and 0.02% for the thalamus. Physiological BVL/year rates were remarkably consistent between the two cohorts and independent from the scanner applied. Average BVL/year was clearly age and compartment dependent. These results need to be taken into account when defining cut-off values for pathological annual brain volume loss in disease models, such as multiple sclerosis.

PIMD: 28035997

Contribution of Gray and White Matter Abnormalities to Cognitive Impairment in Multiple Sclerosis.

Patients with multiple sclerosis (MS) commonly exhibit cognitive impairments (CI). However, the neural mechanisms underlying CI remain unclear. The current study applied diffusion tensor imaging (DTI) and voxel-based morphometric (VBM) magnetic resonance imaging (MRI) techniques to evaluate differences in white matter (WM) integrity and gray matter (GM) volume between MS patients with CI and MS patients with cognitive preservation (CP). Neuropsychological assessment and MRI were obtained from 39 relapsing-remitting MS (RRMS) patients and 29 healthy controls (HCs). Patients were classified as CI or CP according to cognitive ability, and demographic characteristics and MRI images were compared. Compared with HCs, MS patients exhibited widespread damage in WM integrity, and GM loss in several regions. Compared with CP patients, CI patients exhibited more extensive WM impairments, particularly in the corpus callosum, cerebellar peduncle, corona radiata, optic radiation, superior longitudinal fasciculus, anterior limb of the internal capsule, and cingulate, as well as decreased GM volume in the bilateral caudate, left insula and right temporal lobe. MS patients with CI exhibited more significant structural abnormalities than those with CP. Widespread impairments of WM integrity and selective GM atrophy both appear to be associated with impaired cognition in RRMS.

PIMD: 28009439

Sudan black: a fast, easy and non-toxic method to assess myelin repair in demyelinating diseases.

The search for novel drugs that enhance myelin repair in entities such as multiple sclerosis has top priority in neurological research, not least because remyelination can hinder further neurodegeneration in neuro-inflammatory conditions. Recently, several new compounds with the potential to boost remyelination have been identified using high-throughput in vitro screening methods. However, assessing their potential to enhance remyelination in vivo using plastic embedded semi-thin sections or electron microscopy, even though being the gold standard for assessing remyelination, is toxic, extremely time-consuming and expensive.We screened available myelin dyes for a staining candidate which offers a faster and easier alternative to visualize remyelination in cryo-sections.We identified sudan black as a candidate with excellent myelin resolution and we show that our adapted sudan black staining can demonstrate myelin repair in rodent spinal cord cryosections as reliable as in semithin sections, but much faster, easier, less toxic and less expensive. Besides that, it can resolve the small myelinated axons in the corpus callosum. The staining can yet readily be combined with immunostainings which can be challenging in semithin sections. We validated the method in human spinal cord tissue as well as in experimental demyelination of the rat spinal cord by a lysolecithin time course experiment. As proof-of-principle, we demonstrate that sudan black is able to reliably detect the remyelination enhancing properties of benztropine.Our adapted sudan black staining can be used to rapidly and non-toxically screen for remyelinating therapies in demyelinating diseases.

PIMD: 28009079

Acute disseminated encephalomyelitis in China, Singapore and Japan: a comparison with the USA.

Ethnicity-related differences in the incidence of acute disseminated encephalomyelitis (ADEM) and other demyelinating diseases including multiple sclerosis and neuromyelitis optica spectrum disorders have been reported. Little is reported on the influence of ethnicity and geographical location in ADEM.Medical records of patients who presented with ADEM (ICD-9 323.61 and 323.81) at large referral hospitals in China, Singapore and Japan (years 1992-2015) were retrospectively reviewed and data were collected in a centralized database. Presenting features and outcomes of ADEM were compared between this multi-country Asian cohort and a uniformly collected US cohort using risk differences and risk ratios. Both cohorts were standardized to a 35% pediatric population to facilitate the comparison.There were 83 Asian patients (48 male, 16 pediatric) followed for a median of 2 (25th-75th percentile 1-10) months. Asian patients exhibited a 26% higher prevalence of spinal cord involvement on magnetic resonance imaging [95% confidence interval (CI) 0-52%; P = 0.05; 63% vs. 37%], a 39% lower prevalence of preceding events (95% CI 12-65%; P < 0.01; 33% vs. 72%) and a 23% lower prevalence of corpus callosum involvement (95% CI 7-39%; P < 0.01; 8% vs. 31%). No difference was observed between the two cohorts in the probability of relapse over the first year after disease onset.It is hypothesized that the high proportion of Asian patients with spinal cord lesions relates to genetic vulnerability or the higher incidence of neuromyelitis optica spectrum disorders in Asia or could be a spurious association. ADEM presentations most probably vary across geographical settings or ethnicities.

PIMD: 27995735

Midsagittal corpus callosum area and conversion to multiple sclerosis after clinically isolated syndrome: A multicentre Australian cohort study.

Patients presenting with clinically isolated syndrome (CIS) may proceed to clinically definite multiple sclerosis (CDMS). Midsagittal corpus callosum area (CCA) is a surrogate marker for callosal atrophy, and can be obtained from a standard MRI study. This study explores the relationship between CCA measured at CIS presentation (baseline) and at 5 years post presentation, with conversion from CIS to CDMS. The association between CCA and markers of disability progression is explored.Corpus callosum area was measured on MRI scans at presentation and 5-year review following diagnosis of a first demyelinating event, or evidence of progressive MS, in 143 participants in the Ausimmune/AusLong Study. Relationships between CCA (at baseline and follow-up) and clinical outcomes were assessed.Mean CCA at baseline study was 6.63 cm (SD 1.01). Patients who converted to MS by 5-year review (n = 100) had a significantly smaller mean CCA at follow-up (6.22 vs. 6.74, P = 0.007). Greater CCA reduction was associated with higher annualized relapse rate over follow-up.Baseline CCA obtained from standard MRI protocols may be compared with subsequent MRI examinations as a surrogate for neurodegeneration and cerebral atrophy in patients with MS. This study demonstrates an association between CCA and disability in individuals presenting with CIS who convert to MS.

PIMD: 27932696

Corpus Callosum Structural Integrity Is Associated With Postural Control Improvement in Persons With Multiple Sclerosis Who Have Minimal Disability.

Improvement of postural control in persons with multiple sclerosis (PwMS) is an important target for neurorehabilitation. Although PwMS are able to improve postural performance with training, the neural underpinnings of these improvements are poorly understood.To understand the neural underpinnings of postural motor learning in PwMS.Supraspinal white matter structural connectivity in PwMS was correlated with improvements in postural performance (balancing on an oscillating surface over 25 trials) and retention of improvements (24 hours later).Improvement in postural performance was directly correlated to microstructural integrity of white matter tracts, measured as radial diffusivity, in the corpus callosum, posterior parieto-sensorimotor fibers and the brainstem in PwMS. Within the corpus callosum, the genu and midbody (fibers connecting the prefrontal and primary motor cortices, respectively) were most strongly correlated to improvements in postural control. Twenty-four-hour retention was not correlated to radial diffusivity.PwMS who exhibited poorer white matter tract integrity connecting the cortical hemispheres via the corpus callosum showed the most difficulty learning to control balance on an unstable surface. Prediction of improvements in postural control through training (ie, motor learning) via structural imaging of the brain may allow for identification of individuals who are particularly well suited for postural rehabilitation interventions.

PIMD: 27919489

Cognitive event-related potentials in multiple sclerosis: Correlation with MRI and neuropsychological findings.

Cognitive event-related potentials (ERPs) have been previously correlated with T2 lesion load (T2LL) in patients with multiple sclerosis (MS). It is currently unknown, however, whether ERPs also correlate with brain atrophy or the presence of T1 hypointense lesions ("black holes") which reflect tissue destruction and axonal loss. The primary aim of the current study is to explore the effect of neuroradiological parameters such as brain atrophy, T1 and T2 lesion load on auditory ERPs in MS patients. In addition, we correlated cognitive impairment with neurophysiological (ERP) and neuroradiological (MRI) variables and investigated whether a combination of ERP and MRI parameters is capable of distinguishing patients suffering from secondary progressive (SP), primary progressive (PP) and relapsing-remitting (RR) MS.The study sample consisted of fifty nine MS patients (mean age±SD: 37.82±1.38 years; average disease duration: 6.76±5.3 years) and twenty six age-matched controls (mean age±SD: 41.42±15.39 years). The patients' EDSS and NRS scores were 3.77±2.14 (range: 1-7.5) and 75.88±11.99 (range: 42-94) respectively. ERPs were recorded using the auditory "odd-ball" paradigm. T1 and T2 lesions were automatically segmented using an edge-finding tool and total lesion volumes were calculated. MRI measures of brain atrophy included third ventricle width (THIRDVW) and the ratio of mid-sagittal corpus callosum area to the mid-sagittal intracranial skull surface area (CC/MISS). Statistical analysis was performed using multiple regression, principal component (PCA) and discriminant analysis.T1 lesion load emerged as the most significant predictor of P300 and N200 latency. The rest of the endogenous ERPs parameters (P300 amplitude, N200 amplitude) were not significantly correlated with the MRI variables. PCA of pooled neuroradiological and neurophysiological markers suggested that four components accounted for 64.6% of the total variability. Discriminant analysis based on ERP & MRI markers classified correctly 79.63% of patients in RR, PP and SP subgroups.T1 lesion load is the most significant MRI correlate of auditory ERPs in MS patients. Importantly, ERPs in combination with MRI variables can be usefully employed for distinguishing patients with different subtypes of MS.

PIMD: 27904491

Intravenous transplantation of mouse embryonic stem cells attenuates demyelination in an ICR outbred mouse model of demyelinating diseases.

Induction of demyelination in the central nervous system (CNS) of experimental mice using cuprizone is widely used as an animal model for studying the pathogenesis and treatment of demyelination. However, different mouse strains used result in different pathological outcomes. Moreover, because current medicinal treatments are not always effective in multiple sclerosis patients, so the study of exogenous cell transplantation in an animal model is of great importance. The aims of the present study were to establish an alternative ICR outbred mouse model for studying demyelination and to evaluate the effects of intravenous cell transplantation in the present developed mouse model. Two sets of experiments were conducted. Firstly, ICR outbred and BALB/c inbred mice were fed with 0.2% cuprizone for 6 consecutive weeks; then demyelinating scores determined by luxol fast blue stain or immunolabeling with CNPase were evaluated. Secondly, attenuation of demyelination in ICR mice by intravenous injection of mES cells was studied. Scores for demyelination in the brains of ICR mice receiving cell injection (mES cells-injected group) and vehicle (sham-inoculated group) were assessed and compared. The results showed that cuprizone significantly induced demyelination in the cerebral cortex and corpus callosum of both ICR and BALB/c mice. Additionally, intravenous transplantation of mES cells potentially attenuated demyelination in ICR mice compared with sham-inoculated groups. The present study is among the earliest reports to describe the cuprizone-induced demyelination in ICR outbred mice. Although it remains unclear whether mES cells or trophic effects from mES cells are the cause of enhanced remyelination, the results of the present study may shed some light on exogenous cell therapy in central nervous system demyelinating diseases.

PIMD: 27833528

Gray and White Matter Demyelination and Remyelination Detected with Multimodal Quantitative MRI Analysis at 11.7T in a Chronic Mouse Model of Multiple Sclerosis.

Myelin is a component of the nervous system that is disrupted in multiple sclerosis, resulting in neuro-axonal degeneration. The longitudinal effect of chronic cuprizone-induced demyelination was investigated in the cerebral gray and white matter of treated mice and the spontaneous remyelination upon treatment interruption. Multimodal Magnetic Resonance Imaging and a Cryoprobe were used at 11.7T to measure signal intensity ratios, T values and diffusion metrics. The results showed significant and reversible modifications in white matter and gray matter regions such as in the rostral and caudal corpus callosum, the external capsule, the cerebellar peduncles, the caudate putamen, the thalamus, and the somatosensory cortex of treated mice. T and radial diffusivity metrics appeared to be more sensitive than fractional anisotropy, axial diffusivity or mean diffusivity to detect those cuprizone-induced changes. In the gray matter, only signal and T metrics and not diffusion metrics were sensitive to detect any changes. Immunohistochemical qualitative assessments in the same regions confirmed demyelination and remyelination processes. These multimodal data will provide better understanding of the dynamics of cuprizone-induced de- and remyelination in white and gray matter structures, and will be the basis to test therapies in experimental models.

PIMD: 27830115

Reliability of measuring regional callosal atrophy in neurodegenerative diseases.

The Corpus Callosum (CC) is an important structure connecting the two brain hemispheres. As several neurodegenerative diseases are known to alter its shape, it is an interesting structure to assess as biomarker. Yet, currently, the CC-segmentation is often performed manually and is consequently an error prone and time-demanding procedure. In this paper, we present an accurate and automated method for corpus callosum segmentation based on T1-weighted MRI images. After the initial construction of a CC atlas based on healthy controls, a new image is subjected to a mid-sagittal plane (MSP) detection algorithm and a 3D affine registration in order to initialise the CC within the extracted MSP. Next, an active shape model is run to extract the CC. We calculated the reliability of most popular CC features (area, circularity, corpus callosum index and thickness profile) in healthy controls, Alzheimer's Disease patients and Multiple Sclerosis patients. Importantly, we also provide inter-scanner reliability estimates. We obtained an intra-class correlation coefficient (ICC) of over 0.95 for most features and most datasets. The inter-scanner reliability assessed on the MS patients was remarkably well and ranged from 0.77 to 0.97. In summary, we have constructed an algorithm that reliably detects the CC in 3D T1 images in a fully automated way in healthy controls and different neurodegenerative diseases. Although the CC area and the circularity are the most reliable features (ICC > 0.97); the reliability of the thickness profile (ICC > 0.90; excluding the tip) is sufficient to warrant its inclusion in future clinical studies.

PIMD: 27772761

Corpus callosum microstructural changes associated with Kawashima Nintendo Brain Training in patients with multiple sclerosis.

No abstract

PIMD: 27535761

Astrocyte-targeted production of interleukin-6 reduces astroglial and microglial activation in the cuprizone demyelination model: Implications for myelin clearance and oligodendrocyte maturation.

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Interleukin (IL)-6 is a pleiotropic cytokine with a potential role in MS. Here we used transgenic mice with astrocyte-targeted production of IL-6 (GFAP-IL6Tg) to study the effect of IL-6 in the cuprizone-induced demyelination paradigm, which is an experimental model of de- and re-myelination, both hallmarks of MS. Our results demonstrated that cuprizone-treated GFAP-IL6Tg mice showed a significant reduction in astroglial and especially microglial activation/accumulation in the corpus callosum in comparison with the corresponding cuprizone-treated wild type (WT). Production of a key microglial attracting chemokine CXCL10, as well as CXCL1 and CCL4 was lower in cuprizone-treated GFAP-IL6Tg mice compared with cuprizone-treated WT. Reduced microglial cell accumulation was associated with inefficient removal of degraded myelin and axonal protection in cuprizone-treated GFAP-IL6Tg mice, compared with WT mice at the peak of demyelination. In addition, transgenic production of IL-6 did not alter initial oligodendrocyte (OL) apoptosis and oligodendrocyte precursor cell recruitment to the lesion site, but it impaired early OL differentiation, possibly due to impaired removal of degraded myelin. Indeed, a microglial receptor involved in myelin phagocytosis, TREM2, as well as the phagolysosomal protein CD68 were lower in cuprizone-treated GFAP-IL6Tg compared with WT mice. Our results show for the first time that astrocyte-targeted production of IL-6 may play a role in modulating experimental demyelination induced by cuprizone. Further understanding of the IL-6-mediated molecular mechanisms involved in the regulation of demyelination is needed, and may have implications for the development of future therapeutic strategies for the treatment of MS. GLIA 2016;64:2104-2119.

PIMD: 27708613

The Impact of MS-Related Cognitive Fatigue on Future Brain Parenchymal Loss and Relapse: A 17-Month Follow-up Study.

Fatigue is a disabling syndrome in multiple sclerosis (MS), which may be associated with inflammation and faster disease progression.To analyze the significance of cognitive fatigue for subsequent disease progression.We followed 46 MS patients and 14 healthy controls in a study over 17 months. At the beginning (t1) and at the end (t2) of the study participants scored their fatigue, performed the Multiple Sclerosis Functional Composite and received MRI scanning, encompassing MPR T1, FLAIR, and DTI sequences. At t1, MS patients were divided into those with and those without cognitive fatigue (cut-off score for moderate cognitive fatigue of the Fatigue Scale for Motor and Cognition). We calculated ANCOVAs for repeated measurement to analyze the relevance of cognitive fatigue status for the number of relapses and for MRI parameters.At t1, but not at t2, patients with cognitive fatigue showed increased axial and radial diffusivity of corpus callosum fibers. At t2, these patients showed significantly more loss of brain parenchyma and greater enlargement of lateral ventricles. Moreover, they developed more relapses, but there was no difference in lesion load or in performance deterioration. Additional analyses showed that only cognitive fatigue but not a more general score for fatigue (Fatigue Severity Scale) had an impact on the worsening of the disease status.Patients with cognitive fatigue may develop more brain atrophy and relapses during the next 17 months than patients without cognitive fatigue. Hence, experiencing cognitive fatigue might indicate more aggressive inflammatory processes and subsequent neurodegeneration.

PIMD: 27596241

The crucial role of Erk2 in demyelinating inflammation in the central nervous system.

Brain inflammation is a crucial component of demyelinating diseases such as multiple sclerosis. Although the initiation of inflammatory processes by the production of cytokines and chemokines by immune cells is well characterized, the processes of inflammatory aggravation of demyelinating diseases remain obscure. Here, we examined the contribution of Erk2, one of the isoforms of the extracellular signal-regulated kinase, to demyelinating inflammation.We used the cuprizone-induced demyelinating mouse model. To examine the role of Erk2, we used Nestin-cre-driven Erk2-deficient mice. We also established primary culture of microglia or astrocytes in order to reveal the crosstalk between two cell types and to determine the downstream cascades of Erk2 in astrocytes.First, we found that Erk is especially activated in astrocytes within the corpus callosum before the peak of demyelination (at 4 weeks after the start of cuprizone feeding). Then, we found that in our model, genetic ablation of Erk2 from neural cells markedly preserved myelin structure and motor function as measured by the rota-rod test. While the initial activation of microglia was not altered in Erk2-deficient mice, these mice showed reduced expression of inflammatory mediators at 3-4 model weeks. Furthermore, the subsequent inflammatory glial responses, characterized by accumulation of microglia and reactive astrocytes, were significantly attenuated in Erk2-deficient mice. These data indicate that Erk2 in astrocytes is involved in augmentation of inflammation and gliosis. We also found that activated, cultured microglia could induce Erk2 activation in cultured astrocytes and subsequent production of inflammatory mediators such as Ccl-2.Our results suggest that Erk2 activation in astrocytes plays a crucial role in aggravating demyelinating inflammation by inducing inflammatory mediators and gliosis. Thus, therapies targeting Erk2 function in glial cells may be a promising approach to the treatment of distinct demyelinating diseases.

PIMD: 27592741

Acute axonal damage in three different murine models of multiple sclerosis: A comparative approach.

Axonal damage has been identified as a significant contributor to permanent clinical disability in multiple sclerosis. In the context of demyelinating disorders, this destructive event can be the result of inflammation, demyelination and/or the activation of innate defense cells such as microglia or monocytes. The relative contribution of each of these variables to acute axonal injury is, however, unknown. In the present study, we compared the extent of acute axonal damage in three different murine demyelination models using anti-amyloid precursor protein (APP) immunohistochemistry. T cell dependent (MOG-induced experimental autoimmune encephalomyelitis (EAE)) as well as T cell independent demyelination models (cuprizone- and lysolecithin-induced demyelination) were used. APP spheroids were present in all three experimental demyelination models. The number of APP spheroids was highest within LPC-induced lesions. Equal amounts were found in the spinal cord of MOG-EAE animals and the corpus callosum of cuprizone-intoxicated animals. Moreover, we detected increased immunoreactivity of the pre-synaptic protein vesicular glutamate transporter 1 (VGluT1) in demyelinated foci. VGluT1-staining revealed long stretched, ovoid-like axonal structures which co-localized with APP. In summary, we showed that acute axonal damage is evident under various experimental demyelination paradigms. Furthermore, disturbed axonal transport mechanisms, which are responsible for intra-axonal APP accumulation, do not only disturb APP, but also the transport of other synaptic proteins. These results indicate that, despite differences in their characteristics, all three models may serve as valid and suitable systems for investigating responsible mechanisms of axonal damage and potential protective strategies.

PIMD: 27550173

Cuprizone demyelination induces a unique inflammatory response in the subventricular zone.

Cuprizone leads to demyelination of the corpus callosum (CC) and activates progenitor cells in the adjacent subventricular zone (SVZ), a stem cell niche which contributes to remyelination. The healthy SVZ contains semi-activated microglia and constitutively expresses the pro-inflammatory molecule galectin-3 (Gal-3) suggesting the niche uniquely regulates inflammation.We studied the inflammatory response to cuprizone in the SVZ and CC in Gal-3 knockout mice using immunohistochemistry and with the in vitro neurosphere assay.Cuprizone caused loss of myelin basic protein (MBP) immunofluorescence in the CC suggesting demyelination. Cuprizone increased the density of CD45+/Iba1+ microglial cells and also increased Gal-3 expression in the CC. Surprisingly, the number of Gal-3+ and CD45+ cells decreased in the SVZ after cuprizone, suggesting inflammation was selectively reduced therein. Inflammation can regulate SVZ proliferation and indeed the number of phosphohistone H3+ (PHi3+) cells decreased in the SVZ but increased in the CC in both genotypes after cuprizone treatment. BrdU+ SVZ cell numbers also decreased in the SVZ after cuprizone, and this effect was significantly greater at 3 weeks in Gal-3 (-/-) mice compared to WT, suggesting Gal-3 normally limits SVZ cell emigration following cuprizone treatment.This study reveals a uniquely regulated inflammatory response in the SVZ and shows that Gal-3 participates in remyelination in the cuprizone model. This contrasts with more severe models of demyelination which induce SVZ inflammation and suggests the extent of demyelination affects the SVZ neurogenic response.

PIMD: 27400790

Survival and Functionality of Human Induced Pluripotent Stem Cell-Derived Oligodendrocytes in a Nonhuman Primate Model for Multiple Sclerosis.

No abstract

PIMD: 27303273

Parametric Probability Distribution Functions for Axon Diameters of Corpus Callosum.

Axon diameter is an important neuroanatomical characteristic of the nervous system that alters in the course of neurological disorders such as multiple sclerosis. Axon diameters vary, even within a fiber bundle, and are not normally distributed. An accurate distribution function is therefore beneficial, either to describe axon diameters that are obtained from a direct measurement technique (e.g., microscopy), or to infer them indirectly (e.g., using diffusion-weighted MRI). The gamma distribution is a common choice for this purpose (particularly for the inferential approach) because it resembles the distribution profile of measured axon diameters which has been consistently shown to be non-negative and right-skewed. In this study we compared a wide range of parametric probability distribution functions against empirical data obtained from electron microscopy images. We observed that the gamma distribution fails to accurately describe the main characteristics of the axon diameter distribution, such as location and scale of the mode and the profile of distribution tails. We also found that the generalized extreme value distribution consistently fitted the measured distribution better than other distribution functions. This suggests that there may be distinct subpopulations of axons in the corpus callosum, each with their own distribution profiles. In addition, we observed that several other distributions outperformed the gamma distribution, yet had the same number of unknown parameters; these were the inverse Gaussian, log normal, log logistic and Birnbaum-Saunders distributions.

PIMD: 27246837

Diffusion tensor imaging with direct cytopathological validation: characterisation of decorin treatment in experimental juvenile communicating hydrocephalus.

In an effort to develop novel treatments for communicating hydrocephalus, we have shown previously that the transforming growth factor-β antagonist, decorin, inhibits subarachnoid fibrosis mediated ventriculomegaly; however decorin's ability to prevent cerebral cytopathology in communicating hydrocephalus has not been fully examined. Furthermore, the capacity for diffusion tensor imaging to act as a proxy measure of cerebral pathology in multiple sclerosis and spinal cord injury has recently been demonstrated. However, the use of diffusion tensor imaging to investigate cytopathological changes in communicating hydrocephalus is yet to occur. Hence, this study aimed to determine whether decorin treatment influences alterations in diffusion tensor imaging parameters and cytopathology in experimental communicating hydrocephalus. Moreover, the study also explored whether diffusion tensor imaging parameters correlate with cellular pathology in communicating hydrocephalus.Accordingly, communicating hydrocephalus was induced by injecting kaolin into the basal cisterns in 3-week old rats followed immediately by 14 days of continuous intraventricular delivery of either human recombinant decorin (n = 5) or vehicle (n = 6). Four rats remained as intact controls and a further four rats served as kaolin only controls. At 14-days post-kaolin, just prior to sacrifice, routine magnetic resonance imaging and magnetic resonance diffusion tensor imaging was conducted and the mean diffusivity, fractional anisotropy, radial and axial diffusivity of seven cerebral regions were assessed by voxel-based analysis in the corpus callosum, periventricular white matter, caudal internal capsule, CA1 hippocampus, and outer and inner parietal cortex. Myelin integrity, gliosis and aquaporin-4 levels were evaluated by post-mortem immunohistochemistry in the CA3 hippocampus and in the caudal brain of the same cerebral structures analysed by diffusion tensor imaging.Decorin significantly decreased myelin damage in the caudal internal capsule and prevented caudal periventricular white matter oedema and astrogliosis. Furthermore, decorin treatment prevented the increase in caudal periventricular white matter mean diffusivity ($p = 0.032$) as well as caudal corpus callosum axial diffusivity ($p = 0.004$) and radial diffusivity ($p = 0.034$). Furthermore, diffusion tensor imaging parameters correlated primarily with periventricular white matter astrocyte and aquaporin-4 levels.Overall, these findings suggest that decorin has the therapeutic potential to reduce white matter cytopathology in hydrocephalus. Moreover, diffusion tensor imaging is a useful tool to provide surrogate measures of periventricular white matter pathology in communicating hydrocephalus.

PIMD: 27242658

Neuromyelitis Optica Spectrum Disorder with Tumefactive Demyelination mimicking Multiple Sclerosis: A Rare Case.

Neuromyelitis optica spectrum disorder (NMOSD) is a diverse condition which not only encompasses isolated longitudinally extensive transverse myelitis (LETM) and optic neuritis but also includes area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome, and symptomatic cerebral syndrome. Imaging may reveal periependymal lesions surrounding the ventricular system or involvement of corticospinal tracts, area postrema, diencephalon, and corpus callosum. Rarely, there may be hemispheric tumefactive lesions that enhance in a "Cloud-like" fashion on gadolinium injection unlike in tumefactive multiple sclerosis where there is incomplete ring enhancement. Here, we present a case of aquaporin-4 positive relapsing NMOSD who presented to us with recurrent episodes of paraparesis with LETM and tumefactive lesions of brain on imaging, which enhanced in an incomplete ring like pattern resembling multiple sclerosis.

PIMD: 27231712

Laquinimod prevents cuprizone-induced demyelination independent of Toll-like receptor signaling.

To test whether Toll-like receptor (TLR) signaling plays a key role for reduced nuclear factor B (NF-κB) activation after laquinimod treatment in the model of cuprizone-induced demyelination, oligodendrocyte apoptosis, inflammation, and axonal damage.Ten-week-old C57BL/6J, TLR4(-/-), and MyD88(-/-) mice received 0.25% cuprizone for 6 weeks and were treated daily with 25 mg/kg laquinimod or vehicle. After 6 weeks of demyelination, extent of demyelination, oligodendrocyte density, microglia infiltration, and axonal damage were analyzed in the corpus callosum. Additionally, we analyzed primary mouse astrocytes from C57BL/6J, TLR4(-/-), MyD88(-/-), and TRIF(-/-) mice for alteration in NF-κB signaling.Vehicle-treated controls from C57BL/6J, TLR4(-/-), and MyD88(-/-) mice displayed extensive callosal demyelination as well as microglial activation. In contrast, mice treated with 25 mg/kg laquinimod showed mainly intact callosal myelin. The demyelination score was significantly higher in all untreated mice compared to mice treated with laquinimod. There were significantly fewer APP-positive axonal spheroids, Mac3-positive macrophages/microglia, and less oligodendrocyte apoptosis in the corpus callosum of laquinimod-treated mice in comparison to untreated controls. Stimulated primary mouse astrocytes from laquinimod-treated groups show reduced NF-κB activation compared to vehicle-treated controls.Our results confirm that laquinimod prevents demyelination in the cuprizone mouse model for multiple sclerosis via downregulation of NF-κB activation. This laquinimod effect, however, does not involve upstream Toll-like receptor signaling.

PIMD: 27219660

A surface-based technique for mapping homotopic interhemispheric connectivity: Development, characterization, and clinical application.

The functional organization of the human brain consists of a high degree of connectivity between interhemispheric homologous regions. The degree of homotopic organization is known to vary across the cortex and homotopic connectivity is high in regions that share cross-hemisphere structural connections or are activated by common input streams (e.g., the visual system). Damage to one or both regions, as well as damage to the connections between homotopic regions, could disrupt this functional organization. Here were introduce and test a computationally efficient technique, surface-based homotopic interhermispheric connectivity (sHIC), that leverages surface-based registration and processing techniques in an attempt to improve the spatial specificity and accuracy of cortical interhemispheric connectivity estimated with resting state functional connectivity. This technique is shown to be reliable both within and across subjects. sHIC is also characterized in a dataset of nearly 1000 subjects. We confirm previous results showing increased interhemispheric connectivity in primary sensory regions, and reveal a novel rostro-caudal functionally defined network level pattern of sHIC across the brain. In addition, we demonstrate a structural-functional relationship between sHIC and atrophy of the corpus callosum in multiple sclerosis ($r = 0.2979$, $p = 0.0461$). sHIC presents as a sensitive and reliable measure of cortical homotopy that may prove useful as a biomarker in neurologic disease. Hum Brain Mapp 37:2849-2868, 2016.

PIMD: 27161462

Pericallosal Lipomas: A Series of 10 Cases with Clinical and Radiological Features.

A pericallosal lipoma is a fat-containing lesion occurring in the interhemispheric fissure closely related to the corpus callosum, which is often abnormal. This is the most common location for an intracranial lipoma. In this study, we aim to report on the clinical and radiographic aspects of ten patients diagnosed with pericallosal lipomas.A retrospective analysis of patients who presented to the neurology and neurosurgery outpatient clinics of Kayseri Training and Research Hospital between 2010 and 2014 revealed that 10 patients had the diagnosis of pericallosal lipoma. The clinical and magnetic resonance imaging data were obtained by reviewing their files.Ten patients with an average age of 35.8 years (11-80 years) were included in the study. The mean follow-up was 17 months (8-31 months). No neurological deficits related to the lesions were found during neurological examination in any of the patients. Four patients had tubulonodular lipomas while the other 6 presented with curvilinear lipomas. Four patients (40%) displayed a coexistent corpus callosum hypoplasia. In contrast to previous reports, 3 of these patients had a curvilinear lipoma while the remaining one had tubulonodular lipoma. Also, one of the patients displayed plaque lesions attributable to multiple sclerosis. During the follow-up period, no growth in the lipomas was recorded in any of the patients. No surgical intervention was performed as none of the patients displayed symptoms caused by the lipoma.In this study, we found a stronger association of corpus callosum hypoplasia with posteriorly situated curvilinear lipomas. Our results are in disagreement with previous studies, which suggested corpus callosum anomalies were more often associated with anteriorly situated tubulonodular lipomas. Pericallosal lipomas are benign, self-limiting or slow-growing lesions that generally remain asymptomatic. These lesions occur in the midline and surround critical neurovascular structures. Therefore, surgical intervention should be avoided in asymptomatic cases.

PIMD: 27094571

Quantification of normal-appearing white matter tract integrity in multiple sclerosis: a diffusion kurtosis imaging study.

Our aim was to characterize the nature and extent of pathological changes in the normal-appearing white matter (NAWM) of patients with multiple sclerosis (MS) using novel diffusion kurtosis imaging-derived white matter tract integrity (WMTI) metrics and to investigate the association between these WMTI metrics and clinical parameters. Thirty-two patients with relapsing-remitting MS and 19 age- and gender-matched healthy controls underwent MRI and neurological examination. Maps of mean diffusivity, fractional anisotropy and WMTI metrics (intra-axonal diffusivity, axonal water fraction, tortuosity and axial and radial extra-axonal diffusivity) were created. Tract-based spatial statistics analysis was performed to assess for differences in the NAWM between patients and controls. A region of interest analysis of the corpus callosum was also performed to assess for group differences and to evaluate correlations between WMTI metrics and measures of disease severity. Mean diffusivity and radial extra-axonal diffusivity were significantly increased while fractional anisotropy, axonal water fraction, intra-axonal diffusivity and tortuosity were decreased in MS patients compared with controls (p values ranging from <0.001 to <0.05). Axonal water fraction in the corpus callosum was significantly associated with the expanded disability status scale score ($\rho = -0.39$, $p = 0.035$). With the exception of the axial extra-axonal diffusivity, all metrics were correlated with the symbol digits modality test score (p values ranging from 0.001 to <0.05). WMTI metrics are thus sensitive to changes in the NAWM of MS patients and might provide a more pathologically specific, clinically meaningful and practical complement to standard diffusion tensor imaging-derived metrics.

PIMD: 27054832

Spatio-Temporal Patterns of Demyelination and Remyelination in the Cuprizone Mouse Model.

Cuprizone administration in mice provides a reproducible model of demyelination and spontaneous remyelination, and has been useful in understanding important aspects of human disease, including multiple sclerosis. In this study, we apply high spatial resolution quantitative MRI techniques to establish the spatio-temporal patterns of acute demyelination in C57BL/6 mice after 6 weeks of cuprizone administration, and subsequent remyelination after 6 weeks of post-cuprizone recovery. MRI measurements were complemented with Black Gold II stain for myelin and immunohistochemical stains for associated tissue changes. Gene expression was evaluated using the Allen Gene Expression Atlas. Twenty-five C57BL/6 male mice were split into control and cuprizone groups; MRI data were obtained at baseline, after 6 weeks of cuprizone, and 6 weeks post-cuprizone. High-resolution (100 μm isotropic) whole-brain coverage magnetization transfer ratio (MTR) parametric maps demonstrated concurrent caudal-to-rostral and medial-to-lateral gradients of MTR decrease within corpus callosum (CC) that correlated well with demyelination assessed histologically. Our results show that demyelination was not limited to the midsagittal line of the corpus callosum, and also that opposing gradients of demyelination occur in the lateral and medial CC. T2-weighted MRI gray/white matter contrast was strong at baseline, weak after 6 weeks of cuprizone treatment, and returned to a limited extent after recovery. MTR decreases during demyelination were observed throughout the brain, most clearly in callosal white matter. Myelin damage and repair appear to be influenced by proximity to oligodendrocyte progenitor cell populations and exhibit an inverse correlation with myelin basic protein gene expression. These findings suggest that susceptibility to injury and ability to repair vary across the brain, and whole-brain analysis is necessary to accurately characterize this model. Whole-brain parametric mapping across time is essential for gaining a real understanding of disease processes in-vivo. MTR increases in healthy mice throughout adolescence and adulthood were observed, illustrating the need for appropriate age-matched controls. Elucidating the unique and site-specific demyelination in the cuprizone model may offer new insights into in mechanisms of both damage and repair in human demyelinating diseases.

PIMD: 27053635

Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year disability in multiple sclerosis.

Disease progression and treatment efficacy vary among individuals with multiple sclerosis. Reliable predictors of individual disease outcomes are lacking.To examine the accuracy of the early prediction of 12-year disability outcomes using clinical and magnetic resonance imaging (MRI) parameters.A total of 177 patients from the original Avonex-Steroids-Azathioprine study were included. Participants underwent 3-month clinical follow-ups. Cox models were used to model the associations between clinical and MRI markers at baseline or after 12 months with sustained disability progression (SDP) over the 12-year observation period.At baseline, T2 lesion number, T1 and T2 lesion volumes, corpus callosum (CC), and thalamic fraction were the best predictors of SDP (hazard ratio (HR) = 1.7-4.6; p ≤ 0.001-0.012). At 12 months, Expanded Disability Status Scale (EDSS) and its change, number of new or enlarging T2 lesions, and CC volume % change were the best predictors of SDP over the follow-up (HR = 1.7-3.5; p ≤ 0.001-0.017). A composite score was generated from a subset of the best predictors of SDP. Scores of ≥4 had greater specificity (90%-100%) and were associated with greater cumulative risk of SDP (HR = 3.2-21.6; p < 0.001) compared to the individual predictors.The combination of established MRI and clinical indices with MRI volumetric predictors improves the prediction of SDP over long-term follow-up and may provide valuable information for therapeutic decisions.

PIMD: 27043553

Individual Assessment of Brain Tissue Changes in MS and the Effect of Focal Lesions on Short-Term Focal Atrophy Development in MS: A Voxel-Guided Morphometry Study.

We performed voxel-guided morphometry (VGM) investigating the mechanisms of brain atrophy in multiple sclerosis (MS) related to focal lesions. VGM maps detect regional brain changes when comparing 2 time points on high resolution T1-weighted (T1w) magnetic resonace imaging (MRI). Two T1w MR datasets from 92 relapsing-remitting MS patients obtained 12 months apart were analysed with VGM. New lesions and volume changes of focal MS lesions as well as in the surrounding tissue were identified by visual inspection on colour coded VGM maps. Lesions were dichotomized in active and inactive lesions. Active lesions, defined by either new lesions (NL) (volume increase > 5% in VGM), chronic enlarging lesions (CEL) (pre-existent T1w lesions with volume increase > 5%), or chronic shrinking lesions (CSL) (pre-existent T1w lesions with volume reduction > 5%) in VGM, were accompanied by tissue shrinkage in surrounding and/or functionally related regions. Volume loss within the corpus callosum was highly correlated with the number of lesions in its close proximity. Volume loss in the lateral geniculate nucleus was correlated with lesions along the optic radiation. VGM analysis provides strong evidence that all active lesion types (NL, CEL, and CSL) contribute to brain volume reduction in the vicinity of lesions and/or in anatomically and functionally related areas of the brain.

PIMD: 26990645

Heterogeneity of Multiple Sclerosis Lesions in Multislice Myelin Water Imaging.

To assess neuroprotection and remyelination in Multiple Sclerosis (MS), we applied a more robust myelin water imaging (MWI) processing technique, including spatial priors into image reconstruction, which allows for lower SNR, less averages and shorter acquisition times. We sought to evaluate this technique in MS-patients and healthy controls (HC).Seventeen MS-patients and 14 age-matched HCs received a 3T Magnetic Resonance Imaging (MRI) examination including MWI (8 slices, 12 minutes acquisition time), T2w and T1mprage pre and post gadolinium (GD) administration. Black holes (BH), contrast enhancing lesions (CEL) and T2 lesions were marked and registered to MWI. Additionally, regions of interest (ROI) were defined in the frontal, parietal and occipital normal appearing white matter (NAWM)/white matter (WM), the corticospinal tract (CST), the splenium (SCC) and genu (GCC) of the corpus callosum in patients and HCs. Mean values of myelin water fraction (MWF) were determined for each ROI.Significant differences ($p \leq 0.05$) of the MWF were found in all three different MS-lesion types (BH, CEL, T2 lesions), compared to the WM of HCs. The mean MWF values among the different lesion types were significantly differing from each other. Comparing MS-patients vs. HCs, we found a significant ($p \leq 0.05$) difference of the MWF in all measured ROIs except of GCC and SCC. The mean reduction of MWF in the NAWM of MS-patients compared to HCs was 37%. No age, sex, disability score and disease duration dependency was found for the NAWM MWF.MWF measures were in line with previous studies and lesions were clearly visible in MWI. MWI allows for quantitative assessment of NAWM and lesions in MS, which could be used as an additional sensitive imaging endpoint for larger MS studies. Measurements of the MWF also differ between patients and healthy controls.

PIMD: 26971482

Enhanced mirror activity in 'crossed' reaction time tasks in multiple sclerosis.

Execution of unimanual voluntary motor tasks requires appropriate inhibitory control over contralateral motor output. Such inhibition should involve interhemispheric connections, which are often damaged in multiple sclerosis (MS).Twenty mildly-disabled MS patients and 13 healthy subjects performed ipsilateral and contralateral wrist-extension reactions (IR and CR, respectively) to a unilateral somatosensory cue, the latter condition requiring necessarily interhemispheric transfer of information. Prevalence, persistence, latency and amount of mirror electromyographic activity (mEMG) were calculated in each study group, as well as diffusion-tensor-imaging measures of damage in corpus callosum and brainstem for correlation with mEMG.Healthy subjects and patients showed mEMG more often in CR than in IR. In CR tasks, mEMG was larger, more persistent and occurred more often at a shorter latency with respect to voluntary reaction in patients than in healthy subjects ($p<0.05$ for all). Patients with mEMG had significantly higher diffusivity values of damage in corpus callosum and lower brainstem volumes than patients without mEMG ($p<0.05$ for all).MS patients show deficient inhibition of unintended mEMG in 'crossed' reaction time tasks.Enhanced mEMG in MS may be due to microstructural axonal damage and atrophy in inhibitory commissural connections of the corpus callosum and brainstem.

PIMD: 26846989

Fatigue in multiple sclerosis: The contribution of occult white matter damage.

A functional cortico-subcortical disconnection has been recognized in fatigued multiple sclerosis (MS) patients. Normal appearing white matter (NAWM) damage might contribute to the abovementioned disconnectivity.To assess the relationship between fatigue and microstructural NAWM damage in relapsing-remitting (RR) MS.Sixty RRMS patients and 29 healthy controls (HC) underwent a magnetic resonance imaging (MRI) protocol including diffusion tensor imaging (DTI). Patients with a mean Fatigue Severity Scale (FSS) score ≥ 4 were considered fatigued (fatigued MS (F-MS)). Tract-based spatial statistics were applied for voxel-wise analysis of DTI indices. A correlation analysis was performed between FSS score and DTI indices in the entire MS group.Thirty MS patients were F-MS. Compared to HC, F-MS patients showed a more extensive NAWM damage than not fatigued MS (NF-MS) patients, with additional damage in the following tracts: frontal and occipital juxtacortical fibers, external capsule, uncinate fasciculus, forceps minor, superior longitudinal fasciculus, cingulum, and pons. No differences were found between F-MS and NF-MS patients. Fatigue severity correlated to DTI abnormalities of corona radiata, cingulum, corpus callosum, forceps minor, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, thalamus and anterior thalamic radiation, cerebral peduncle, and midbrain.Fatigue is associated to a widespread microstructural NAWM damage, particularly in associative tracts connected to frontal lobes.

PIMD: 26844268

White Matter Lipids as a Ketogenic Fuel Supply in Aging Female Brain: Implications for Alzheimer's Disease.

White matter degeneration is a pathological hallmark of neurodegenerative diseases including Alzheimer's. Age remains the greatest risk factor for Alzheimer's and the prevalence of age-related late onset Alzheimer's is greatest in females. We investigated mechanisms underlying white matter degeneration in an animal model consistent with the sex at greatest Alzheimer's risk. Results of these analyses demonstrated decline in mitochondrial respiration, increased mitochondrial hydrogen peroxide production and cytosolic-phospholipase-A2 sphingomyelinase pathway activation during female brain aging. Electron microscopic and lipidomic analyses confirmed myelin degeneration. An increase in fatty acids and mitochondrial fatty acid metabolism machinery was coincident with a rise in brain ketone bodies and decline in plasma ketone bodies. This mechanistic pathway and its chronologically phased activation, links mitochondrial dysfunction early in aging with later age development of white matter degeneration. The catabolism of myelin lipids to generate ketone bodies can be viewed as a systems level adaptive response to address brain fuel and energy demand. Elucidation of the initiating factors and the mechanistic pathway leading to white matter catabolism in the aging female brain provides potential therapeutic targets to prevent and treat demyelinating diseases such as Alzheimer's and multiple sclerosis. Targeting stages of disease and associated mechanisms will be critical.

PIMD: 26805386

Thymosin beta4 promotes oligodendrogenesis in the demyelinating central nervous system.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). No effective remyelination therapies are in use. We hypothesized that thymosin beta4 (Tβ4) is an effective remyelination treatment by promoting differentiation of oligodendrocyte progenitor cells (OPCs), and that the epidermal growth factor receptor (EGFR) signaling pathway contributes to this process. Two demyelination animal models were employed in this study: 1) experimental autoimmune encephalomyelitis (EAE), an animal model of MS. EAE mice were treated daily for 30days, with Tβ4 or saline treatment initiated on the day of EAE onset; and 2) cuprizone diet model, a non-inflammatory demyelination model. The mice were treated daily for 4weeks with Tβ4 or saline after fed a cuprizone diet for 5weeks. Immunofluorescent staining and Western blot were performed to measure the differentiation of OPCs, myelin and axons, respectively. To obtain insight into mechanisms of action, the expression and activation of the EGFR pathway was measured. AG1478, an EGFR inhibitor, was employed in a loss-of-function study. Data revealed that animals in both demyelination models exhibited significant reduction of myelin basic protein (MBP(+)) levels and CNPase(+) oligodendrocytes. Treatment of EAE mice with Tβ4 significantly improved neurological outcome. Double immunofluorescent staining showed that Tβ4 significantly increased the number of newly generated oligodendrocytes identified by BrdU(+)/CNPase(+) cells and MBP(+) mature oligodendrocytes, and reduced axonal damage in the EAE mice compared with the saline treatment. The newly generated mature oligodendrocytes remyelinated axons, and the increased mature oligodendrocytes significantly correlated with functional improvement ($r=0.73$, $p<0.05$). Western blot analysis revealed that Tβ4 treatment increased expression and activation of the EGFR pathway. In the cuprizone demyelination model, Tβ4 treatment was confirmed that significantly increased OPC differentiation and remyelination, and increased the expression of EGFR and activated the EGFR pathway in the demyelinating corpus callosum. In cultured OPCs, blockage of the activation of the EGFR pathway with AG1478 abolished the Tβ4-increased OPC differentiation. Collectively, these findings indicate that: 1) Tβ4 increases proliferation of OPCs and the maturation of OPCs to myelinating oligodendrocytes which in concert, likely contribute to the beneficial effect of Tβ4 on EAE, 2) EGFR upregulated and activated by Tβ4 may mediate the process of OPC differentiation, and 3) Tβ4 could potentially be developed as a therapy for MS patients, and for other demyelinating neurological disorders.

PIMD: 26782312

Changes in brain atrophy indices in patients with relapsing-remitting multiple sclerosis treated with natalizumab.

To evaluate the effect of natalizumab on progression of brain atrophy in multiple sclerosis (MS) patients and to search for a clinical or radiological marker of progression of brain atrophy.We retrospectively recorded demographic and clinical data, as well as the corpus callosum index (CCI) using MRI, in MS patients treated with natalizumab for 1-4 years.In the study population (n = 29), baseline mean CCI was 0.37 ± 0.04 and final CCI 0.36 ± 0.04. 17 patients did not develop brain atrophy during follow-up. There was no statistically significant relationship between progression of atrophy and clinical and radiological parameters.Natalizumab may have a neuroprotective effect.

PIMD: 26747276

Post-CNS-inflammation expression of CXCL12 promotes the endogenous myelin/neuronal repair capacity following spontaneous recovery from multiple sclerosis-like disease.

Demyelination and axonal degeneration, hallmarks of multiple sclerosis (MS), are associated with the central nervous system (CNS) inflammation facilitated by C-X-C motif chemokine 12 (CXCL12) chemokine. Both in MS and in experimental autoimmune encephalomyelitis (EAE), the deleterious CNS inflammation has been associated with upregulation of CXCL12 expression in the CNS. We investigated the expression dynamics of CXCL12 in the CNS with progression of clinical EAE and following spontaneous recovery, with a focus on CXCL12 expression in the hippocampal neurogenic dentate gyrus (DG) and in the corpus callosum (CC) of spontaneously recovered mice, and its potential role in promoting the endogenous myelin/neuronal repair capacity.CNS tissue sections from mice with different clinical EAE phases or following spontaneous recovery and in vitro differentiated adult neural stem cell cultures were analyzed by immunofluorescent staining and confocal imaging for detecting and enumerating neuronal progenitor cells (NPCs) and oligodendrocyte precursor cells (OPCs) and for expression of CXCL12.Our expression dynamics analysis of CXCL12 in the CNS with EAE progression revealed elevated CXCL12 expression in the DG and CC, which persistently increases following spontaneous recovery even though CNS inflammation has subsided. Correspondingly, the numbers of NPCs and OPCs in the DG and CC, respectively, of EAE-recovered mice increased compared to that of naïve mice (NPCs, $p < 0.0001$; OPCs, $p < 0.00001$) or mice with active disease (OPCs, $p < 0.0005$). Notably, about 30 % of the NPCs and unexpectedly also OPCs (~50 %) express CXCL12, and their numbers in DG and CC, respectively, are higher in EAE-recovered mice compared with naïve mice and also compared with mice with ongoing clinical EAE (CXCL12(+) NPCs, $p < 0.005$; CXCL12(+) OPCs, $p < 0.0005$). Moreover, a significant proportion (>20 %) of the CXCL12(+) NPCs and OPCs co-express the CXCL12 receptor, CXCR4, and their numbers significantly increase with recovery from EAE not only relative to naïve mice ($p < 0.0002$) but also to mice with ongoing EAE ($p < 0.004$).These data link CXCL12 expression in the DG and CC of EAE-recovering mice to the promotion of neuro/oligodendrogenesis generating CXCR4(+) CXCL12(+) neuronal and oligodendrocyte progenitor cells endowed with intrinsic neuro/oligondendroglial differentiation potential. These findings highlight the post-CNS-inflammation role of CXCL12 in augmenting the endogenous myelin/neuronal repair capacity in MS-like disease, likely via CXCL12/CXCR4 autocrine signaling.

PIMD: 26731278

Alterations in Functional and Structural Connectivity in Pediatric-Onset Multiple Sclerosis.

Reduced white matter (WM) integrity is a fundamental aspect of pediatric multiple sclerosis (MS), though relations to resting-state functional MRI (fMRI) connectivity remain unknown. The objective of this study was to relate diffusion-tensor imaging (DTI) measures of WM microstructural integrity to resting-state network (RSN) functional connectivity in pediatric-onset MS to test the hypothesis that abnormalities in RSN reflects changes in structural integrity.This study enrolled 19 patients with pediatric-onset MS (mean age = 19, range 13-24 years, 14 female, mean disease duration = 65 months, mean age of disease onset = 13 years) and 16 age- and sex-matched healthy controls (HC). All subjects underwent 3.0T anatomical and functional MRI which included DTI and resting-state acquisitions. DTI processing was performed using Tract-Based Spatial Statistics (TBSS). RSNs were identified using Independent Components Analysis, and a dual regression technique was used to detect between-group differences in the functional connectivity of RSNs. Correlations were investigated between DTI measures and RSN connectivity.Lower fractional anisotropy (FA) was observed in the pediatric-onset MS group compared to HC group within the entire WM skeleton, and particularly the corpus callosum, posterior thalamic radiation, corona radiata and sagittal stratum (all $p < .01$, corrected). Relative to HCs, MS patients showed higher functional connectivity involving the anterior cingulate cortex and right precuneus of the default-mode network, as well as involving the anterior cingulate cortex and left middle frontal gyrus of the frontoparietal network (all $p < .005$ uncorrected, $k \geq 30$ voxels). Higher functional connectivity of the right precuneus within the default-mode network was associated with lower FA of the entire WM skeleton ($r = -.525$, $p = .02$), genu of the corpus callosum ($r = -.553$, $p = .014$), and left ($r = -.467$, $p = .044$) and right ($r = -.615$, $p = .005$) sagittal stratum.Loss of WM microstructural integrity is associated with increased resting-state functional connectivity in pediatric MS, which may reflect a diffuse and potentially compensatory activation early in MS.

PIMD: 26727496

Brain magnetic resonance imaging helps to differentiate atypical multiple sclerosis with cavitary lesions and vanishing white matter disease.

Multiple sclerosis (MS) patients can present with atypical cavitary lesions mimicking vanishing white matter disease (VWMD). Our objective was to identify brain magnetic resonance imaging (MRI) findings that differentiate these two disorders.A cross-sectional study was performed including 14 patients with MS with cavitary lesions and 14 patients with VWMD. Two neuroradiologists retrospectively reviewed the MRI including at least T1-, T2- and fluid-attenuated inversion recovery weighted images.The main differences included ovoid lesions perpendicular to the lateral ventricle, punctate isolated juxtacortical lesions (both 100% in MS versus 0% in VWMD) and symmetrical infratentorial hyperintensities (0% in MS versus 50% in VWMD). Other statistically significant differences included midbrain (79% in MS versus 29% in VWMD) and thalamus lesions (71% vs. 7%) as well as extensive external capsule involvement (29% vs. 86%) and extensive corpus callosum lesions (64% vs. 100%). Cavitary lesions usually had periventricular predominance in MS (36% vs. 0%) whereas they were more frequently anterior in VWMD (0% in MS versus 57% in VWMD).Despite many similar MRI findings, our results suggest that a careful analysis of the morphology and the location of the lesions is helpful to differentiate these distinct disorders.

PIMD: 26674332

White and gray matter damage in primary progressive MS: The chicken or the egg?

The temporal relationship between white matter (WM) and gray matter (GM) damage in vivo in early primary progressive multiple sclerosis (PPMS) was investigated testing 2 hypotheses: (1) WM tract abnormalities predict subsequent changes in the connected cortex ("primary WM damage model"); and (2) cortical abnormalities predict later changes in connected WM tracts ("primary GM damage model").Forty-seven patients with early PPMS and 18 healthy controls had conventional and magnetization transfer imaging at baseline; a subgroup of 35 patients repeated the protocol after 2 years. Masks of the corticospinal tracts, genu of the corpus callosum and optic radiations, and of connected cortical regions, were used for extracting the mean magnetization transfer ratio (MTR). Multiple regressions within each of 5 tract-cortex pairs were performed, adjusting for the dependent variable's baseline MTR; tract lesion load and MTR, spinal cord area, age, and sex were examined for potential confounding.The baseline MTR of most regions was lower in patients than in healthy controls. The tract-cortex pair relationships in the primary WM damage model were significant for the bilateral motor pair and right visual pair, while those in the primary GM damage model were only significant for the right motor pair. Lower lesion MTR at baseline was associated with lower MTR in the same tract normal-appearing WM at 2 years in 3 tracts.These results are consistent with the hypothesis that in early PPMS, cortical damage is for the most part a sequela of normal-appearing WM pathology, which, in turn, is predicted by abnormalities within WM lesions.

PIMD: 26662919

S1P1 deletion in oligodendroglial lineage cells: Effect on differentiation and myelination.

Sphingosine 1-phosphate (S1P) receptors are G protein-coupled receptors expressed by many cell types, including cells of oligodendrocyte (OLG) lineage. We had previously shown that targeted deletion of S1P1 in OLG lineage cells did not result in obvious clinical phenotype or altered number of OLGs at 3 months, but there were subtle abnormalities in myelin. In this study, we examined the role of S1P1 in developmental myelination and cell survival, focusing on age 3 weeks. We found that S1P1 deficiency led to delayed differentiation of OLG progenitors (OPCs) into OLGs that is independent of p38 phosphorylation. This was accompanied by decreased levels of myelin basic protein (MBP) but not of myelin-OLG glycoprotein (MOG), and slight decrease in myelin thickness in the corpus callosum of S1P1 conditional knockout (CKO) mice. S1P1 -deficient OLGs exhibited slower process extension, which was associated with attenuated phosphorylation of extracellular signal regulated kinases (ERKs) and p21-activated kinases (PAKs), and with upregulation of tropomodulin1. Basal levels of pAkt were not affected, though expectedly, no response to a selective S1P1 agonist SEW2871 was observed. S1P1 -deficient OLGs did not exhibit increased cell death in response to cuprizone, tumor necrosis factor-α, or deprivation of nutrients and growth factors. We conclude that S1P1 signaling regulates OLG development, morphological maturation and early myelination.

PIMD: 26553080

Remyelination of the Corpus Callosum by Olfactory Ensheathing Cell in an Experimental Model of Multiple Sclerosis.

Multiple Sclerosis (MS) causes loss of the myelin sheath, which leads to loss of neurons. Regeneration of myelin sheath stimulates axon regeneration and neurons' survival. In this study, olfactory ensheathing cell (OEC) transplantation is investigated to restore myelin sheath in an experimental model of MS in male mice.OECs were isolated from the olfactory mucosa of seven-day-old infant rats and cultured. Then, cells were evaluated and approved by flow cytometry by p75 and GFAP markers. A total of 32 mice (C57BL /6) were studied in four groups; 1) without any treatment (control), 2) Sham (receiving PBS), 3) MS model and 4) MS and OEC transplantation. MS was induced by adding Cuprizon in the diet of animals for six weeks. After the expiration of 20 days, histologic analysis was performed with approval of the presence of cells in the graft area and the removal of myelin and myelin regeneration with two types of luxal fast blue (LFB) staining and immunohistochemistry. The purity of the cells ensheathing the olfactory was 90%. There was a significant difference in Myelin percentage of PBS and OEC recipient groups ($P \leq 0.05$). MBP and PLP of the myelin sheath in the group receiving OECs were more than MS group.According to the findings, in MS model MBP and PLP of the myelin sheath is reduced. In the group receiving OECs, it was returned to a normal level significantly compared to the sham group received only PBS significant differences were observed. The OECs transplantation can improve myelin restoration.

PIMD: 26538779

Progesterone Enhanced Remyelination in the Mouse Corpus Callosum after Cuprizone Induced Demyelination.

Progesterone as a sex steroid hormone is thought to affect and prevent demyelination, but its role in promoting myelin repair is far less investigated. In this study, remyelinating potential of progesterone in corpus callosum was evaluated on an experimental model of MS.In this experimental study, adult male C57BL/6 mice were fed with 0.2% (w/w) cuprizone in ground breeder chow ad libitum for 6 weeks. At day zero, after cuprizone removal, mice were divided randomly into two groups: (a) placebo group, which received saline pellet implant, (b) progesterone group, which received progesterone pellet implant. Some mice of the same age were fed with their normal diet to serve as the healthy control group. Two weeks after progesterone administration, Myelin content was assessed by Luxol-fast blue staining. The myelin basic protein (MBP) and proteolipid protein (PLP) expression were assessed using Western blot analysis and the changes in the number of oligodendrocytes and oligodendroglial progenitor cells were assessed by immunohistochemistry (IHC) and flow cytometry.Luxol-fast blue staining revealed enhanced remyelination in the progesterone group when compared with the placebo group. Densitometry measurements of immunoblots demonstrated that MBP and PLP proteins contents were significantly increased in the progesterone group compared with the placebo group. Flow cytometry and IHC analysis showed increases in Olig2 and O4 cells in the progesterone group compared with the placebo group.Overall, our results indicate that progesterone treatment can stimulate myelin production and that it may provide a feasible and practical way for remyelination in diseases such as multiple sclerosis.

PIMD: 26525654

Diffusion kurtosis imaging probes cortical alterations and white matter pathology following cuprizone induced demyelination and spontaneous remyelination.

Although MRI is the gold standard for the diagnosis and monitoring of multiple sclerosis (MS), current conventional MRI techniques often fail to detect cortical alterations and provide little information about gliosis, axonal damage and myelin status of lesioned areas. Diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) provide sensitive and complementary measures of the neural tissue microstructure. Additionally, specific white matter tract integrity (WMTI) metrics modelling the diffusion in white matter were recently derived. In the current study we used the well-characterized cuprizone mouse model of central nervous system demyelination to assess the temporal evolution of diffusion tensor (DT), diffusion kurtosis tensor (DK) and WMTI-derived metrics following acute inflammatory demyelination and spontaneous remyelination. While DT-derived metrics were unable to detect cuprizone induced cortical alterations, the mean kurtosis (MK) and radial kurtosis (RK) were found decreased under cuprizone administration, as compared to age-matched controls, in both the motor and somatosensory cortices. The MK remained decreased in the motor cortices at the end of the recovery period, reflecting long lasting impairment of myelination. In white matter, DT, DK and WMTI-derived metrics enabled the detection of cuprizone induced changes differentially according to the stage and the severity of the lesion. More specifically, the MK, the RK and the axonal water fraction (AWF) were the most sensitive for the detection of cuprizone induced changes in the genu of the corpus callosum, a region less affected by cuprizone administration. Additionally, microgliosis was associated with an increase of MK and RK during the acute inflammatory demyelination phase. In regions undergoing severe demyelination, namely the body and splenium of the corpus callosum, DT-derived metrics, notably the mean diffusion (MD) and radial diffusion (RD), were among the best discriminators between cuprizone and control groups, hence highlighting their ability to detect both acute and long lasting changes. Interestingly, WMTI-derived metrics showed the aptitude to distinguish between the different stages of the disease. Both the intra-axonal diffusivity (Da) and the AWF were found to be decreased in the cuprizone treated group, Da specifically decreased during the acute inflammatory demyelinating phase whereas the AWF decrease was associated to the spontaneous remyelination and the recovery period. Altogether our results demonstrate that DKI is sensitive to alterations of cortical areas and provides, along with WMTI metrics, information that is complementary to DT-derived metrics for the characterization of demyelination in both white and grey matter and subsequent inflammatory processes associated with a demyelinating event.

PIMD: 26516389

Evaluation of the Degradation of the Selected Projectile, Commissural and Association White Matter Tracts Within Normal Appearing White Matter in Patients with Multiple Sclerosis Using Diffusion Tensor MR Imaging - a Preliminary Study.

The aim of the study was to assess the impairment of the selected white matter tracts within normal appearing white matter (NAWM) in multiple sclerosis (MS) patients using diffusion tensor imaging (DTI).Thirty-six patients (mean age 33.4 yrs) with clinically definite, relapsing-remitting MS and mild disability (EDSS - Expanded Disability Status Scale 1-3.5) and 16 control subjects (mean age 34.4 yrs) were enrolled in the study. DTI examinations were performed on a 1.5T MR scanner. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were obtained with a small ROI method in several white matter tracts within NAWM including: the middle cerebellar peduncles (MCP), the inferior longitudinal fasciculi (ILF), inferior frontooccipital fasciculi (IFOF), genu (GCC) and splenium of the corpus callosum (SCC), posterior limbs of the internal capsules (PLIC), superior longitudinal fasciculi (SLF) and posterior cingula (CG). There were no demyelinative lesions within the ROIs in any of the patients.A significant decrease in FA was found in MS patients in both the ILFs and IFOFs ($p<0.001$) and in the left MCP and right SLF ($p<0.05$), compared to the normal subjects. There were no significant differences in FA values in the remaining evaluated ROIs, between MS patients and the control group. A significant increase in ADC ($p<0.05$) was found only in the right PLIC and the right SLF in MS subjects, compared to the control group.The FA values could be a noninvasive neuroimaging biomarker for assessing the microstructural changes within NAWM tracts in MS patients.

PIMD: 26514969

Scutellarin Alleviates Behavioral Deficits in a Mouse Model of Multiple Sclerosis, Possibly Through Protecting Neural Stem Cells.

Scutellarin, a flavonoid extracted from an herbal medication (Erigeron breviscapus Hand-Mazz), has been shown to protect neurons against damage and to promote neurogenesis, and thus has therapeutic potential in the treatment of a variety of neurodegenerative diseases. Since neural stem cells (NSCs) could differentiate into myelin-producing oligodendrocytes, we speculate that scutellarin could also be used to treat multiple sclerosis (MS). In the current study, we examined potential effects of scutellarin using a mouse model of MS. Briefly, adult C57BL/6 mice exposed to cuprizone (8 mg/day through diet, for 6 consecutive weeks) randomly received scutellarin (50 mg/kg/day) or vehicle for 10 consecutive days. In the scutellarin-treated group, rotarod testing at the end of the treatment showed significant improvement of motor function (increased time to fall); myelin basic protein (MBP) staining of the corpus callosum revealed decreased demyelination; TUNEL staining followed by Nestin or Sox2 staining revealed increased number of NSCs and decreased rate of NSC apoptosis in the subventricular zone (SVZ) of the lateral ventricles (LV). In a series of experiments using cultured NSCs subjected to cuprizone injury, we confirmed the protective effects of scutellarin. At 30 μM, scutellarin increased the commitment of NSCs to the oligodendrocyte and neuronal lineages, as evidenced by NG2 chondroitin sulfate proteoglycan (NG2) and doublecortin (DCX) staining. Differentiation into astrocytes (as revealed by glial fibrillary acidic protein (GFAP) staining) was decreased. Maturation of the NSCs committed to the oligodendrocyte lineage, as evidenced by oligodendrocyte marker O4 antibody (O4) staining and MBP staining, was also promoted by scutellarin. Further analysis revealed that scutellarin might suppress the phosphorylation of p38 in cuprizone-induced NSCs. In summary, scutellarin could alleviate motor deficits in a mouse model for MS, possibly by inhibiting NSC apoptosis and promoting differentiation of NSCs to myelin-producing oligodendrocytes.

PIMD: 26489686

A Distinct Class of Antibodies May Be an Indicator of Gray Matter Autoimmunity in Early and Established Relapsing Remitting Multiple Sclerosis Patients.

*These authors contributed equally to the work in this manuscript.We have previously identified a distinct class of antibodies expressed by B cells in the cerebrospinal fluid (CSF) of early and established relapsing remitting multiple sclerosis (RRMS) patients that is not observed in healthy donors. These antibodies contain a unique pattern of mutations in six codons along VH4 antibody genes that we termed the antibody gene signature (AGS). In fact, patients who have such B cells in their CSF are identified as either having RRMS or developing RRMS in the future. As mutations in antibody genes increase antibody affinity for particular antigens, the goal for this study was to investigate whether AGS(+) antibodies bind to brain tissue antigens. Single B cells were isolated from the CSF of 10 patients with early or established RRMS. We chose 32 of these B cells that expressed antibodies enriched for the AGS for further study. We generated monoclonal full-length recombinant human antibodies (rhAbs) and used both immunological assays and immunohistochemistry to investigate the capacity of these AGS(+) rhAbs to bind brain tissue antigens. AGS(+) rhAbs did not recognize myelin tracts in the corpus callosum. Instead, AGS(+) rhAbs recognized neuronal nuclei and/or astrocytes, which are prevalent in the cortical gray matter. This pattern was unique to the AGS(+) antibodies from early and established RRMS patients, as AGS(+) antibodies from an early neuromyelitis optica patient did not display the same reactivity. Prevalence of CSF-derived B cells expressing AGS(+) antibodies that bind to these cell types may be an indicator of gray matter-directed autoimmunity in early and established RRMS patients.

PIMD: 26458494

Gadolinium-Enhancing Lesions Lead to Decreases in White Matter Tract Fractional Anisotropy in Multiple Sclerosis.

Although MRI identification of new lesions forms the basis for monitoring disease progression in multiple sclerosis patients, how lesion activity relates to longitudinal white matter changes in the brain is unknown. We hypothesized that patients with gadolinium-enhancing lesions would show greater longitudinal decline in fractional anisotropy in major tracts compared to those with stable disease.Thirty patients with relapsing-remitting multiple sclerosis were included in this study-13 had enhancing lesions at baseline and 17 did not. Each patient underwent at least two 3 Tesla contrast-enhanced MRI scans with a DTI sequence with a median interval of 2.1 years between scans. The forceps major and minor of the corpus callosum and the bilateral corticospinal tracts were selected as the major white matter tracts of interest. These tracts were reconstructed using region-of-interest placement on standard anatomical landmarks and a fiber assignment by continuous tracking algorithm using TrackVis (version 0.5.2.2) software. Mixed-effects regression models were used to determine the association between enhancing lesions and subsequent longitudinal change in fractional anisotropy.In patients with enhancing lesions, there was greater decline in fractional anisotropy compared to those with stable disease in the forceps major (P = .026), right corticospinal tract (P = .032), and marginally in the left corticospinal tract (P = .050), but not the forceps minor (P = .11).Fractional anisotropy of major white matter tracts declined more rapidly in patients with enhancing lesions, suggesting greater diffuse white matter injury with active inflammatory disease. DTI may provide a means of monitoring white matter injury following relapses.

PIMD: 26372950

Remyelination after Lysophosphatidyl Choline-Induced Demyelination Is Stimulated by Bone Marrow Stromal Cell-Derived Oligoprogenitor Cell Transplantation.

Bone marrow stromal cells (BMSCs) are a desirable cell source that may be useful for the treatment of neurodegenerative diseases given their capacity to differentiate into various types of cells. The current study aimed to investigate whether oligoprogenitor cell (OPC)-derived BMSCs have therapeutic benefits in an animal model of local demyelination. BMSCs were transdifferentiated into OPCs using a defined culture medium supplemented with a combination of inducers. The differentiation capacity of the BMSCs was evaluated at the end of the induction phase by assessing the expression levels of the glial-specific markers oligodendrocyte transcription factor 2 and O4 surface antigen. Local demyelination was induced in the corpus callosum of adult female rats via direct injection of lysophosphatidylcholine (LPC) followed by engraftment of BMSC-generated OPCs. The rats were divided into sham control, vehicle control, and cell-transplanted groups. The changes in the extent of demyelination and the robustness of the remyelination event were assessed using Luxol Fast Blue staining and immunohistochemical analysis 1 week after LPC injection and 2 weeks after cell transplantation. Consequently, transplantation of OPCs into the demyelinated corpus callosum model resulted in differentiation of the cells into mature oligodendrocytes that were immunopositive for myelin basic protein. Furthermore, OPC transplantation mitigated demyelination and augmented remyelination relative to controls. These findings suggest that BMSC-derived OPCs can be utilized in therapeutic approaches for the management of demyelination-associated diseases such as multiple sclerosis.

PIMD: 26365504

Callosal anatomical and effective connectivity between primary motor cortices predicts visually cued bimanual temporal coordination performance.

Default in-phase coupling of hand movements needs to be suppressed when temporal coordination is required for out-of-phase bimanual movements. There is lack of knowledge on how the brain overrides these default in-phase movements to enable a required interval of activity between hands. We used a visually cued bimanual temporal coordination (vc-BTC) paradigm with a constant rhythmical time base of 1 s, to test the accuracy of in-phase and out-of-phase (0.1, 0.2,…,0.9) finger tapping. We hypothesized that (1) stronger anatomical and effective interhemispheric connectivity between the hand areas of the primary motor cortex (M1HAND) predict higher temporal offsets between hands in the out-of-phase conditions of the vc-BTC; (2) patients with relapsing-remitting multiple sclerosis (RRMS) and clinically isolated syndrome (CIS) have reduced interhemispheric connectivity and altered between-hand coupling. Anatomical connectivity was determined by fractional anisotropy of callosal hand motor fibers (FA-hCMF). Effective connectivity was probed by short interval interhemispheric inhibition (S-IHI) using paired-coil transcranial magnetic stimulation (TMS). In healthy subjects, higher FA-hCMF and S-IHI correlated with higher temporal offsets between hands in the out-of-phase conditions of the tapping test. FA-hCMF was reduced in patients with RRMS but not in CIS, while S-IHI was reduced in both patient groups. These abnormalities were associated with smaller temporal offsets between hands leading to less deviation from the required phasing in the out-of-phase tapping conditions. Findings provide multiple levels of evidence that callosal anatomical and effective connectivity between the hand areas of the motor cortices play important roles in visually cued bimanual temporal coordination performance.

PIMD: 26362893

Increased albumin quotient (QAlb) in patients after first clinical event suggestive of multiple sclerosis is associated with development of brain atrophy and greater disability 48 months later.

The utility of blood-brain barrier (BBB) biomarkers for clinical and magnetic resonance imaging progression in multiple sclerosis (MS) has not been extensively investigated.To determine whether cerebrospinal fluid (CSF) measures of BBB at clinical onset predict radiological and clinical deterioration over 48 months.This longitudinal study included 182 patients after first clinical event suggestive of MS treated with weekly intramuscular interferon beta-1a. CSF and serum samples were analyzed for leukocytes, total protein, albumin, immunoglobulins, and oligoclonal bands. Optimal thresholds for the albumin quotient (QAlb) were determined. Mixed-effect model analyses, adjusted for age, gender, and treatment escalation, were used to analyze relationship between CSF measures and disease activity outcomes over 48 months of follow-up.Increased QAlb at clinical onset was associated with enlargement of lateral ventricles ($p = .001$) and greater whole brain ($p = .003$), white matter ($p < .001$), corpus callosum ($p < .001$), and thalamus ($p = .003$) volume loss over 48 months. Higher QAlb was associated with higher Expanded Disability Status Scale score over 48 months ($p = .002$).Increased QAlb at clinical onset is associated with increased brain atrophy and greater disability in patients after first clinical event suggestive of MS.

PIMD: 26359854

Thalamic atrophy predicts cognitive impairment in relapsing remitting multiple sclerosis. Effect on instrumental activities of daily living and employment status.

Cognitive impairment is an important predictor of quality of life at all stages of MS. Magnetic Resonance Imaging (MRI) markers have been used to associate tissue damage with cognitive dysfunction.The aim of the study was to designate the MRI marker that predicts cognitive decline and explore its effect on every day activities and employment status.50 RRMS patients and 31 healthy participants underwent neuropsychological assessment using the Trail Making Test (TMT) parts A and B, semantic and phonological verbal fluency task and a computerized cognitive screening battery (Central Nervous System Vital Signs). Everyday activities were evaluated with the instrumental activities of daily living (IADL) scale and employment status. Brain MRI was performed in all participants. We measured total lesion volume, third ventricle width, corpus callosum and thalamic atrophy.The frequency of cognitive dysfunction for our RRMS patients was 38%. RRMS patients differed significantly from controls on the TMTA, TMTB, phonological verbal fluency task, memory, psychomotor speed, reaction time and cognitive flexibility. Neuropsychological measures had a strong correlation with all MRI atrophy measures and a weak or moderate correlation with lesion volume. Psychomotor speed was the most sensitive marker for IADL, while memory and TMTB for employment status. Thalamic area was the most sensitive MRI marker for memory, psychomotor speed and TMTB..Thalamic atrophy predicts the clinically meaningful cognitive decline in our RRMS patients.

PIMD: 26338327

Inactivation of Protein Tyrosine Phosphatase Receptor Type Z by Pleiotrophin Promotes Remyelination through Activation of Differentiation of Oligodendrocyte Precursor Cells.

No abstract

PIMD: 26337870

Loss of galectin-3 decreases the number of immune cells in the subventricular zone and restores proliferation in a viral model of multiple sclerosis.

Multiple sclerosis (MS) frequently starts near the lateral ventricles, which are lined by subventricular zone (SVZ) progenitor cells that can migrate to lesions and contribute to repair. Because MS-induced inflammation may decrease SVZ proliferation and thus limit repair, we studied the role of galectin-3 (Gal-3), a proinflammatory protein. Gal-3 expression was increased in periventricular regions of human MS in post-mortem brain samples and was also upregulated in periventricular regions in a murine MS model, Theiler's murine encephalomyelitis virus (TMEV) infection. Whereas TMEV increased SVZ chemokine (CCL2, CCL5, CCL, and CXCL10) expression in wild type (WT) mice, this was inhibited in Gal-3(-/-) mice. Though numerous CD45+ immune cells entered the SVZ of WT mice after TMEV infection, their numbers were significantly diminished in Gal-3(-/-) mice. TMEV also reduced neuroblast and proliferative SVZ cell numbers in WT mice but this was restored in Gal-3(-/-) mice and was correlated with increased numbers of doublecortin+ neuroblasts in the corpus callosum. In summary, our data showed that loss of Gal-3 blocked chemokine increases after TMEV, reduced immune cell migration into the SVZ, reestablished SVZ proliferation and increased the number of progenitors in the corpus callosum. These results suggest Gal-3 plays a central role in modulating the SVZ neurogenic niche's response to this model of MS.

PIMD: 26321022

A manic episode with psychotic features improved by methylprednisolone in a patient with multiple sclerosis.

Several studies have reported a higher prevalence of unipolar depression and bipolar disorder among patients with multiple sclerosis (MS). However, only a few studies have reported manic episodes concomitant with new lesions enhanced by gadolinium on brain magnetic resonance imaging (MRI). Here we report the case of a 47-year-old woman suffering from MS admitted for a manic episode with psychotic features. Brain MRI revealed three new T2 lesions enhanced by gadolinium located in the corpus callosum and in ventromedial prefrontal regions. She rapidly recovered with intravenous methylprednisolone in combination with risperidone. In conclusion, in this patient, the fact that gadolinium-enhancing lesion coincided with new symptoms which responded quickly to corticosteroids suggests that the manic episode was an acute manifestation of MS.

PIMD: 26310973

The Effect of Melatonin on Behavioral, Molecular, and Histopathological Changes in Cuprizone Model of Demyelination.

Multiple sclerosis (MS) is an autoimmune, demyelinating disease of the central nervous system. The protective effects of melatonin (MLT) on various neurodegenerative diseases, including MS, have been suggested. In the present study, we examined the effect of MLT on demyelination, apoptosis, inflammation, and behavioral dysfunctions in the cuprizone toxic model of demyelination. C57BL/6J mice were fed a chaw containing 0.2 % cuprizone for 5 weeks and received two doses of MLT (50 and 100 mg/kg) intraperitoneally for the last 7 days of cuprizone diet. Administration of MLT improved motor behavior deficits induced by cuprizone diet. MLT dose-dependently decreased the mean number of apoptotic cells via decreasing caspase-3 and Bax as well as increasing Bcl-2 levels. In addition, MLT significantly enhanced nuclear factor-κB activation and decreased heme oxygenase-1 level. However, MLT had no effect on interleukin-6 and myelin protein production. Our data revealed that MLT improved neurological deficits and enhanced cell survival but was not able to initiate myelin production in the cuprizone model of demyelination. These findings may be important for the design of potential MLT therapy in demyelinating disorders, such as MS.

PIMD: 26289756

[A case of multiple sclerosis with bilateral intermediate uveitis].

We describe a case of 20-year-old woman with visual impairment in her left eye. Her left visual acuity was 0.07 and an ophthalmoscopic examination demonstrated bilateral intermediate uveitis (IU). A neurological examination on admission revealed lower nasal quadrantanopsia in her left eye and an exaggerated right patellar tendon reflex. A T2-weighted MRI showed multiple high-intensity lesions in the bilateral periventricular region, corpus callosum, medulla. A short T1 inversion recovery MRI also showed a swollen left retrobulbar optic nerve and posterior thoracic cord lesion at Th 9 level. The latter longitudinal length was approximately 20 mm. Laboratory investigation demonstrated no abnormalities including an anti-aquaporin-4 antibody. A cerebrospinal fluid examination revealed an increased IgG-index (1.21) with oligoclonal IgG babds. Initially, a diagnosis of retrobulbar optic neuritis with IU was made. She received subtenon corticosteroid injection with intravenous methylprednisolone pulse and oral prednisolone therapy. An immediate improvement of her visual symptoms and MRI abnormalities was observed. Approximately 1 year later, a new high-intensity lesion in the right internal capsule was present on a follow-up T2-weighted brain MRI, established a diagnosis of multiple sclerosis (MS) based on the McDonald criteria in 2010. Previous reports in Japan demonstrated few cases of uveitis in patients with MS and this is the first report of MS with IU in Japan.

PIMD: 26278274

On the relation between self-reported cognitive fatigue and the posterior hypothalamic-brainstem network.

Various causes have been suggested for multiple sclerosis (MS) related fatigue. Hypothalamus-brainstem fibres play a role in sleep-wake regulation and in hypothalamic deactivation during inflammatory states. Hence, they may play a role for experiencing fatigue by changing bottom-up hypothalamic activation.Multiple sclerosis patients with and without self-reported cognitive fatigue and healthy controls were analysed with respect to the integrity of hypothalamus-brainstem fibres using diffusion-tensor imaging based tractography, focusing on the anterior, medial and posterior hypothalamic areas, controlling for clinical impairment and excluding participants with depressive mood.Multiple sclerosis patients without self-reported cognitive fatigue showed increased axial and radial diffusivity levels specifically for fibres connecting the right posterior hypothalamus with the right locus coeruleus, but not for the medial hypothalamus and the corpus callosum. Moreover, there were no differences between MS patients with and without fatigue in brain atrophy and lesion load, which could explain our results.Multiple sclerosis patients not experiencing fatigue show increased axial and radial diffusivity for fibres connecting the posterior hypothalamus and the brainstem, which might prevent bottom-up activation of the posterior hypothalamus and therefore downregulation of structures responsible for wakefulness and exploratory states of mind.

PIMD: 26246109

Brain atrophy and physical disability in primary progressive multiple sclerosis: A volumetric study.

Grey matter atrophy has been shown in primary progressive multiple sclerosis (PPMS), but its association with physical incapacity is unclear. We submitted 19 patients with PPMS to a neurological evaluation and brain magnetic resonance imaging (MRI) with volumetric analysis using FreeSurfer. We found no relation between the Expanded Disability Status Scale or disease duration and the grey matter or white matter structures analysed. Lesion load was negatively correlated with cortical and subcortical grey matter volumes, but not with total white matter volume. We concluded that physical disability in PPMS is not directly related to brain atrophy and that focal inflammatory white matter lesions may contribute to progressive neuronal degeneration.Primary progressive multiple sclerosis (PPMS) is characterized by chronic progression since onset, with predominant involvement of the spinal cord and prominent neurodegeneration. Grey matter atrophy has been shown in patients with PPMS, but its association with clinical incapacity is uncertain. We investigated the relationship between regional brain atrophy and physical disability in patients with PPMS.Patients with an established diagnosis of PPMS underwent a neurological evaluation followed by brain MRI at 1.5 T. Volumetric analysis was performed with FreeSurfer software, and evaluated the neocortex, total white matter, total subcortical grey matter, putamen, caudate, globus pallidus, thalamus, hippocampus, brainstem, corpus callosum and pre-central gyrus volumes. Clinical data obtained included physical disability as measured by the Expanded Disability Status Scale (EDSS).Nineteen patients were included, 14 female (73.7%), mean age of 55.7 (SD 7.6) and mean disease duration of 13.0 years (SD 8.8). Median EDSS score was 6.0 (3.5-8.0). The average T1 lesion load (4.9 cm^3, SD 3.4) and T2 load (10.5 cm^3, SD 9.9) did not relate to disease duration. There was no significant correlation between EDSS score or disease duration and the cortical grey matter, deep grey matter or white matter structures analysed. Lesion load was negatively correlated with cortical and subcortical grey matter volumes ($p < 0.05$), but not with total white matter volume.Physical disability in PPMS is not directly related to brain volume loss. Grey matter atrophy correlates with lesion load in patients with PPMS, indicating that focal inflammatory white matter lesions may contribute to progressive neuronal degeneration.

PIMD: 26199355

Diffusion tensor magnetic resonance imaging in very early onset pediatric multiple sclerosis.

Active myelination during childhood may influence the impact of multiple sclerosis (MS) on brain structural integrity. We studied normal-appearing white matter (NAWM) in children with MS onset before age 12 years using diffusion tensor (DT) magnetic resonance imaging (MRI).DT MRI scans were obtained from 22 MS children with their first attack before age 12 years, and 31 healthy controls from two referral centers. Using probabilistic tractography, brain tissue integrity within interhemispheric, intrahemispheric, and projection tracts was compared between patients and site-matched controls. The impact of disease and age at MRI on tract NAWM fractional anisotropy (FA) and mean diffusivity (MD) values was evaluated using linear models.Compared to controls, pediatric MS patients had reduced FA and increased MD of the bilateral superior longitudinal fasciculus and corpus callosum (CC), without center-by-group interaction. CC NAWM average FA was correlated with brain T2 lesion volume. In controls, the majority of the tracts analyzed showed a significant increase of FA and decrease of MD with age. Such a linear correlation was lost in patients.In very young pediatric MS patients, DT MRI abnormalities affect brain WM tracts differentially, and are only partially correlated with focal WM lesions. Impaired maturation of WM tracts with age may be an additional factor contributing to these findings.

PIMD: 26182501

[Clinical characteristics and follow-up of pediatric patients with neuromyelitis optica and neuromyelitis optica spectrum disorders].

To analyze the clinical characteristics of pediatric neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorders (NMOSD).A retrospective analysis was performed evaluating clinical and laboratory characteristics of ten NMO and NMOSD children who were seen in our hospital from December 2010 to May 2014. Median age at onset was 8.9 years (range 0.8-13.8 years). Seven cases were female and three were male. Median disease duration was 1.5 months (range 1-18.5 months).Eight patients fulfilled diagnostic criteria for NMO and two patients fulfilled diagnostic criteria for NMOSD. The two NMOSD patients had recurrent longitudinally extensive transverse myelitis. Four cases had a monophasic disease course, and six cases had a recurrent course. In eight NMO patients, neuritis was the initial presentation. The two NMOSD patients had no neuritis in the first attack. Nine cases had clinical manifestations of myelitis, one case had asymptomatic spinal cord MRI anomaly. Among the ten patients, seven cases had brain lesions, wherein, four cases had the midbrain involvement and in four cases extensive hemispheric white matter was involved. Three cases had medullary involvement. And two cases had posterior limb of the internal capsule involvement, two cases had thalamus involvement. In one case there was pons, cerebellum or corpus callosum involvement, respectively. One case had accompanied brain symptoms. Of the five patients who had symptomatic brain lesions, four cases had encephalopathy accompanied by large hemispheric lesions on MRI, having a presentation similar to acute disseminated encephalomyelitis. And one case had multiple sclerosis like brain lesion. Of the ten patients tested, nine were seropositive for anti-aquaporin-4 autoantibody. One-patient was complicated with systemic lupus erythematosus. Oligoclonal bands were negative in all cases. All patients received treatment for acute attacks with high-dose intravenous methylprednisolone and intravenous gammaglobulin. The symptoms of 8 cases mitigated. Two cases whose symptoms showed no sign of improvement received plasmapheresis for acute attacks. Seven of the patients were followed up. The median duration of follow-up was 19 months (ranged from 13 months to 30 months). The median Expanded disability status (EDSS) score was 3 (range 1-7).Pediatric NMO and(or) NMOSD have a diverse clinical presentation which are more than just optic neuritis and transverse myelitis, including brain symptom. So it may be difficult to distinguish NMO and(or) NMOSD from acute disseminating encephalomyelitis and multiple sclerosis in the early stages of the disease. Antibodies to aquapoin-4 (AQP-Ab) testing is very important for differential diagnosis.

PIMD: 26157006

Functional Magnetic Resonance Imaging of Rats with Experimental Autoimmune Encephalomyelitis Reveals Brain Cortex Remodeling.

No abstract

PIMD: 26140734

Mesenchymal stem cells do not exert direct beneficial effects on CNS remyelination in the absence of the peripheral immune system.

Remyelination is the natural repair mechanism in demyelinating disorders such as multiple sclerosis (MS) and it was proposed that it might protect from axonal loss. For unknown reasons, remyelination is often incomplete or fails in MS lesions and therapeutic treatments to enhance remyelination are not available. Recently, the transplantation of exogenous mesenchymal stem cells (MSC) has emerged as a promising tool to enhance repair processes. This included the animal model experimental autoimmune encephalomyelitis (EAE), a commonly used model for the autoimmune mechanisms of MS. However, in EAE it is not clear if the beneficial effect of MSC derives from a direct influence on brain resident cells or if this is an indirect phenomenon via modulation of the peripheral immune system. The aim of this study was to determine potential regenerative functions of MSC in the toxic cuprizone model of demyelination that allows studying direct effects on de- and remyelination without the influence of the peripheral immune system. MSC from three different species (human, murine, canine) were transplanted either intraventricularly into the cerebrospinal fluid or directly into the lesion of the corpus callosum at two time points: at the onset of oligodendrocyte progenitor cell (OPC) proliferation or the peak of OPC proliferation during cuprizone induced demyelination. Our results show that MSC did not exert any regenerative effects after cuprizone induced demyelination and oligodendrocyte loss. During remyelination, MSC did not influence the dynamics of OPC proliferation and myelin formation. In conclusion, MSC did not exert direct regenerative functions in a mouse model where peripheral immune cells and especially T lymphocytes do not play a role. We thus suggest that the peripheral immune system is required for MSC to exert their effects and this is independent from a direct influence of the central nervous system.

PIMD: 26130146

Clinical and cognitive implications of cerebrospinal fluid oligoclonal bands in multiple sclerosis patients.

The presence of cerebrospinal fluid oligoclonal bands (CSF-OCB) in Caucasian patients with multiple sclerosis (MS) is supportive of diagnosis, though the relation with patients' clinical and specifically cognitive features has never been established or thoroughly examined. Thus, we investigated the clinical and for the first time the cognitive profile of MS patients in relation to CSF-OCB. We studied 108 patients with and without OCB and recorded demographic characteristics and detailed clinical data. A comprehensive neuropsychological battery covering different cognitive domains (attention/processing speed, memory, perception/constructions, reasoning, executive functions) was administered to MS patients and 142 demographically related healthy controls (HC). We did not find any significant differences between patients with and without OCB on demographic and clinical parameters ($p > 0.05$), including subtype and brain neuroimaging findings. Results revealed significantly higher cognitive scores in HC compared to both OCB subgroups, with more widespread cognitive changes in patients with OCB. Analysis between OCB subgroups showed significantly worse performance in patients with OCB on visual memory (Rey's complex figure test-recall; $p = 0.006$). Concluding, the presence of CSF-OCB in our MS patients tends to be related to more widespread cognitive changes, specifically worse visual memory. Future longitudinal studies in different populations are warranted to better clarify the clinical and cognitive characteristics related to CSF-OCB which could serve as early biomarker in disease monitoring.

PIMD: 26106550

Injury to white matter tracts in relapsing-remitting multiple sclerosis: A possible therapeutic window within the first 5 years from onset using diffusion-tensor imaging tract-based spatial statistics.

DTI studies in multiple sclerosis (MS) reveal white matter (WM) injury that occurs with disease progression. In the present study we aimed to elucidate the relationship of microstructural WM damage in patients with varying periods of disease duration. DTI scans were acquired from 90 MS patients and 25 healthy controls. Patients were grouped to short (<1 year), moderate (1 up to 6 years) and long (6-10 years) disease duration periods. Statistical analyses of the fractional anisotropy (FA) data were performed using tract-based spatial statistics (TBSS). Whole-brain skeletal FA measurements showed a significant decrease between healthy controls and the short MS disease duration group, as well as between moderate disease duration and long disease duration groups, but failed to show a significant difference between short and moderate disease duration groups. Voxelwise analysis revealed clusters of diffuse FA reductions in 40 WM tracts when comparing healthy controls and MS short disease duration group, with the point of maximal significant difference located in the left inferior longitudinal fasciculus. Comparing short with long disease duration groups, progressive FA reduction was demonstrated across 30 WM tracts, with the point of maximal significant difference migrating to the body of the corpus callosum. A non-linear pattern of WM microstructure disruption occurs in RRMS. Alterations are seen early in the disease course within 1 year from onset, reach a plateau within the next 5 years, and only later additional WM changes are detected. An important period of a possible therapeutic window therefore exists within the early disease stage.

PIMD: 26084563

Reproducibility and optimization of in vivo human diffusion-weighted MRS of the corpus callosum at 3 T and 7 T.

Diffusion-weighted MRS (DWS) of brain metabolites enables the study of cell-specific alterations in tissue microstructure by probing the diffusion of intracellular metabolites. In particular, the diffusion properties of neuronal N-acetylaspartate (NAA), typically co-measured with N-acetylaspartyl glutamate (NAAG) (NAA + NAAG = tNAA), have been shown to be sensitive to intraneuronal/axonal damage in pathologies such as stroke and multiple sclerosis. Lacking, so far, are empirical assessments of the reproducibility of DWS measures across time and subjects, as well as a systematic investigation of the optimal acquisition parameters for DWS experiments, both of which are sorely needed for clinical applications of the method. In this study, we acquired comprehensive single-volume DWS datasets of the human corpus callosum at 3 T and 7 T. We investigated the inter- and intra-subject variability of empirical and modeled diffusion properties of tNAA [D(avg) (tNAA) and D(model) (tNAA), respectively]. Subsequently, we used a jackknife-like resampling approach to explore the variance of these properties in partial data subsets reflecting different total scan durations. The coefficients of variation (C(V)) and repeatability coefficients (C(R)) for D(avg) (tNAA) and D(model) (tNAA) were calculated for both 3 T and 7 T, with overall lower variability in the 7 T results. Although this work is limited to the estimation of the diffusion properties in the corpus callosum, we show that a careful choice of diffusion-weighting conditions at both field strengths allows the accurate measurement of tNAA diffusion properties in clinically relevant experimental time. Based on the resampling results, we suggest optimized acquisition schemes of 13-min duration at 3T and 10-min duration at 7 T, whilst retaining low variability (C(V) ≈ 8%) for the tNAA diffusion measures. Power calculations for the estimation of D(model)(tNAA) and D(avg) (tNAA) based on the suggested schemes show that less than 21 subjects per group are sufficient for the detection of a 10% effect between two groups in case-control studies.

PIMD: 26067431

The Anti-Aging Protein Klotho Enhances Remyelination Following Cuprizone-Induced Demyelination.

The current study examined whether overexpression of Klotho (KL) in transgenic mice can enhance remyelination following cuprizone-induced demyelination and improves the clinical outcome in experimental autoimmune encephalomyelitis (EAE). Demyelination was achieved by feeding transgenic mice overexpressing the transmembrane form of Klotho (KL-OE) and wild-type (WT) littermates cuprizone-containing chow for 6 weeks. The animals were then allowed to remyelinate for 3 weeks. Paraphenylenediamine staining and platelets-derived growth factor receptor α (PDGFRα) and glutathione S-transferase pi (GSTpi) immunohistochemistry were performed on corpus callosum (CC) sections for quantification of myelin and progenitor and mature oligodendrocytes, respectively. The EAE model was induced with the MOG35-55 peptide. The animals were scored daily for clinical symptoms for 30 days. Following 6 weeks of demyelination, both KL-OE mice and WT littermates demonstrated almost complete and comparable demyelination of the CC. However, the level of spontaneous remyelination was increased approximately two-fold in KL-OE mice, although no significant differences in the numbers of PDGFRα and GSTpi-positive cells were observed. Following EAE induction, Klotho overexpression did not affect the clinical scores, likely due to the different roles Klotho plays in the brain and spinal cord. Thus, increasing Klotho expression should be considered as a therapy for enhancing remyelination in the brains of individuals with multiple sclerosis.

PIMD: 26067430

Anatomical Distribution of Cuprizone-Induced Lesions in C57BL6 Mice.

Although multiple sclerosis (MS) has been considered a white matter disease, MS lesions occur frequently in the gray matter parts of the brain. Gray matter demyelination and atrophy are found during earliest disease stages, and a growing body of evidence demonstrates a positive correlation between gray matter pathology and various measures of motor disability and cognitive impairment. The cuprizone model is classically regarded as white matter demyelination model. However, recent evidence suggests that different gray matter areas are also affected. In this study, we address the vulnerability of white and gray matter forebrain regions in the cuprizone model. While the corpus callosum as interhemispheric white matter tract is affected in this model, other white matter tracts such as the mammillo-thalamic tract, the columns of the fornix, the stria terminalis, the optic tract, or hippocampal fimbria do not present overt demyelination after 5-week cuprizone intoxication. In contrast, gray matter demyelination is widespread in this model. Furthermore, vulnerable white matter tracts display extensive acute axonal damage. These results highlight the relevance of the cuprizone model to study MS-related gray matter pathology and neurodegeneration.

PIMD: 26066628

Cognitive and White Matter Tract Differences in MS and Diffuse Neuropsychiatric Systemic Lupus Erythematosus.

Multiple sclerosis and neuropsychiatric systemic lupus erythematosus are autoimmune diseases with similar CNS inflammatory and neurodegenerative characteristics. Our aim was to investigate white matter tract changes and their association with cognitive function in patients with MS and those with neuropsychiatric systemic lupus erythematosus compared with healthy controls by using diffusion tensor imaging.Thirty patients with relapsing-remitting MS and 23 patients with neuropsychiatric systemic lupus erythematosus matched for disease severity and duration and 43 healthy controls were scanned with 3T MR imaging. The DTI was postprocessed, corrected for lesions, and analyzed with tract-based spatial statistics. Cognitive assessment included examination of processing speed; visual, auditory/verbal, and visual-spatial memory; and sustained attention and executive function. Differences were considered significant at $P < .05$.Tract-based spatial statistics analysis revealed significantly decreased fractional anisotropy and increased mean diffusivity in patients with MS compared with healthy controls, decreased fractional anisotropy in patients with MS compared with those with neuropsychiatric systemic lupus erythematosus, and an increased mean diffusivity in patients with neuropsychiatric systemic lupus erythematosus compared with healthy controls. Patients with MS showed decreased fractional anisotropy throughout central WM pathways, including the corpus callosum and the inferior longitudinal and fronto-occipital fasciculi compared with those with neuropsychiatric systemic lupus erythematosus. Altered cognitive scores in patients with MS were significantly associated with decreased fractional anisotropy and increased mean diffusivity in all examined domains, while in patients with diffuse neuropsychiatric systemic lupus erythematosus, only decreased fractional anisotropy in the superior WM pathways showed significant association with executive function.Patients with MS and neuropsychiatric systemic lupus erythematosus showed widespread WM tract alterations outside overt lesions, though more severe changes were identified in patients with MS. The WM tract changes were associated with cognitive dysfunction in all explored domains only in patients with MS.

PIMD: 26059535

Neuromyelitis optica with linear enhancement of corpus callosum in brain magnetic resonance imaging with contrast: a case report.

Neuromyelitis optica is a demyelinating disease of the central nervous system with various patterns of brain lesions. Corpus callosum may be involved in both multiple sclerosis and neuromyelitis optica. Previous case reports have demonstrated that callosal lesions in neuromyelitis optica are usually large and edematous and have a heterogeneous intensity showing a "marbled pattern" in the acute phase. Their size and intensity may reduce with time or disappear in the chronic stages.In this report, we describe a case of a 25-year-old Caucasian man with neuromyelitis optica who presented clinically with optic neuritis and myelitis. His brain magnetic resonance imaging demonstrated linear enhancement of the corpus callosum. Brain images with contrast agent added also showed linear ependymal layer enhancement of the lateral ventricles, which has been reported in this disease previously.Linear enhancement of corpus callosum in magnetic resonance imaging with contrast agent could help in diagnosing neuromyelitis optica and differentiating it from other demyelinating disease, especially multiple sclerosis.

PIMD: 26041801

Clinical and MRI phenotype of children with MOG antibodies.

To investigate the clinical and magnetic resonance imaging (MRI) features of anti-myelin oligodendrocyte glycoprotein (MOG) antibody-seropositive pediatric demyelinating syndromes.Serum samples collected from 74 children with suspected demyelinating disorders whom were being followed at Massachusetts General Hospital were incubated with control green fluorescent protein (GFP)- and MOG-GFP-transfected Jurkat cell clones. The binding ratios were calculated using flow cytometry. Using statistical analyses, we compared the demographic, clinical and radiological features in our seropositive and seronegative patients.We found that 13 out of 74 (17.5%) patients were seropositive for MOG. The MOG-seropositive patients were younger than the seronegative patients ($p = 0.049$). No single disease category predominated among the seropositive patients, nor was one group more likely to have a polyphasic course. There were two out of four neuromyelitis optica (NMO) patients who had MOG antibodies; both were seronegative for aquaporin -4 (AQP4) antibodies. One had monophasic disease and the other had frequent relapses. There was a bimodal distribution of the MOG-seropositive patients by age at onset, with a distinct younger group (4-8 years) having a high prevalence of encephalopathy and an older group (13-18 years), whom presented almost exclusively with optic neuritis. MRI analysis demonstrated the absence of corpus callosum lesions in the seropositive patients ($p = 0.012$). The annualized relapse rate (ARR) and the Expanded Disability Status Scale (EDSS) results at 2 years did not differ between the seropositive and seronegative patients.MOG antibodies are found across a variety of pediatric demyelinating syndromes having some distinct clinical and MRI features.

PIMD: 26041799

Functional connectivity changes and their relationship with clinical disability and white matter integrity in patients with relapsing-remitting multiple sclerosis.

To define the pathological substrate underlying disability in multiple sclerosis by evaluating the relationship of resting-state functional connectivity with microstructural brain damage, as assessed by diffusion tensor imaging, and clinical impairments.Thirty relapsing-remitting patients and 24 controls underwent 3T-MRI; motor abilities were evaluated by using measures of walking speed, hand dexterity and balance capability, while information processing speed was evaluated by a paced auditory serial addiction task. Independent component analysis and tract-based spatial statistics were applied to RS-fMRI and diffusion tensor imaging data using FSL software. Group differences, after dual regression, and clinical correlations were modelled with General-Linear-Model and corrected for multiple comparisons.Patients showed decreased functional connectivity in 5 of 11 resting-state-networks (cerebellar, executive-control, medial-visual, basal ganglia and sensorimotor), changes in inter-network correlations and widespread white matter microstructural damage. In multiple sclerosis, corpus callosum microstructural damage positively correlated with functional connectivity in cerebellar and auditory networks. Moreover, functional connectivity within the medial-visual network inversely correlated with information processing speed. White matter widespread microstructural damage inversely correlated with both the paced auditory serial addiction task and hand dexterity.Despite the within-network functional connectivity decrease and the widespread microstructural damage, the inter-network functional connectivity changes suggest a global brain functional rearrangement in multiple sclerosis. The correlation between functional connectivity alterations and callosal damage uncovers a link between functional and structural connectivity. Finally, functional connectivity abnormalities affect information processing speed rather than motor abilities.

PIMD: 26004502

In vivo histology of the myelin g-ratio with magnetic resonance imaging.

The myelin g-ratio, defined as the ratio between the inner and the outer diameter of the myelin sheath, is a fundamental property of white matter that can be computed from a simple formula relating the myelin volume fraction to the fiber volume fraction or the axon volume fraction. In this paper, a unique combination of magnetization transfer, diffusion imaging and histology is presented, providing a novel method for in vivo magnetic resonance imaging of the axon volume fraction and the myelin g-ratio. Our method was demonstrated in the corpus callosum of one cynomolgus macaque, and applied to obtain full-brain g-ratio maps in one healthy human subject and one multiple sclerosis patient. In the macaque, the g-ratio was relatively constant across the corpus callosum, as measured by both MRI and electron microscopy. In the human subjects, the g-ratio in multiple sclerosis lesions was higher than in normal appearing white matter, which was in turn higher than in healthy white matter. Measuring the g-ratio brings us one step closer to fully characterizing white matter non-invasively, making it possible to perform in vivo histology of the human brain during development, aging, disease and treatment.

PIMD: 25970835

Paroxysmal dystonia as a manifestation of multiple sclerosis.

Paroxysmal dystonia is a rare manifestation of multiple sclerosis (MS).A 41-year-old man presented to our Emergency Department with sudden and repeated episodes of left upper limb flexion and lower limb extension. His medical history included an episode of left facial palsy a year earlier. Neurological examination demonstrated only brisk deep tendon reflexes on the left upper limb. Routine blood and urine analyses were normal. Computed tomography of the brain and cervical Doppler were normal. Aspirin and sodium valproate were started, without improvement. Video-EEG monitoring revealed no electrographic abnormality synchronous with these paroxysmal events, excluding epileptic nature. Cerebral magnetic resonance imaging showed multiple T2 white matter lesions at the midbrain, right diencephalon, corpus callosum, cervical, and thoracic spinal cord. The right diencephalic lesion enhanced with gadolinium. Complete basic and immunologic analysis and serological studies were normal or negative. Oligoclonal bands were positive in cerebrospinal fluid (negative in serum). Methylprednisolone (1 g/d for 5 d) was started without clinical improvement. Carbamazepine (400 mg/d) was promptly effective, and discontinued after 1 month without recurrence.The patient met the criteria for the diagnosis of MS according to the 2010 McDonald criteria. The timely and accurate diagnosis of MS requires the recognition of its varied and atypical clinical manifestations.

PIMD: 25913734

Fibroblast growth factor signaling in oligodendrocyte-lineage cells facilitates recovery of chronically demyelinated lesions but is redundant in acute lesions.

Remyelination is a potent regenerative process in demyelinating diseases, such as multiple sclerosis, the effective therapeutic promotion of which will fill an unmet clinical need. The development of proregenerative therapies requires the identification of key regulatory targets that are likely to be involved in the integration of multiple signaling mechanisms. Fibroblast growth factor (FGF) signaling system, which comprises multiple ligands and receptors, potentially provides one such target. Since the FGF/FGF receptor (FGFR) interactions are complex and regulate multiple diverse functions of oligodendrocyte lineage cells, it is difficult to predict their overall therapeutic potential in the regeneration of oligodendrocytes and myelin. Therefore, to assess the integrated effects of FGFR signaling on this process, we simultaneously inactivated both FGFR1 and FGFR2 in oligodendrocytes and their precursors using two Cre-driver mouse lines. Acute and chronic cuprizone-induced or lysolecithin-induced demyelination was established in Fgfr1/Fgfr2 double knockout mice (dKO). We found that in the acute cuprizone model, there was normal differentiation of oligodendrocytes and recovery of myelin in the corpus callosum of both control and dKO mice. Similarly, in the spinal cord, lysolecithin-induced demyelinated lesions regenerated similarly in the dKO and control mice. In contrast, in the chronic cuprizone model, fewer differentiated oligodendrocytes and less efficient myelin recovery were observed in the dKO compared to control mice. These data suggest that while cell-autonomous FGF signaling is redundant during recovery of acute demyelinated lesions, it facilitates regenerative processes in chronic demyelination. Thus, FGF-based therapies have potential value in stimulating oligodendrocyte and myelin regeneration in late-stage disease.

PIMD: 25904020

Early magnetic resonance imaging predictors of clinical progression after 48 months in clinically isolated syndrome patients treated with intramuscular interferon β-1a.

Our aim was to identify early imaging surrogate markers of clinical progression in patients after the first demyelinating event suggestive of multiple sclerosis treated with weekly intramuscular interferon β-1a. In a prospective observational study, the predictive role of baseline and 6-month changes in magnetic resonance imaging outcomes was investigated with respect to relapse activity and development of confirmed disability progression in patients after 48 months.This study examined 210 patients. Multivariate Cox proportional hazard models were used to analyse predictors of relapse activity and confirmed disability progression after 48 months.Greater T2 lesion volume [hazard ratio (HR) 1.81; P = 0.005] and the presence of contrast-enhancing lesions (HR 2.13; P < 0.001) at baseline were significantly associated with increased cumulative risk of a second clinical attack over 48 months. A greater decrease of the corpus callosum volume (HR 2.74; P = 0.001) and greater lateral ventricle volume enlargement (HR 2.43; P = 0.002) at 6 months relative to baseline were associated with increased cumulative risk of a second clinical attack between months 6 and 48. In addition, increased risk of confirmed disability progression over 48 months in patients with greater lateral ventricle volume enlargement between baseline and 6 months (HR 4.70; P = 0.001) was detected.A greater T2 lesion volume, the presence of contrast-enhancing lesions at baseline, decrease of corpus callosum volume and lateral ventricle volume enlargement over the first 6 months in patients after the first demyelinating event treated with weekly intramuscular interferon β-1a may assist in identification of patients with the highest risk of a second clinical attack and progression of disability.

PIMD: 25871629

Longitudinal monitoring of metabolic alterations in cuprizone mouse model of multiple sclerosis using 1H-magnetic resonance spectroscopy.

Non-invasive measures of well-known pathological hallmarks of multiple sclerosis (MS) such as demyelination, inflammation and axonal injury would serve as useful markers to monitor disease progression and evaluate potential therapies. To this end, in vivo localized proton magnetic resonance spectroscopy ((1)H-MRS) provides a powerful means to monitor metabolic changes in the brain and may be sensitive to these pathological hallmarks. In our study, we used the cuprizone mouse model to study pathological features of MS, such as inflammation, de- and remyelination, in a highly reproducible manner. C57BL/6J mice were challenged with a 0.2% cuprizone diet for 6-weeks to induce demyelination, thereafter the mice were put on a cuprizone free diet for another 6weeks to induce spontaneous remyelination. We employed in vivo (1)H-MRS to longitudinally monitor metabolic changes in the corpus callosum of cuprizone-fed mice during the demyelination (weeks 4 and 6) and spontaneous remyelination (week 12) phases. The MRS spectra were quantified with LCModel and since the total creatine (tCr) levels did not change over time or between groups, metabolite concentrations were expressed as ratios relative to tCr. After 4 and 6weeks of cuprizone treatment a significant increase in taurine/tCr and a significant reduction in total N-acetylaspartate/tCr, total choline-containing compounds/tCr and glutamate/tCr could be observed compared to mice under normal diet. At week 12, when almost full remyelination was established, no statistically significant metabolic differences were present between the control and cuprizone group. Our results suggest that these metabolic changes may represent sensitive markers for cuprizone induced demyelination, axonal injury and inflammation. To the best of our knowledge, this is the first longitudinal in vivo (1)H-MRS study that monitored biochemical changes in the corpus callosum of cuprizone fed mice.

PIMD: 25857658

The corpus callosum in the diagnosis of multiple sclerosis and other CNS demyelinating and inflammatory diseases.

Lesions in the corpus callosum (CC) are important radiological clues to the diagnosis of multiple sclerosis (MS), but may also occur in other neuroinflammatory and non-neuroinflammatory conditions. In this article, we discuss the radiological features of lesions within the CC in MS and other central nervous system inflammatory and acquired demyelinating diseases. An understanding of the appearance and location of lesions in the CC is important not only for accurate diagnosis and treatment of these various conditions, but as it also provides insights into pathogenesis.

PIMD: 25852473

Alteration of synaptic connectivity of oligodendrocyte precursor cells following demyelination.

Oligodendrocyte precursor cells (OPCs) are a major source of remyelinating oligodendrocytes in demyelinating diseases such as Multiple Sclerosis (MS). While OPCs are innervated by unmyelinated axons in the normal brain, the fate of such synaptic contacts after demyelination is still unclear. By combining electrophysiology and immunostainings in different transgenic mice expressing fluorescent reporters, we studied the synaptic innervation of OPCs in the model of lysolecithin (LPC)-induced demyelination of corpus callosum. Synaptic innervation of reactivated OPCs in the lesion was revealed by the presence of AMPA receptor-mediated synaptic currents, VGluT1+ axon-OPC contacts in 3D confocal reconstructions and synaptic junctions observed by electron microscopy. Moreover, 3D confocal reconstructions of VGluT1 and NG2 immunolabeling showed the existence of glutamatergic axon-OPC contacts in post-mortem MS lesions. Interestingly, patch-clamp recordings in LPC-induced lesions demonstrated a drastic decrease in spontaneous synaptic activity of OPCs early after demyelination that was not caused by an impaired conduction of compound action potentials. A reduction in synaptic connectivity was confirmed by the lack of VGluT1+ axon-OPC contacts in virtually all rapidly proliferating OPCs stained with EdU (50-ethynyl-20-deoxyuridine). At the end of the massive proliferation phase in lesions, the proportion of innervated OPCs rapidly recovers, although the frequency of spontaneous synaptic currents did not reach control levels. In conclusion, our results demonstrate that newly-generated OPCs do not receive synaptic inputs during their active proliferation after demyelination, but gain synapses during the remyelination process. Hence, glutamatergic synaptic inputs may contribute to inhibit OPC proliferation and might have a physiopathological relevance in demyelinating disorders.

PIMD: 25787189

Subclinical MRI disease activity influences cognitive performance in MS patients.

The pathological mechanisms underlying cognitive dysfunction in multiple sclerosis (MS) are not yet fully understood and, in addition to demyelinating lesions and gray-matter atrophy, subclinical disease activity may play a role.To evaluate the contribution of asymptomatic gadolinium-enhancing lesions to cognitive dysfunction along with gray-matter damage and callosal atrophy in relapsing-remitting MS (RRMS) patients.Forty-two treated RRMS and 30 controls were evaluated. MRI (3T) variables of interest were brain white-matter and cortical lesion load, cortical and deep gray-matter volumes, corpus callosum volume and presence of gadolinium-enhancing lesions. Outcome variables included EDSS, MS Functional Composite (MSFC) subtests and the Brief Repeatable Battery of Neuropsychological tests. Cognitive dysfunction was classified as deficits in two or more cognitive subtests. Multivariate regression analyses assessed the contribution of MRI metrics to outcomes.Patients with cognitive impairment (45.2%) had more cortical lesions and lower gray-matter and callosal volumes. Patients with subclinical MRI activity (15%) had worse cognitive performance. Clinical disability on MSFC was mainly associated with putaminal atrophy. The main independent predictors for cognitive deficits were high burden of cortical lesions and number of gadolinium-enhancing lesions.Cognitive dysfunction was especially related to high burden of cortical lesions and subclinical disease activity. Cognitive studies in MS should look over subclinical disease activity as a potential contributor to cognitive impairment.

PIMD: 25787051

Integrity of hypothalamic fibers and cognitive fatigue in multiple sclerosis.

Cognitive fatigue is a common and disabling symptom of multiple sclerosis (MS), but little is known about its pathophysiology. The present study investigated whether the posterior hypothalamus, which is considered as the waking center, is associated with MS-related cognitive fatigue. We analyzed the integrity of posterior hypothalamic fibers in 49 patients with relapsing-remitting MS and 14 healthy controls. Diffusion tensor imaging (DTI) parameters were calculated for fibers between the posterior hypothalamus and, respectively, the mesencephalon, pons and prefrontal cortex. In addition, DTI parameters were computed for fibers between the anterior hypothalamus and these regions and for the corpus callosum. Cognitive fatigue was assessed using the Fatigue Scale for Motor and Cognitive Functions. Analyses of variance with repeated measures were performed to investigate the impact of cognitive fatigue on diffusion parameters. Cognitively fatigued patients (75.5%) showed a significantly lower mean axial and radial diffusivity for fibers between the posterior hypothalamus and the mesencephalon than cognitively non-fatigued patients (Group(×)Target area(×)Diffusion orientation: F=4.047; p=0.023). For fibers of the corpus callosum, MS patients presented significantly higher axial and radial diffusivity than healthy controls (Group(×)Diffusion orientation: F=9.904; p<0.001). Depressive mood, used as covariate, revealed significant interaction effects for anterior hypothalamic fibers (Target area(×)Diffusion orientation(×)Depression: F=5.882; p=0.021; Hemisphere(×)Diffusion orientation(×) Depression: F=8.744; p=0.008). Changes in integrity of fibers between the posterior hypothalamus and the mesencephalon appear to be associated with MS-related cognitive fatigue. These changes might cause an altered modulation of hypothalamic centers responsible for wakefulness. Furthermore, integrity of anterior hypothalamic fibers might be related to depression in MS.

PIMD: 25786805

MRI-Defined Corpus Callosal Atrophy in Multiple Sclerosis: A Comparison of Volumetric Measurements, Corpus Callosum Area and Index.

To compare corpus callosum area (CCA) and corpus callosum index (CCI) in terms of feasibility and their performance as biomarkers for cognitive and physical disability in multiple sclerosis (MS). A secondary aim was to compare these two methods with volumetric measurements.This study was based on a cohort of 37 MS patients and a group of age- and gender-matched healthy controls. Physical disability was assessed with the expanded disability status scale (EDSS) and cognitive disability with the symbol digit modalities test (SDMT). CCA and CCI were assessed on midsagittal brain MRI by 3 raters with varying radiological experience. Volumes of the brain, gray and white matter, corpus callosum, and MS lesions were acquired with Freesurfer and Lesion Segmentation Toolbox for Statistical Parametric Mapping.CCA and CCI were obtained within seconds with excellent intra- and inter-rater agreement, and outperformed volumetric measurements. CCA had the strongest correlations with both SDMT ($r = .82$, $P < .001$) and EDSS ($r = -.56$, $P < .001$), and the highest accuracy in differentiating patients from controls (95%) and relapse-remitting MS from progressive forms of MS (77%). CCI performed less well ($r = .73$, $P < .001$; $r = -.45$, $P < .001$; 94%; 71%). CCA also outperformed the volumetric measurements in these regards.CCA is a time-effective and robust biomarker that has stronger correlations with both EDSS and information processing speed than CCI and volumetric measurements that are commonly used as outcome measures in MS research and clinical trials.

PIMD: 25683762

Criteria improving multiple sclerosis diagnosis at the first MRI.

The introduction of the McDonald criteria has enabled earlier diagnosis of multiple sclerosis (MS). However, even with the 2010 revised criteria, nearly 50% of patients remain classified as "possible MS" following the first MRI. The present study aimed to demonstrate that time to MS diagnosis could be shorter than 2010 revised criteria, and established after a single early MRI in most patients with the association of the symptomatic lesion and at least one suggestive asymptomatic lesion. We also evaluated the short-term predictive capacity of an individual suggestive lesion on disease activity. We analyzed initial MRI results from 146 patients with MS from a multicenter retrospective study. Visualization of the symptomatic lesion was used as a primary criterion. Secondary criteria included one suggestive lesion (SL) aspect or topography on MRI, or one non-specific lesion associated with positive CSF. The proposed criteria led to a positive diagnosis of MS in 100% of cases, from information available from the time of the first MRI for 145 patients (99.3%). At least one SL was observed for 143 patients (97.9%), and positive CSF for the 3 others. Compared to the McDonald criteria, the proposed criteria had 100% sensitivity, with a significantly shorter mean time to reach a positive diagnosis. Furthermore, the simultaneous presence of corpus callosum, temporal horn, and ovoid lesions was associated with radiological or clinical activity after a year of follow-up. The proposed diagnostic criteria are easy to apply, have a good sensitivity, and allow an earlier diagnosis than the 2010 McDonald criteria. Nevertheless, prospective studies are needed to establish specificity and to confirm these findings.

PIMD: 25663955

Longitudinal High-Dimensional Principal Components Analysis with Application to Diffusion Tensor Imaging of Multiple Sclerosis.

We develop a flexible framework for modeling high-dimensional imaging data observed longitudinally. The approach decomposes the observed variability of repeatedly measured high-dimensional observations into three additive components: a subject-specific imaging random intercept that quantifies the cross-sectional variability, a subject-specific imaging slope that quantifies the dynamic irreversible deformation over multiple realizations, and a subject-visit specific imaging deviation that quantifies exchangeable effects between visits. The proposed method is very fast, scalable to studies including ultra-high dimensional data, and can easily be adapted to and executed on modest computing infrastructures. The method is applied to the longitudinal analysis of diffusion tensor imaging (DTI) data of the corpus callosum of multiple sclerosis (MS) subjects. The study includes 176 subjects observed at 466 visits. For each subject and visit the study contains a registered DTI scan of the corpus callosum at roughly 30,000 voxels.

PIMD: 25663299

Epimedium flavonoids ameliorate neuropathological changes and increases IGF-1 expression in C57BL/6 mice exposed to cuprizone.

The cuprizone (CPZ)-induced toxic demyelinating model, characterized by the degeneration of oligodendrocytes, has been utilized to study multiple sclerosis-related lesions. The present study was designed to determine the effect of epimedium flavonoids (EF), the main component extracted from Epimedium sagittatum, on CPZ-induced neuropathological changes in the corpus callosum of C57BL/6 mice. Once we determined an EF-based protective effect on the corpus callosum, we sought to explore the underlying mechanism of this protection. To induce demyelination, 8-week-old mice were fed with 0.2% CPZ for a maximum period of 6 weeks. EF treatment for a period of 3 weeks effectively decreased the breakdown of myelin, OL loss, and oligodendrocyte precursor cell accumulation in CPZ-fed mice. In addition, EF administration significantly increased the cortical expression level of insulin-like growth factor 1 (IGF-1). This study provides the first in vivo evidence of EF-based protection against CPZ-induced neuropathological changes. Furthermore, our study suggests that upregulated IGF-1 may play a role in this protection.

PIMD: 25663168

Absence of CCL2 and CCL3 Ameliorates Central Nervous System Grey Matter But Not White Matter Demyelination in the Presence of an Intact Blood-Brain Barrier.

A broad spectrum of diseases is characterized by myelin abnormalities, oligodendrocyte pathology, and concomitant glia activation, among multiple sclerosis (MS). Our knowledge regarding the factors triggering gliosis and demyelination is scanty. Chemokines are pivotal for microglia and astrocyte activation and orchestrate critical steps during the formation of central nervous system (CNS) demyelinating lesions. Redundant functions of chemokines complicate, however, the study of their functional relevance. We used the cuprizone model to study redundant functions of two chemokines, CCL2/MCP1 and CCL3/MIP1α, which are critically involved in the pathological process of cuprizone-induced demyelination. First, we generated a mutant mouse strain lacking functional genes of both chemokines and demonstrated that double-mutant animals are viable, fertile, and do not present with gross abnormalities. Astrocytes and peritoneal macrophages, cultured form tissues of these animals did neither express CCL2 nor CCL3. Exposure to cuprizone resulted in increased CCL2 and CCL3 brain levels in wild-type but not mutant animals. Cuprizone-induced demyelination, oligodendrocyte loss, and astrogliosis were significantly ameliorated in the cortex but not corpus callosum of chemokine-deficient animals. In summary, we provide a novel powerful model to study the redundant function of two important chemokines. Our study reveals that chemokine function in the CNS redounds to region-specific pathophysiological events.

PIMD: 25645891

[Optic neuropathy after retrobulbar neuritis in multiple sclerosis: are optical coherence tomography and magnetic resonance imaging useful and necessary follow-up parameters?].

This study evaluated whether progressive optic neuropathy (ON) is commonly found after retrobulbar neuritis and whether optical coherence tomography (OCT) is a useful tool for follow-up of patients with multiple sclerosis (MS).An observational study of 86 MS patients (currently treated with immunomodulation) with a past medical history of ON was carried out. Patients were assessed in 2010 and 2012 using the expanded disability status scale (EDSS), visual acuity, visual evoked potentials (VEP) and OCT but magnetic resonance imaging (MRI) was performed only in 2012.In this study 16 men and 70 women with a mean age of 41.6 and 43.8 years, respectively, were evaluated (28 patients post bilateral and 58 patients post unilateral ON including 114 eyes post-ON and 58 eyes without previous ON). Visual acuity and VEPs improved or remained the same over the study period. Visual acuity, VEPs, retinal nerve fiber layer (RNFL) thickness and macular volume were significantly worse in eyes post-ON compared to eyes without previous ON. The RNFL significantly decreased over the study period in eyes post-ON from an average of 79.9 ± 13.3 µm to 77.0 ± 12.9 µm ($p < 0.0001$) and eyes without previous ON from 89.5 ± 12.9 µm to 86.0 ± 12.5 µm ($p < 0.0001$). The number of VEPs and RNFL thickness were significantly correlated with visual acuity in all eyes. In patients after unilateral ON the brain atrophy parameters corpus callosum index (CCI) and cella media index (CMI) were negatively correlated with the EDSS.Initially MS often begins with an episode of ON which can be stabilized by immunomodulation. A mild progressive ON was generally detectable in this study but severe progressive ON was rarely observed. The OCT measurements showed no better correlation than the VEPs with visual acuity; however, OCT can be applied for confirmation of atypical ON. The corpus callosum index seems to be best associated with the degree of disability while, as already described in the literature, the number of T2 lesions is not well correlated with disability, probably due to the small-world network function of the brain and the position of the lesions in areas with no clinical relevance.

PIMD: 25610764

The relationship between regional microstructural abnormalities of the corpus callosum and physical and cognitive disability in relapsing-remitting multiple sclerosis.

Significant corpus callosum (CC) involvement has been found in relapsing-remitting multiple sclerosis (RRMS), even if conventional magnetic resonance imaging measures have shown poor correlation with clinical disability measures. In this work, we tested the potential of multimodal imaging of the entire CC to explain physical and cognitive disability in 47 patients with RRMS. Values of thickness, fractional anisotropy (FA) and mean diffusivity (MD) were extracted from 50 regions of interest (ROIs) sampled along the bundle. The relationships between clinical, neuropsychological and imaging variables were assessed by using Spearman's correlation. Multiple linear regression analysis was employed in order to identify the relative importance of imaging metrics in modeling different clinical variables. Regional fiber composition of the CC differentially explained the response variables (Expanded Disability Status Scale [EDSS], cognitive impairment). Increases in EDSS were explained by reductions in CC thickness and MD. Cognitive impairment was mainly explained by FA reductions in the genu and splenium. Regional CC imaging properties differentially explained disability within RRMS patients revealing strong, distinct patterns of correlation with clinical and cognitive status of patients affected by this specific clinical phenotype.

PIMD: 25595039

Abnormal morphology of myelin and axon pathology in murine models of multiple sclerosis.

Demyelination and axonal damage are responsible for neurological deficits in multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system. However, the pathology of axonal damage in MS is not fully understood. In this study, histological analysis of morphological changes of axonal organelles during demyelination in murine models was investigated by scanning electron microscopy (SEM) using an osmium-maceration method. In cuprizone-induced demyelination, SEM showed typical morphology of demyelination in the corpus callosum of mouse brain. In contrast, SEM displayed variations in ultrastructural abnormalities of myelin structures and axonal organelles in spinal cord white matter of experimental autoimmune encephalomyelitis (EAE) mice, an animal model of MS. Myelin detachment and excessive myelin formation were observed as typical morphological myelin abnormalities in EAE. In addition, well-developed axoplasmic reticulum-like structures and accumulated mitochondria were observed in tortuous degenerating/degenerated axons and the length of mitochondria in axons of EAE spinal cord was shorter compared with naïve spinal cord. Immunohistochemistry also revealed dysfunction of mitochondrial fusion/fission machinery in EAE spinal cord axons. Moreover, the number of Y-shaped mitochondria was significantly increased in axons of the EAE spinal cord. Axonal morphologies in myelin basic protein-deficient shiverer mice were similar to those in EAE. However, shiverer mice had "tortuous" (S-curve shaped mitochondria) and larger mitochondria compared with wild-type and EAE mice. Lastly, analysis of human MS patient autopsied brains also demonstrated abnormal myelin structures in demyelinating lesions. These results indicate that morphological abnormalities of myelin and axonal organelles play important role on the pathogenesis of axonal injury in demyelinating diseases.

PIMD: 25577802

Thyroid hormone alleviates demyelination induced by cuprizone through its role in remyelination during the remission period.

Multiple sclerosis (MS) is a disease induced by demyelination in the central nervous system, and the remission period of MS is crucial for remyelination. In addition, abnormal levels of thyroid hormone (TH) have been identified in MS. However, in the clinic, insufficient attention has been paid to the role of TH in the remission period. Indeed, TH not only functions in the development of the brain but also affects myelination. Therefore, it is necessary to observe the effect of TH on remyelination during this period. A model of demyelination induced by cuprizone (CPZ) was used to observe the function of TH in remyelination during the remission period of MS. Through weighing and behavioral tests, we found that TH improved the physical symptoms of mice impaired by CPZ. Supplementation of TH led to the repair of myelin as detected by immunohistochemistry and western blot. In addition, a sufficient TH supply resulted in an increase in myelinated axons without affecting myelin thickness and g ratio in the corpus callosum, as detected by electron microscopy. Double immunostaining with myelin basic protein and neurofilament 200 (NF200) showed that the CPZ-induced impairment of axons was alleviated by TH. Conversely, insufficient TH induced by 6-propyl-2-thiouracil resulted in the enlargement of mitochondria. Furthermore, we found that an adequate supply of TH promoted the proliferation and differentiation of oligodendrocyte lineage cells by immunofluorescence, which was beneficial to remyelination. Further, we found that TH reduced the number of astrocytes without affecting microglia. Conclusively, it was shown that TH alleviated demyelination induced by CPZ by promoting the development of oligodendrocyte lineage cells and remyelination. The critical time for remyelination is the remission period of MS. TH plays a significant role in alleviating demyelination during the remission period in the clinical treatment of MS.

PIMD: 25564492

Gain of Olig2 function in oligodendrocyte progenitors promotes remyelination.

The basic helix-loop-helix transcription factor Olig2 is a key determinant for the specification of neural precursor cells into oligodendrocyte progenitor cells. However, the functional role of Olig2 in oligodendrocyte migration and differentiation remains elusive both during developmental myelination and under demyelinating conditions of the adult central nervous system. To decipher Olig2 functions, we generated transgenic mice (TetOlig2:Sox10(rtTA/+)) overexpressing Olig2 in Sox10(+) oligodendroglial cells in a doxycycline inducible manner. We show that Olig2 overexpression increases the generation of differentiated oligodendrocytes, leading to precocious myelination of the central nervous system. Unexpectedly, we found that gain of Olig2 function in oligodendrocyte progenitor cells enhances their migration rate. To determine whether Olig2 overexpression in adult oligodendrocyte progenitor cells promotes oligodendrocyte regeneration for myelin repair, we induced lysophosphatidylcholine demyelination in the corpus callosum of TetOlig2:Sox10(rtTA/+) and control mice. We found that Olig2 overexpression enhanced oligodendrocyte progenitor cell differentiation and remyelination. To assess the relevance of these findings in demyelinating diseases, we also examined OLIG2 expression in multiple sclerosis lesions. We demonstrate that OLIG2 displays a differential expression pattern in multiple sclerosis lesions that correlates with lesion activity. Strikingly, OLIG2 was predominantly detected in NOGO-A(+) (now known as RTN4-A) maturing oligodendrocytes, which prevailed in active lesion borders, rather than chronic silent and shadow plaques. Taken together, our data provide proof of principle indicating that OLIG2 overexpression in oligodendrocyte progenitor cells might be a possible therapeutic mechanism for enhancing myelin repair.

PIMD: 25530119

TIP30 inhibits oligodendrocyte precursor cell differentiation via cytoplasmic sequestration of Olig1.

Differentiation of oligodendrocyte precursor cells (OPCs) is a prerequisite for both developmental myelination and adult remyelination in the central nervous system. The molecular mechanisms underlying OPC differentiation remain largely unknown. Here, we show that the thirty-kDa HIV-1 Tat interacting protein (TIP30) is a negative regulator in oligodendrocyte development. The TIP30(-/-) mice displayed an increased myelin protein level at postnatal day 14 and 21. By using a primary OPC culture system, we demonstrated that overexpression of TIP30 dramatically inhibited the stage progression of differentiating OPCs, while knockdown of TIP30 enhanced the differentiation of oligodendroglial cells remarkably. Moreover, overexpression of TIP30 was found to sequester the transcription factor Olig1 in the cytoplasm and weaken its nuclear translocation due to the interaction between TIP30 and Olig1, whereas knockdown of TIP30 led to more Olig1 localized in the nucleus in the initiation stage during OPC differentiation. In the cuprizone-induced demyelination model, there was a dramatic increase in NG2-expressing cells with nuclear location of Olig1 in the corpus callosum during remyelination. In contrast, within chronic demyelinated lesions in multiple sclerosis, TIP30 was abnormally expressed in NG2-expressing cells, and few nuclear Olig1 was observed in these cells. Taken together, our findings suggest that TIP30 plays a negative regulatory role in oligodendroglial differentiation.

PIMD: 25519970

[MRI comparison between hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) and primary progressive multiple sclerosis (PPMS)].

Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) is an autosomal dominant inherited leukoencephalopathy characterized by numerous cerebral neuroaxonal spheroids. To date, detection of colony stimulating factor 1 receptor (CSF-1R) gene mutation in HDLS gave us hint to think its pathophysiology as a microglial dysfunction, so called "primary microgliopathy". Clinical features of HDLS are variable. Typically, psychiatric symptoms and cognitive decline are initial features of HDLS. However, in some cases, when motor symptoms precede cognitive decline, HDLS may mimic primary progressive multiple sclerosis (PPMS). Herein we tried to clarify MRI features of HDLS (2 women, age 22-28 years, average 25.0 years, EDSS 7.00) in comparison with PPMS (6 men and 10 women, age 29-64 years, average 33.7 years, EDSS 6.03). In consequence, our MRI findings suggesting HDLS rather than PPMS are as follows: restricted diffusivity, severe corpus callosum atrophy, and preferential involvement of deep white matter lesion compared with periventricular white matter. In contrast, characteristic features suggesting PPMS are as follows: prevailing periventricular white matter lesion, cerebellar lesions, optic neuritis, and cervical spinal cord lesion. Sagittal fluid-attenuated inversion recovery (FLAIR) images of brain and cervical cord are highly useful to discriminate these two diseases.

PIMD: 25487315

Selected extracellular microRNA as potential biomarkers of multiple sclerosis activity--preliminary study.

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS). Four distinct disease courses are known, although approximately 90% of patients are diagnosed with the relapsing-remitting form (RRMS). The name "multiple sclerosis" pertains to the underlying pathology: the presence of demyelinating plaques in the CNS, in particular in the periventricular region, corpus callosum, cervical spine, and the cerebellum. There are ongoing efforts to discover biomarkers that would allow for an unequivocal diagnosis, assess the activity of inflammatory and neurodegenerative processes, or warn of disease progression. At present, small noncoding RNA particles-microRNA (miRNA, miR) seem to be particularly noteworthy, as they take part in posttranscriptional regulation of expression of various genes. Changes in composition as well as function of miRNA found in body fluids of MS patients are subjects of research, in the hope they prove accurate markers of MS activity. This preliminary study aims to evaluate the expression of selected extracellular microRNA particles (miRNA-let-7a, miRNA-92a, miRNA-684a) in patients experiencing MS relapse and remission, with healthy volunteers serving as a control group and to evaluate the correlation between miRNA expression and selected clinical parameters of those patients. Thirty-seven patients suffering from MS formed two examined groups: 20 patients undergoing relapse and 17 in remission. Thirty healthy volunteers formed the control group. All patients who were subjects to peripheral blood sampling had been hospitalized in the Department of Neurology and Stroke(1). Four milliliters of venous whole blood had been collected into EDTA tubes. The basis for the selection of the three particular miRNA investigated in this study (miRNA-let-7a, miRNA-92a, miRNA-684a) was a preliminary bioinformatic analysis of data compiled from several medical databases, including Ovid MEDLINE®, Embase, Cochrane Database of Systematic Reviews (CDSR), miRWalk, and miRBase. The isolation of extracellular microRNA from plasma was carried out using miRNeasy Mini Kit (Qiagen) reagents. The reverse transcription was carried out with TaqMan® MicroRNA Reverse Transcription Kit (Applied Biosystems), as per manufacturers' instructions. Standard microRNA TaqMan® tests (Applied Biosystems) were used for miRNA quantification. The qPCR were performed on a 7900 HT Fast Real-Time PCR System (Applied Biosystems) and analyzed using Sequence Detection System 2.3 software. In addition, all patients at the Department of Neurology and Stroke undergo a routine complete blood count with differential. The main objective of this study was to evaluate the expression of selected microRNA (has-miR-let-7a, miR-92a, and miR-648a) in the plasma of patients with MS during a relapse as well as in remission and attempt to correlate the acquired data with clinically relevant parameters of the disease. Finding such correlations may potentially lead to the use of miRNA as a biomarker of MS, which could help diagnose the disease and assess its severity and the efficacy of treatment. The difference in the expression of has-miR-let-7a in the remission group and the control group was statistically significant ($p = 0.002$). Similarly, the expression of miRNA-648a in patients in remission was significantly different from the expression in the control group ($p = 0.02$). Analysis of the correlation between the expression of miRNA-92a and the severity of the disease as measured by the EDSS scale in patients undergoing relapse showed significant negative linear correlation ($r = -0.54$, $p = 0.01$). Higher miR-648a expression correlated with more frequent flare-ups in the joint group of patients in remission and relapse ($p = 0.03$). This study is one of the few that demonstrate significantly changed expression of selected extracellular miRNA in plasma of MS patients and correlate those findings with clinical parameters. These observations may suggest that some miRNA subsets may be potential biomarkers for MS activity.

PIMD: 25480866

Corpus callosum atrophy is strongly associated with cognitive impairment in multiple sclerosis: Results of a 17-year longitudinal study.

Cognitive impairment is common in multiple sclerosis (MS) and may be subtle. The corpus callosum is essential for connectivity-demanding cognitive tasks and is significantly affected in MS, therefore it may serve as a marker for cognitive function.The objective of this paper is to longitudinally study the normalized corpus callosum area (nCCA) as a marker of cognitive function and disability in MS.Thirty-seven MS patients were followed from 1996 with follow-ups in 2004 and 2013. A healthy matched control group was recruited. The Expanded Disability Status Scale (EDSS) and Symbol Digit Modalities Test (SDMT) were assessed. The nCCA was measured on T2-weighted images. Volumetry was performed with FreeSurfer.Disease duration spanned five decades (1.6-46 years). Annual corpus callosal atrophy rate decreased with disease duration. nCCA was strongly correlated with SDMT ($r = 0.793$, $p < 0.001$) and moderately correlated with EDSS ($r = -0.545$, $p < 0.001$) after adjusting for disease duration, age and sex. The correlations of brain parenchymal fraction, white matter fraction, gray matter fraction and normalized lesion volume were less strong.The nCCA correlates well with physical and cognitive disability in time perspectives close to two decades, outperforming volumetric measurements. The nCCA is fast and could be feasible for clinical implementation where it may help identify patients in need of neuropsychological evaluation.

PIMD: 25475350

Defective sensorimotor integration in preparation for reaction time tasks in patients with multiple sclerosis.

Slowness of voluntary movements in patients with multiple sclerosis (MS) may be due to various factors, including attentional and cognitive deficits, delays in motor conduction time, and impairment of specific central nervous system circuits. In 13 healthy volunteers and 20 mildly disabled, relapsing-remitting MS patients, we examined simple reaction time (SRT) tasks requiring sensorimotor integration in circuits involving the corpus callosum and the brain stem. A somatosensory stimulus was used as the imperative signal (IS), and subjects were requested to react with either the ipsilateral or the contralateral hand (uncrossed vs. crossed SRT). In 33% of trials, a startling auditory stimulus was presented together with the IS, and the percentage reaction time change with respect to baseline SRT trials was measured (StartReact effect). The difference between crossed and uncrossed SRT, which requires interhemispheric conduction, was significantly larger in patients than in healthy subjects ($P = 0.021$). The StartReact effect, which involves activation of brain stem motor pathways, was reduced significantly in patients with respect to healthy subjects (uncrossed trials: $P = 0.015$; crossed trials: $P = 0.005$). In patients, a barely significant correlation was found between SRT delay and conduction abnormalities in motor and sensory pathways ($P = 0.02$ and $P = 0.04$, respectively). The abnormalities found specifically in trials reflecting interhemispheric transfer of information, as well as the evidence for reduced subcortical motor preparation, indicate that a delay in reaction time execution in MS patients cannot be explained solely by conduction slowing in motor and sensory pathways but suggest, instead, defective sensorimotor integration mechanisms in at least the two circuits examined.

PIMD: 25416468

Relationship between iron accumulation and white matter injury in multiple sclerosis: a case-control study.

Despite the increasing development and applications of iron imaging, the pathophysiology of iron accumulation in multiple sclerosis (MS), and its role in disease progression and development of clinical disability, is poorly understood. The aims of our study were to determine the presence and extent of iron in T2 visible lesions and gray and white matter using magnetic field correlation (MFC) MRI and correlate with microscopic white matter (WM) injury as measured by diffusion tensor imaging (DTI). This is a case-control study including a series of 31 patients with clinically definite MS. The mean age was 39 years [standard deviation (SD) = 9.55], they were 11 males and 20 females, with a disease duration average of 3 years (range 0-13) and a median EDSS of 2 (0-4.5). Seventeen healthy volunteers (6 males and 11 females) with a mean age of 36 years (SD = 11.4) were recruited. All subjects underwent MR imaging on a 3T scanner using T2-weighted sequence, 3D T1 MPRAGE, MFC, single-shot DTI and post-contrast T1. T2-lesion volumes, brain volumetry, DTI parameters and iron quantification were calculated and multiple correlations were exploited. Increased MFC was found in the putamen ($p = 0.061$), the thalamus ($p = 0.123$), the centrum semiovale ($p = 0.053$), globus pallidus ($p = 0.008$) and gray matter (GM) ($p = 0.004$) of MS patients compared to controls. The mean lesional MFC was 121 s(-2) (SD = 67), significantly lower compared to the GM MFC (<0.0001). The GM mean diffusivity (MD) was inversely correlated with the MFC in the centrum semiovale ($p < 0.001$), and in the splenium of the corpus callosum ($p < 0.001$). Patients with MS have increased iron in the globus pallidus, putamen and centrum with a trend toward increased iron in all the brain structures. Quantitative iron evaluation of WM and GM may improve the understanding of MS pathophysiology, and might serve as a surrogate marker of disease progression.

PIMD: 25224839

Prostaglandin F2α FP receptor inhibitor reduces demyelination and motor dysfunction in a cuprizone-induced multiple sclerosis mouse model.

Previously, we have demonstrated that prostamide/PGF synthase, which catalyzes the reduction of prostaglandin (PG) H2 to PGF2α, is constitutively expressed in myelin sheaths and cultured oligodendrocytes, suggesting that PGF2α has functional significance in myelin-forming oligodendrocytes. To investigate the effects of PGF2α/FP receptor signaling on demyelination, we administrated FP receptor agonist and antagonist to cuprizone-exposed mice, a model of multiple sclerosis. Mice were fed a diet containing 0.2% cuprizone for 5 weeks, which induces severe demyelination, glial activation, proinflammatory cytokine expression, and motor dysfunction. Administration of the FP receptor antagonist AL-8810 attenuated cuprizone-induced demyelination, glial activation, and TNFα expression in the corpus callosum, and also improved the motor function. These data suggest that during cuprizone-induced demyelination, PGF2α/FP receptor signaling contributes to glial activation, neuroinflammation, and demyelination, resulting in motor dysfunction. Thus, FP receptor inhibition may be a useful symptomatic treatment in multiple sclerosis.

PIMD: 25220526

The sphingosine 1-phosphate receptor agonist FTY720 is neuroprotective after cuprizone-induced CNS demyelination.

Modulation of the sphingosine 1-phosphate receptor is an approved treatment for relapsing multiple sclerosis because of its anti-inflammatory effect of retaining lymphocytes within the lymph nodes. Here, we evaluated the potential of an agonist at this receptor, FTY720 (fingolimod), to activate the promyelinating pathways within the brain to encourage remyelination and neuroprotection.In this study, we used the cuprizone model in male C57BL/6 mice and tested the promyelinating and neuroprotective effects of FTY720 after acute and chronic toxin-induced experimental demyelination. We used histological, immunohistochemical and gene expression methods.The midline of the corpus callosum was severely demyelinated after acute and chronic cuprizone-induced demyelination. Robust endogenous remyelination was evident after acute, but impaired after chronic, demyelination. FTY720 treatment modestly accelerated myelin recovery after acute but not chronic cuprizone exposure. Markers of gliosis (astrocyte and microglia activation) were not affected by FTY720 treatment. Remarkably, the accumulation of amyloid precursor protein-positive spheroids in axons was less distinct in FTY720-treated animals, indicating that this compound alleviated ongoing axonal damage.We show that even during endogenous remyelination, axonal degeneration continued at a low level, accumulating over time. This continuous neurodegenerative process was ameliorated by FTY720 treatment. FTY720 preserved CNS integrity by direct interaction with brain resident cells, the actions of which are still to be defined.

PIMD: 25165881

Dock3 protects myelin in the cuprizone model for demyelination.

Dedicator of cytokinesis 3 (Dock3) belongs to an atypical family of the guanine nucleotide exchange factors. It is predominantly expressed in the neural tissues and causes cellular morphological changes by activating the small GTPase Rac1. We previously reported that Dock3 overexpression protects retinal ganglion cells from excitotoxic cell death. Oligodendrocytes are the myelinating cells of axons in the central nervous system and these cells are damaged in demyelinating disorders including multiple sclerosis (MS) and optic neuritis. In this study, we examined if Dock3 is expressed in oligodendrocytes and if increasing Dock3 signals can suppress demyelination in a cuprizone-induced demyelination model, an animal model of MS. We demonstrate that Dock3 is expressed in oligodendrocytes and Dock3 overexpression protects myelin in the corpus callosum following cuprizone treatment. Furthermore, we show that cuprizone demyelinates optic nerves and the extent of demyelination is ameliorated in mice overexpressing Dock3. Cuprizone treatment impairs visual function, which was demonstrated by multifocal electroretinograms, an established non-invasive method, and Dock3 overexpression prevented this effect. In mice overexpressing Dock3, Erk activation is increased, suggesting this may at least partly explain the observed protective effects. Our findings suggest that Dock3 may be a therapeutic target for demyelinating disorders including optic neuritis.Cell Death and Disease (2014) 5, e1395; doi:10.1038/cddis.2014.357; published online 28 August 2014.

PIMD: 25128030

Protective Effect of a cAMP Analogue on Behavioral Deficits and Neuropathological Changes in Cuprizone Model of Demyelination.

Multiple sclerosis (MS) is an inflammatory demyelinating disease that leads to neuronal cell loss. Cyclic AMP and its analogs are well known to decrease inflammation and apoptosis. In the present study, we examined the effects of bucladesine, a cell-permeable analogue of cyclic adenosine monophosphate (cAMP), on myelin proteins (PLP, PMP-22), inflammation, and apoptotic, as well as anti-apoptotic factors in cuprizone model of demyelination. C57BL/6J mice were fed with chow containing 0.2% copper chelator cuprizone or vehicle by daily oral gavage for 5 weeks to induce reversible demyelination predominantly of the corpus callosum. Bucladesine was administered intraperitoneally at different doses (0.24, 0.48, or 0.7 μg/kg body weight) during the last 7 days of 5-week cuprizone treatment. Bucladesine exhibited a protective effect on myelination. Furthermore, bucladesine significantly decreased the production of interleukin-6 pro-inflammatory mediator as well as nuclear factor-κB activation and reduced the mean number of apoptotic cells compared to cuprizone-treated mice. Bucladesine also decreased production of caspase-3 as well as Bax and increased Bcl-2 levels. Our data revealed that enhancement of intracellular cAMP prevents demyelination and plays anti-inflammatory and anti-apoptotic properties in mice cuprizone model of demyelination. This suggests the modulation of intracellular cAMP as a potential target for treatment of MS.

PIMD: 25092984

Cognitive dysfunction in pediatric multiple sclerosis.

Cognitive and neuropsychological impairments are well documented in adult multiple sclerosis (MS). Research has only recently focused on cognitive disabilities in pediatric cases, highlighting some differences between pediatric and adult cases. Impairments in several functions have been reported in children, particularly in relation to attention, processing speed, visual-motor skills, and language. Language seems to be particularly vulnerable in pediatric MS, unlike in adults in whom it is usually preserved. Deficits in executive functions, which are considered MS-specific in adults, have been inconsistently reported in children. In children, as compared to adults, the relationship between cognitive dysfunctions and the two other main symptoms of MS, fatigue and psychiatric disorders, was poorly explored. Furthermore, data on the correlations of cognitive impairments with clinical and neuroimaging features are scarce in children, and the results are often incongruent; interestingly, involvement of corpus callosum and reduced thalamic volume differentiated patients identified as having a cognitive impairment from those without a cognitive impairment. Further studies about pediatric MS are needed in order to better understand the impact of the disease on brain development and the resulting effect on cognitive functions, particularly with respect to different therapeutic strategies.

PIMD: 25092805

Progesterone and nestorone promote myelin regeneration in chronic demyelinating lesions of corpus callosum and cerebral cortex.

Multiple Sclerosis affects mainly women and consists in intermittent or chronic damages to the myelin sheaths, focal inflammation, and axonal degeneration. Current therapies are limited to immunomodulators and antiinflammatory drugs, but there is no efficient treatment for stimulating the endogenous capacity of myelin repair. Progesterone and synthetic progestins have been shown in animal models of demyelination to attenuate myelin loss, reduce clinical symptoms severity, modulate inflammatory responses and partially reverse the age-dependent decline in remyelination. Moreover, progesterone has been demonstrated to promote myelin formation in organotypic cultures of cerebellar slices. In the present study, we show that progesterone and the synthetic 19-nor-progesterone derivative Nestorone® promote the repair of severe chronic demyelinating lesions induced by feeding cuprizone to female mice for up to 12 weeks. Progesterone and Nestorone increase the density of NG2(+) oligodendrocyte progenitor cells and CA II(+) mature oligodendrocytes and enhance the formation of myelin basic protein (MBP)- and proteolipid protein (PLP)-immunoreactive myelin. However, while demyelination in response to cuprizone was less marked in corpus callosum than in cerebral cortex, remyelination appeared earlier in the former. The remyelinating effect of progesterone was progesterone receptor (PR)-dependent, as it was absent in PR-knockout mice. Progesterone and Nestorone also decreased (but did not suppress) neuroinflammatory responses, specifically astrocyte and microglial cell activation. Therefore, some progestogens are promising therapeutic candidates for promoting the regeneration of myelin.

PIMD: 25003756

Detection of reduced interhemispheric cortical communication during task execution in multiple sclerosis patients using functional near-infrared spectroscopy.

Multiple sclerosis (MS) impairs brain activity through demyelination and loss of axons. Increased brain activity is accompanied by increases in microvascular hemoglobin oxygen saturation (oxygenation) and total hemoglobin, which can be measured using functional near-infrared spectroscopy (fNIRS). Due to the potentially reduced size and integrity of the white matter tracts within the corpus callosum, it may be expected that MS patients have reduced functional communication between the left and right sides of the brain; this could potentially be an indicator of disease progression. To assess interhemispheric communication in MS, we used fNIRS during a unilateral motor task and the resting state. The magnitude of the change in hemoglobin parameters in the motor cortex was significantly reduced in MS patients during the motor task relative to healthy control subjects. There was also a significant decrease in interhemispheric communication between the motor cortices (expressed as coherence) in MS patients compared to controls during the motor task, but not during the resting state. fNIRS assessment of interhemispheric coherence during task execution may be a useful marker in disorders with white matter damage or axonal loss, including MS.

PIMD: 24999245

Multiple sclerosis patients lacking oligoclonal bands in the cerebrospinal fluid have less global and regional brain atrophy.

To investigate whether multiple sclerosis (MS) patients with and without cerebrospinal fluid (CSF) oligoclonal immunoglobulin G bands (OCB) differ in brain atrophy. Twenty-eight OCB-negative and thirty-five OCB-positive patients were included. Larger volumes of total CSF and white matter (WM) lesions; smaller gray matter (GM) volume in the basal ganglia, diencephalon, cerebellum, and hippocampus; and smaller WM volume in corpus callosum, periventricular-deep WM, brainstem, and cerebellum, were observed in OCB-positives. OCB-negative patients, known to differ genetically from OCB-positives, are characterized by less global and regional brain atrophy. This finding supports the notion that OCB-negative MS patients may represent a clinically relevant MS subgroup.

PIMD: 24994830

Whole-brain diffusion tensor imaging in correlation to visual-evoked potentials in multiple sclerosis: a tract-based spatial statistics analysis.

Functional correlates of microstructural damage of the brain affected by MS are incompletely understood. The purpose of this study was to evaluate correlations of visual-evoked potentials with microstructural brain changes as determined by DTI in patients with demyelinating central nervous disease.Sixty-one patients with clinically isolated syndrome or MS were prospectively recruited. The mean P100 visual-evoked potential latencies of the right and left eyes of each patient were calculated and used for the analysis. For DTI acquisition, a single-shot echo-planar imaging pulse sequence with 80 diffusion directions was performed at 3T. Fractional anisotropy, radial diffusivity, and axial diffusivity were calculated and correlated with mean P100 visual-evoked potentials by tract-based spatial statistics.Significant negative correlations between mean P100 visual-evoked potentials and fractional anisotropy and significant positive correlations between mean P100 visual-evoked potentials and radial diffusivity were found widespread over the whole brain. The highest significance was found in the optic radiation, frontoparietal white matter, and corpus callosum. Significant positive correlations between mean P100 visual-evoked potentials and axial diffusivity were less widespread, notably sparing the optic radiation.Microstructural changes of the whole brain correlated significantly with mean P100 visual-evoked potentials. The distribution of the correlations showed clear differences among axial diffusivity, fractional anisotropy, and radial diffusivity, notably in the optic radiation. This finding suggests a stronger correlation of mean P100 visual-evoked potentials to demyelination than to axonal damage.

PIMD: 24989965

Restoration of axon conduction and motor deficits by therapeutic treatment with glatiramer acetate.

Glatiramer acetate (GA; Copaxone) is an approved drug for the treatment of multiple sclerosis (MS). The underlying multifactorial anti-inflammatory, neuroprotective effect of GA is in the induction of reactive T cells that release immunomodulatory cytokines and neurotrophic factors at the injury site. These GA-induced cytokines and growth factors may have a direct effect on axon function. Building on previous findings that suggest a neuroprotective effect of GA, we assessed the therapeutic effects of GA on brain and spinal cord pathology and functional correlates using the chronic experimental autoimmune encephalomyelitis (EAE) mouse model of MS. Therapeutic regimens were utilized based on promising prophylactic efficacy. More specifically, C57BL/6 mice were treated with 2 mg/mouse/day GA for 8 days beginning at various time points after EAE post-induction day 15, yielding a thorough, clinically relevant assessment of GA efficacy within the context of severe progressive disease. Therapeutic treatment with GA significantly decreased clinical scores and improved rotorod motor performance in EAE mice. These functional improvements were supported by an increase in myelinated axons and fewer amyloid precursor protein-positive axons in the spinal cords of GA-treated EAE mice. Furthermore, therapeutic GA decreased microglia/macrophage and T cell infiltrates and increased oligodendrocyte numbers in both the spinal cord and corpus callosum of EAE mice. Finally, GA improved callosal axon conduction and nodal protein organization in EAE. Our results demonstrate that therapeutic GA treatment has significant beneficial effects in a chronic mouse model of MS, in which its positive effects on both myelinated and non-myelinated axons results in improved axon function.

PIMD: 24989845

IL-17A induces MIP-1α expression in primary astrocytes via Src/MAPK/PI3K/NF-kB pathways: implications for multiple sclerosis.

Neuroinflammation plays critical roles in multiple sclerosis (MS). In addition to the part played by the lymphocytes, the underlying mechanisms could, in part, be also attributed to activation mediated by astrocytes. Macrophage inflammatory protein-1α (MIP-1α) has been implicated in a number of pathological conditions, specifically attributable to its potent chemottractant effects. Its modulation by IL-17, however, has received very little attention. In the present study, we demonstrated IL-17-mediated induction of MIP-1α in rat primary astroctyes through its binding to the cognate IL-17RA. Furthermore, this effect was mediated via the activation of Src, mitogen-activated protein kinases (MAPKs), PI3K/Akt and NF-kB pathways, culminating ultimately into increased expression of MIP-1α. Exposure of primary mouse astrocytes to IL-17 resulted in increased expression of glial fibrillary acidic protein and, this effect was abrogated in cells cultured in presence of the MIP-1α neutralizing antibody, thus underscoring its role in the activation of astrocytes. In vivo relevance of these findings was further corroborated in experimental autoimmune encephalomyelitis mice that demonstrated significantly increased activation of astrocytes with concomitant increased expression of MIP-1α in the corpus callosum compared with control group. Understanding the regulation of MIP-1α expression may provide insights into the development of potential therapeutic targets for neuroinflammation associated with multiple sclerosis.

PIMD: 24916672

Crying and suicidal, but not depressed. Pseudobulbar affect in multiple sclerosis successfully treated with valproic acid: Case report and literature review.

Pseudobulbar affect/emotional incontinence is a potentially disabling condition characterized by expressions of affect or emotions out of context from the normal emotional basis for those expressions. This condition can result in diagnostic confusion and unrelieved suffering when clinicians interpret the emotional expressions at face value. In addition, the nomenclature, etiology, and treatment for this condition remain unclear in the medical literature.We report the case of a 60-year-old woman with multiple sclerosis who was referred to an inpatient psychiatry unit with complaints of worsening depression along with hopelessness, characterized by unrelenting crying. Our investigation showed that her symptoms were caused by pseudobulbar affect/emotional incontinence stemming from multiple sclerosis.The patient's history of multiple sclerosis and the fact that she identified herself as depressed only because of her incessant crying suggested that her symptoms might be due to the multiple sclerosis rather than to a depressive disorder. Magnetic resonance imaging demonstrated a new plaque consistent with multiple sclerosis lateral to her corpus callosum. Her symptoms resolved completely within three days on valproic acid but returned after she was cross-tapered to dextromethorphan plus quinidine, which is the FDA-approved treatment for this condition.This case provides important additional information to the current literature on pseudobulbar affect/emotional incontinence. The existing literature suggests a selective serotonin reuptake inhibitor (SSRI) and dextromethorphan/quinidine (Nuedexta) as first-line treatments; however, our patient was taking an SSRI at the time of presentation without appreciable benefit, and her symptoms responded to valproic acid but not to the dextromethorphan/quinidine. In addition, the case and the literature review suggest that the current nomenclature for this constellation of symptoms can be misleading.

PIMD: 24867222

Diagnostic value of 3D fluid attenuated inversion recovery sequence in multiple sclerosis.

Magnetic resonance imaging (MRI) is an indispensable tool in the diagnostic work-up of multiple sclerosis (MS). To date, guidelines suggest MRI protocols containing axial dual-echo, unenhanced and post-contrast T1-weighted sequences. Especially the usage of dual-echo sequences has markedly improved the ability of MRI to detect cortical and infratentorial lesions. Newer 3D FLAIR sequences are supposed to provide even more positive imaging features such as improved detection of white matter lesions and a better resolution due to smaller slice thickness.To evaluate the diagnostic impact of 3D FLAIR sequences in comparison to conventional T2 and PD sequences.Examinations of 20 MS patients (10 women, 10 men) were reviewed retrospectively. All patients received MRI standard protocol containing PD and T2 sequences and a mid-sagittal T2 sequence. Additionally an isotropic 3D FLAIR sequence was performed. Whole-brain lesion load and number of lesions in juxtacortical, infratentorial, and midcallosal localizations were assessed by two observers independently and compared.Whole lesion load and the count of detectable lesions at the 3D FLAIR sequence were significantly higher in the juxtacortical and infratentorial regions compared to the PD/T2 sequence. Detection rate of midcallosal lesions did not differ significantly in sagittal T2 and 3D FLAIR sequence.3D FLAIR sequences can improve the detection of brain lesions in patients with MS and are even more sensitive in depicting lesions in cortical and infratentorial locations than current dual-echo sequences. The sequence can replace both PD/T2 sequences and mid-sagittal T2 sequences of the corpus callosum.

PIMD: 24842962

Retinal nerve fibre layer thickness correlates with brain white matter damage in multiple sclerosis: a combined optical coherence tomography and diffusion tensor imaging study.

We investigated the association of retinal nerve fibre layer thickness (RNFL) with white matter damage assessed by diffusion tensor imaging (DTI). Forty-four MS patients and 30 healthy subjects underwent optical coherence tomography. DTI was analysed with a voxel-based whole brain and region-based analysis of optic radiation, corpus callosum and further white matter. Correlations between RNFL, fractional anisotropy (FA) and other DTI-based parameters were assessed in patients and controls. RNFL correlated with optic radiation FA, but also with corpus callosum and remaining white matter FA. Our findings demonstrate that RNFL changes indicate white matter damage exceeding the visual pathway.

PIMD: 24831599

Extensive white matter dysfunction in cognitively impaired patients with secondary-progressive multiple sclerosis.

Cognitive impairment is a common, disabling symptom of MS. We investigated the association between cognitive impairment and WM dysfunction in secondary-progressive multiple sclerosis using DTI.Cognitive performance was assessed with a standard neuropsychological battery, the Minimal Assessment of Cognitive Function in Multiple Sclerosis. Cognitive impairment was defined as scoring >1.5 standard deviations below healthy controls on ≥2 subtests. Fractional anisotropy maps were compared against cognitive status using tract-based spatial statistics with threshold-free cluster enhancement.Forty-five patients with secondary-progressive multiple sclerosis (median age: 55 years, female/male: 27/18, median Expanded Disability Status Scale Score: 6.5) were prospectively recruited. Cognitively impaired patients (25/45) displayed significantly less normalized global GM and WM volumes (P = .001, P = .024), more normalized T2-weighted and T1-weighted WM lesion volumes (P = .002, P = .006), and lower WM skeleton fractional anisotropy (P < .001) than non-impaired patients. Impaired patients also had significantly lower fractional anisotropy (p(corr) < .05) in over 50% of voxels within every major WM tract. The most extensively impinged tracts were the left posterior thalamic radiation (100.0%), corpus callosum (97.8%), and right sagittal stratum (97.5%). No WM voxels had significantly higher fractional anisotropy in patients with cognitive impairment compared with their non-impaired counterparts (p(corr) > .05). After the inclusion of confounders in a multivariate logistic regression, only fractional anisotropy remained a significant predictor of cognitive status.Cognitively impaired patients with secondary-progressive multiple sclerosis exhibited extensive WM dysfunction, though preferential involvement of WM tracts associated with cognition, such as the corpus callosum, was apparent. Multivariate analysis revealed that only WM skeleton fractional anisotropy was a significant predictor of cognitive status.

PIMD: 24816394

Corpus callosum atrophy correlates with gray matter atrophy in patients with multiple sclerosis.

Atrophy of the corpus callosum is a recognized characteristic of multiple sclerosis (MS). We describe a new reliable method for measuring corpus callosum atrophy and correlate this with global cerebral atrophy measures.Whole brain 3T MRI was performed in 38 relapsing-remitting MS subjects and 21 healthy controls (HC). Brain global gray and white matter volumes were segmented with SPM8. The contour of the corpus callosum was outlined on the midline of 3-D T1-weighted images by a semiautomated edge-detection technique to determine the corpus callosum area (CCA). Normalized CCA was correlated with other brain atrophy measures in MS subjects.CCA was disproportionately lower in MS subjects vs. HC (20.1% mean decrease; $P < .001$), with a large effect size ($d = .62$) when compared with global atrophy measures. In MS subjects, CCA correlated with brain parenchymal fraction ($r = .55$; $P < .001$) and gray matter fraction ($r = .45$; $P = .005$) but not white matter fraction ($r = .18$; $P = .29$). An inverse correlation with FLAIR hyperintense lesion volume ($r = -.40$; $P = .01$) was detected for CCA.Measurement of atrophy of the corpus callosum can have sensitivity as a useful imaging biomarker in patients with MS, even in patients with low disability levels. Both gray and white matter involvement in MS contribute to corpus callosum atrophy.

PIMD: 24803736

Intermittent alien hand syndrome and callosal apraxia in multiple sclerosis: implications for interhemispheric communication.

We report a case of a 47-year-old woman with 35-year history of multiple sclerosis, who showed alien hand signs, a rare behavioural disorder that involves unilateral goal-directed movements that are contrary to the individual's intention. Alien hand syndrome has been described in multiple sclerosis (MS) only occasionally and is generally suggestive of callosal disconnection. The patient presented also with bilateral limb apraxia and left hand agraphia, raising the possibility of cortical dysfunction or disconnection, in addition to corpus callosum and white matter involvement. Her specific pattern of symptoms supports the role of the corpus callosum in interhemispheric communication for complex as well as fine motor activities and may indicate that it can serve as both an inhibitory and excitatory function depending on task demands.

PIMD: 24798398

Protective effects of melatonin against mitochondrial injury in a mouse model of multiple sclerosis.

Multiple sclerosis (MS) is the most prevalent inflammatory demyelinating disease of the central nervous system. Besides other pathophysiological mechanisms, mitochondrial injury is crucially involved in the development and progression of this disease. Mitochondria have been identified as targets for the peptide hormone melatonin. In the present study, we sought to evaluate the impact of oxidative stress on mitochondrial density and enzyme transcription during experimentally induced demyelination and the protective influence of melatonin. Adult male mice were fed with cuprizone for 5 weeks which caused severe demyelination of the corpus callosum (CC). Animals were simultaneously treated with melatonin by daily intra-peritoneal injections. Melatonin exposure reversed cuprizone-induced demyelination and axon protection. Transmission electron microscopy demonstrated significantly increased mitochondrial numbers and slightly increased mitochondrial size within CC axons after cuprizone exposure. Melatonin antagonized these effects and, in addition, induced the expression of subunits of the respiratory chain complex over normal control values reflecting a mechanism to compensate cuprizone-mediated down-regulation of these genes. Similarly, melatonin modulated gene expression of mitochondrial fusion and fission proteins. Biochemical analysis showed that oxidative stress induced by cuprizone was regulated by melatonin. The data implicate that melatonin abolishes destructive cuprizone effects in the CC by decreasing oxidative stress, restoring mitochondrial respiratory enzyme activity and fusion and fission processes as well as decreasing intra-axonal mitochondria accumulation.

PIMD: 24788131

Brain changes in Kallmann syndrome.

Kallmann syndrome is a rare inherited disorder due to defective intrauterine migration of olfactory axons and gonadotropin-releasing hormone neurons, leading to rhinencephalon hypoplasia and hypogonadotropic hypogonadism. Concomitant brain developmental abnormalities have been described. Our aim was to investigate Kallmann syndrome-related brain changes with conventional and novel quantitative MR imaging analyses.Forty-five male patients with Kallmann syndrome (mean age, 30.7 years; range, 9-55 years) and 23 age-matched male controls underwent brain MR imaging. The MR imaging study protocol included 3D-T1, FLAIR, and diffusion tensor imaging (32 noncollinear gradient-encoding directions; b-value=800 s/mm2). Voxel-based morphometry, sulcation, curvature, and cortical thickness analyses and tract-based spatial statistics were performed by using Statistical Parametric Mapping 8, FreeSurfer, and the fMRI of the Brain Software Library.Corpus callosum partial agenesis, multiple sclerosis-like white matter abnormalities, and acoustic schwannoma were found in 1 patient each. The total amount of gray and white matter volume and tract-based spatial statistics measures (fractional anisotropy and mean, radial, and axial diffusivity) did not differ between patients with Kallmann syndrome and controls. By specific analyses, patients with Kallmann syndrome presented with symmetric clusters of gray matter volume increase and decrease and white matter volume decrease close to the olfactory sulci; reduced sulcal depth of the olfactory sulci and deeper medial orbital-frontal sulci; lesser curvature of the olfactory sulcus and sharper curvature close to the medial orbital-frontal sulcus; and increased cortical thickness within the olfactory sulcus.This large MR imaging study on male patients with Kallmann syndrome featured significant morphologic and structural brain changes, likely driven by olfactory bulb hypo-/aplasia, selectively involving the basal forebrain cortex.

PIMD: 24647027

Posterior brain damage and cognitive impairment in pediatric multiple sclerosis.

We combined structural and functional MRI to better understand the mechanisms responsible for cognitive impairment in pediatric patients with multiple sclerosis (MS).Brain dual-echo, diffusion tensor, 3D T1-weighted, and resting-state (RS) fMRI scans were acquired from 35 consecutive pediatric patients with MS and 16 sex- and age-matched healthy controls. Patients with abnormalities in ≥2 neuropsychological tests were classified as cognitively impaired. The regional distribution of white matter (WM) and gray matter (GM) damage was assessed using voxel-wise analyses. Default mode network (DMN) RS functional connectivity (FC) was also measured.Sixteen patients (45%) were classified as cognitively impaired. Compared to cognitively preserved (CP) patients, cognitively impaired patients with MS had higher occurrence of T2 lesions as well as more severe damage to the WM and GM, as measured by atrophy and diffusivity abnormalities, in the posterior regions of the parietal lobes close to the midline (precuneus, posterior cingulum, and corpus callosum). Compared to the other study groups, they also showed reduced RS FC of the precuneus, whereas CP patients experienced an increased RS FC of the anterior cingulate cortex. A multivariable model identified diffusivity abnormalities of the cingulum and corpus callosum and RS FC of the precuneus as the covariates more strongly associated with cognitive impairment (C-index = 0.99).In pediatric patients with MS, cognitive dysfunction is associated with structural and functional abnormalities of the posterior core regions of the DMN. WM structural abnormalities co-occurring at this level are likely to be the substrate of such modifications.

PIMD: 24622349

PET imaging of glucose metabolism, neuroinflammation and demyelination in the lysolecithin rat model for multiple sclerosis.

Injection of lysolecithin in the central nervous system results in demyelination accompanied by local activation of microglia and recruitment of monocytes. Positron-emission tomography (PET) imaging, using specific tracers, may be an adequate technique to monitor these events in vivo and therefore may become a tool for monitoring disease progression in multiple sclerosis (MS) patients.The objective of this paper is to evaluate the potential of PET imaging in monitoring local lesions, using [(11)C]MeDAS, [(11)C]PK11195 and [(18)F]FDG as PET tracers for myelin density, microglia activation and glucose metabolism, respectively.Sprague-Dawley rats were stereotactically injected with either 1% lysolecithin or saline in the corpus callosum and striatum of the right brain hemisphere. PET imaging was performed three days, one week and four weeks after injection. Animals were terminated after PET imaging and the brains were explanted for (immuno)histochemical analysis.PET imaging was able to detect local demyelination induced by lysolecithin in the corpus callosum and striatum with [(11)C]MeDAS and concomitant microglia activation and monocyte recruitment with [(11)C]PK11195. [(18)F]FDG imaging demonstrated that glucose metabolism was maintained in the demyelinated lesions.PET imaging with multiple tracers allows simultaneous in vivo monitoring of myelin density, neuroinflammation and brain metabolism in small MS-like lesions, indicating its potential to monitor disease progression in MS patients.

PIMD: 24607968

Neuronopathy in the motor neocortex in a chronic model of multiple sclerosis.

We provide evidence of cortical neuronopathy in myelin oligodendrocyte glycoprotein peptide-induced experimental autoimmune encephalomyelitis, an established model of chronic multiple sclerosis. To investigate phenotypic perturbations in neurons in this model, we used apoptotic markers and immunohistochemistry with antibodies to NeuN and other surrogate markers known to be expressed by adult pyramidal Layer V somas, including annexin V, encephalopsin, and Emx1. We found no consistent evidence of chronic loss of Layer V neurons but detected both reversible and chronic decreases in the expression of these markers in conjunction with evidence of cortical demyelination and presynaptic loss. These phenotypic perturbations were present in, but not restricted to, the neocortical Layer V. We also investigated inflammatory responses in the cortex and subcortical white matter of the corpus callosum and spinal dorsal funiculus and found that those in the cortex and corpus callosum were delayed compared with those in the spinal cord. Inflammatory infiltrates initially included T cells, neutrophils, and Iba1-positive microglia/macrophages in the corpus callosum, whereas only Iba1-positive cells were present in the cortex. These data indicate that we have identified a new temporal pattern of subtle phenotypic perturbations in neocortical neurons in this chronic multiple sclerosis model.

PIMD: 28360602

A Case of ADEM Mimicking Cerebral Adrenoleukodystrophy Based on Supratentorial MRI Findings.

A 9-year-old male admitted for syncope also had the complains of pain and numbness in his legs and frequent falling down. There was a history of upper respiratory tract infection 10 days before. On neurologic examination, paraparesia and fall a sleep were identified. On magnetic resonance imaging, the symetric signal increases were seen in biparieto-occipital white matter intented to corpus callosum at T2-weighted sequences and cytotoxic edema was seen at diffusion-weighted images. Heterogeneous contrast enhancement was seen on these areas. In addition, at the C7-Th5 vertebrae levels, spinal cord had diffuse increased signal intensity and contrast enhancement. Acute disseminated encephalomyelitis was thought based on clinical and radiological findings. Steroid therapy was started. Significant improvement was shown after treatment. On 2-year follow-up, there was no recurrence. In conclusion, it must be kept in mind that acute disseminated encephalomyelitis can rarely present with biparieto-occipital involvement which extends to corpus callosum and can mimic adrenoleukodystrophy. For the differential diagnosis butterfly glioma, tumefactive demyelinating lesions or multiple sclerosis should be considered.

PIMD: 24571105

Atypical hereditary spastic paraplegia mimicking multiple sclerosis associated with a novel SPG11 mutation.

No abstract

PIMD: 24552689

Brain MRI of nasal MOG therapeutic effect in relapsing-progressive EAE.

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) considered to be a T cell-mediated autoimmune disease. Mucosally administered antigens induce regulatory T cells that secrete anti-inflammatory cytokines at the anatomic site where the mucosally administered Ag is located. We have previously reported in a mouse model of stroke that nasal treatment with MOG35-55 peptide reduces ischemic infarct size and improves behavior, by inducing IL-10-secreting T cells. We have also demonstrated that an experimental autoimmune encephalomyelitis (EAE) model in non-obese diabetic (NOD) mice leads to a relapsing progressive disease and that brain lesions can be visualized noninvasively by magnetic resonance imaging (MRI). Here, we investigated whether nasal treatment with 25μg of MOG35-55 after the first attack affects clinical progression and MRI outcome in the NOD model. We found that nasal MOG35-55 treatment administered three times after the first attack and then weekly reduced both the peak clinical disease score and clinical score during remission. Pathology revealed less infiltration of cells and reduction in white-matter damage as measured by Luxol blue staining in treated animals. This model is unique in that there are lesions in the corpus callosum, external capsule, fimbria, internal capsule and thalamus, which is analogous to what is observed in MS. MRI of individual animals using fractional anisotropy (FA) and T1-gadolinum (T1-Gd) imaging was able to identify lesions in all of these anatomic areas, and we found lower levels of brain pathology by MRI in treated mice with both methods. Our results indicate a beneficial effect of nasal MOG on relapsing-progressive EAE and demonstrate that non-invasive MRI imaging may be used to monitor treatment of ongoing disease in this model for testing new therapies for MS.

PIMD: 24499866

PET imaging of focal demyelination and remyelination in a rat model of multiple sclerosis: comparison of [11C]MeDAS, [11C]CIC and [11C]PIB.

In this study, we compared the ability of [(11)C]CIC, [(11)C]MeDAS and [(11)C]PIB to reveal temporal changes in myelin content in focal lesions in the lysolecithin rat model of multiple sclerosis. Pharmacokinetic modelling was performed to determine the best method to quantify tracer uptake.Sprague-Dawley rats were stereotactically injected with either 1 % lysolecithin or saline into the corpus callosum and striatum of the right brain hemisphere. Dynamic PET imaging with simultaneous arterial blood sampling was performed 7 days after saline injection (control group), 7 days after lysolecithin injection (demyelination group) and 4 weeks after lysolecithin injection (remyelination group).The kinetics of [(11)C]CIC, [(11)C]MeDAS and [(11)C]PIB was best fitted by Logan graphical analysis, suggesting that tracer binding is reversible. Compartment modelling revealed that all tracers were fitted best with the reversible two-tissue compartment model. Tracer uptake and distribution volume in lesions were in agreement with myelin status. However, the slow kinetics and homogeneous brain uptake of [(11)C]CIC make this tracer less suitable for in vivo PET imaging. [(11)C]PIB showed good uptake in the white matter in the cerebrum, but [(11)C]PIB uptake in the cerebellum was low, despite high myelin density in this region. [(11)C]MeDAS distribution correlated well with myelin density in different brain regions.This study showed that PET imaging of demyelination and remyelination processes in focal lesions is feasible. Our comparison of three myelin tracers showed that [(11)C]MeDAS has more favourable properties for quantitative PET imaging of demyelinated and remyelinated lesions throughout the CNS than [(11)C]CIC and [(11)C]PIB.

PIMD: 24486438

Inter-hemispheric functional connectivity changes with corpus callosum morphology in multiple sclerosis.

Multiple sclerosis (MS) affects myelin sheaths within the central nervous system, concurring to cause brain atrophy and neurodegeneration as well as gradual functional disconnections. To explore early signs of altered connectivity in MS from a structural and functional perspective, the morphology of corpus callosum (CC) was correlated with a dynamic inter-hemispheric connectivity index. Twenty mildly disabled patients affected by a relapsing-remitting (RR) form of MS (EDSS≤3.5) and 15 healthy subjects underwent structural MRI to measure CC thickness over 100 sections and electroencephalography to assess a spectral coherence index between primary regions devoted to hand control, at rest and during an isometric handgrip. In patients, an overall CC atrophy was associated with increased lesion load. A less efficacious inter-hemispheric coherence (IHCoh) during movement was associated with CC atrophy in sections interconnecting homologous primary motor areas (anterior mid-body). In healthy controls, less efficacious IHCoh at rest was associated with a thinner CC splenium. Our data suggest that in mildly disabled RR-MS patients a covert impairment may be detected in the correlation between the structural (CC thickness) and functional (IHCoh) measures of homologous networks, whereas these two counterparts do not yet differ individually from controls.

PIMD: 24462295

Early-onset of multiple sclerosis in a 5-year-old girl.

Childhood multiple sclerosis is a rare demyelinating autoimmune disease with particular features. Onset of multiple sclerosis is extremely uncommon in early childhood, particularly before 6 years of age. We report the case of a 5-year-old girl admitted to the hospital for altered consciousness and rapid onset of right hemiparaplegia. Magnetic resonance imaging (MRI) of the brain showed multifocal white matter disease with T2 hyperintense oval lesions in subcortical, periventricular, and cerebellar hemispheres. Treatment with high dose intravenous methylprednisolone (30 mg/kg/day for 3 days) improved symptoms. Intravenous corticosteroid therapy was followed by 1mg/kg/day of oral prednisone. A second MRI, 40 days later, revealed new disseminated T2 hyperintense lesions in the frontal periventricular white matter, corpus callosum, left middle cerebellar peduncle, and dorsal spinal cord, leading to the diagnosis of multiple sclerosis. Azathioprine (2.5 mg/kg/day) was started and the steroid dose was tapered before being stopped after 3 months. After 2 years of follow-up, the patient has remained asymptomatic with a normal neurological exam and with no relapse or side effects of azathioprine. This work shows the particularities in clinical and radiological features of multiple sclerosis in a child aged less than 6 years.

PIMD: 24433093

Interhemispheric cooperation in global-local visual processing in pediatric multiple sclerosis.

Impairments in visuospatial abilities are commonly reported in children and adolescents with multiple sclerosis (MS). Corpus callosum (CC) pathology occurs in patients with MS and may contribute to impairment in visuospatial perception, particularly when interhemispheric information transfer is required. This study used a global-local hierarchical letter paradigm to examine the relationship between interhemispheric information transfer and white matter integrity in the CC assessed using diffusion tensor imaging. Thirteen cognitively preserved pediatric-onset MS patients and 15 age-matched healthy controls were asked to determine whether a target letter E appeared at the attended level of the stimulus. As expected, both groups processed global and local information more slowly under divided than selective attention conditions. The MS group performed similarly to the control group with respect to reaction time and accuracy on selective and divided attention conditions, with one exception. Specifically, the presence of a global target when attending to a local target caused greater response conflict in the MS group than in controls ($p = .01$). Pooling both the patient and control data, greater response conflict was associated with reduced white matter integrity as indicated by lower fractional anisotropy in the anterior body of the CC ($r = -.33$, $p < .05$). Results suggest that reduced white matter integrity in anterior regions of the CC may lead to less efficient inhibition of task-irrelevant global information in the hierarchal processing of visual information.

PIMD: 24386344

Deep gray matter demyelination detected by magnetization transfer ratio in the cuprizone model.

In multiple sclerosis (MS), the correlation between lesion load on conventional magnetic resonance imaging (MRI) and clinical disability is weak. This clinico-radiological paradox might partly be due to the low sensitivity of conventional MRI to detect gray matter demyelination. Magnetization transfer ratio (MTR) has previously been shown to detect white matter demyelination in mice. In this study, we investigated whether MTR can detect gray matter demyelination in cuprizone exposed mice. A total of 54 female C57BL/6 mice were split into one control group () and eight cuprizone exposed groups ([Formula: see text]). The mice were exposed to [Formula: see text] (w/w) cuprizone for up to six weeks. MTR images were obtained at a 7 Tesla Bruker MR-scanner before cuprizone exposure, weekly for six weeks during cuprizone exposure, and once two weeks after termination of cuprizone exposure. Immunohistochemistry staining for myelin (anti-Proteolopid Protein) and oligodendrocytes (anti-Neurite Outgrowth Inhibitor Protein A) was obtained after each weekly scanning. Rates of MTR change and correlations between MTR values and histological findings were calculated in five brain regions. In the corpus callosum and the deep gray matter a significant rate of MTR value decrease was found, [Formula: see text] per week ([Formula: see text]) and [Formula: see text] per week ([Formula: see text]) respectively. The MTR values correlated to myelin loss as evaluated by immunohistochemistry (Corpus callosum: [Formula: see text]. Deep gray matter: [Formula: see text]), but did not correlate to oligodendrocyte density. Significant results were not found in the cerebellum, the olfactory bulb or the cerebral cortex. This study shows that MTR can be used to detect demyelination in the deep gray matter, which is of particular interest for imaging of patients with MS, as deep gray matter demyelination is common in MS, and is not easily detected on conventional clinical MRI.

PIMD: 24373026

Hemodynamic evidence linking cognitive deficits in clinically isolated syndrome to regional brain inflammation.

To investigate the relation between hemodynamic measurements and memory function in patients with clinically isolated syndrome (CIS).Forty CIS patients were administered tests of verbal short-term/working memory and passage learning. Using dynamic susceptibility contrast MRI cerebral blood volume (CBV), cerebral blood flow and mean transit time values were estimated in 20 cerebral regions of interest, placed in normal appearing white matter (NAWM) and normal appearing deep gray matter structures, bilaterally.CIS patients showed significantly impaired scores on working memory and secondary verbal memory that correlated inversely with elevated CBV values in the left frontal and periventricular NAWM, thalamus, right caudate and corpus callosum.Verbal memory in CIS correlates inversely with elevated CBV values of brain structures involved in memory. As these hemodynamic changes, detected in CIS, are indicative of inflammation, the observed cognitive disturbances may relate to widespread brain inflammatory processes that prevail in early multiple sclerosis.

PIMD: 24370819

Upper limb motor rehabilitation impacts white matter microstructure in multiple sclerosis.

Upper limb impairments can occur in patients with multiple sclerosis, affecting daily living activities; however there is at present no definite agreement on the best rehabilitation treatment strategy to pursue. Moreover, motor training has been shown to induce changes in white matter architecture in healthy subjects. This study aimed at evaluating the motor behavioral and white matter microstructural changes following a 2-month upper limb motor rehabilitation treatment based on task-oriented exercises in patients with multiple sclerosis. Thirty patients (18 females and 12 males; age=43.3 ± 8.7 years) in a stable phase of the disease presenting with mild or moderate upper limb sensorimotor deficits were randomized into two groups of 15 patients each. Both groups underwent twenty 1-hour treatment sessions, three times a week. The "treatment group" received an active motor rehabilitation treatment, based on voluntary exercises including task-oriented exercises, while the "control group" underwent passive mobilization of the shoulder, elbow, wrist and fingers. Before and after the rehabilitation protocols, motor performance was evaluated in all patients with standard tests. Additionally, finger motor performance accuracy was assessed by an engineered glove. In the same sessions, every patient underwent diffusion tensor imaging to obtain parametric maps of fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. The mean value of each parameter was separately calculated within regions of interest including the fiber bundles connecting brain areas involved in voluntary movement control: the corpus callosum, the corticospinal tracts and the superior longitudinal fasciculi. The two rehabilitation protocols induced similar effects on unimanual motor performance, but the bimanual coordination task revealed that the residual coordination abilities were maintained in the treated patients while they significantly worsened in the control group ($p=0.002$). Further, in the treatment group white matter integrity in the corpus callosum and corticospinal tracts was preserved while a microstructural integrity worsening was found in the control group (fractional anisotropy of the corpus callosum and corticospinal tracts: $p=0.033$ and $p=0.022$; radial diffusivity of the corpus callosum and corticospinal tracts: $p=0.004$ and $p=0.008$). Conversely, a significant increase of radial diffusivity was observed in the superior longitudinal fasciculi in both groups ($p=0.02$), indicating lack of treatment effects on this structure, showing damage progression likely due to a demyelination process. All these findings indicate the importance of administering, when possible, a rehabilitation treatment consisting of voluntary movements. We also demonstrated that the beneficial effects of a rehabilitation treatment are task-dependent and selective in their target; this becomes crucial towards the implementation of tailored rehabilitative approaches.

PIMD: 24363970

Therapeutic laquinimod treatment decreases inflammation, initiates axon remyelination, and improves motor deficit in a mouse model of multiple sclerosis.

Therapeutic strategies that induce effective neuroprotection and enhance intrinsic repair mechanisms are central goals for future treatment of multiple sclerosis (MS), as well as other diseases. Laquinimod (LQ) is an orally administered, central nervous system (CNS)-active immunomodulator with demonstrated efficacy in MS clinical trials and a favorable safety and tolerability profile.We aimed to explore the pathological, functional, and behavioral consequences of prophylactic and therapeutic (after presentation of peak clinical disease) LQ treatment in the chronic experimental autoimmune encephalomyelitis (EAE) mouse model of MS.Active EAE-induced 8-week-old C57BL/6 mice were treated with 5 or 25 mg/kg/day LQ via oral gavage beginning on EAE post-immunization day 0, 8, or 21. Clinical scores and rotorod motor performance were assessed throughout the disease course. Immune analysis of autoantigen-stimulated splenocytes, electrophysiological conduction of callosal axons, and immunohistochemistry of white matter-rich corpus callosum and spinal cord were performed.Prophylactic and therapeutic treatment with LQ significantly decreased mean clinical disease scores, inhibited Th1 cytokine production, and decreased the CNS inflammatory response. LQ-induced improvement in axon myelination and integrity during EAE was functional, as evidenced by significant recovery of callosal axon conduction and axon refractoriness and pronounced improvement in rotorod motor performance. These improvements correlate with LQ-induced attenuation of EAE-induced demyelination and axon damage, and improved myelinated axon numbers.Even when initiated at peak disease, LQ treatment has beneficial effects within the chronic EAE mouse model. In addition to its immunomodulatory effects, the positive effects of LQ treatment on oligodendrocyte numbers and myelin density are indicative of significant, functional neuroprotective and neurorestorative effects.Our results support a potential neuroprotective, in addition to immunomodulatory, effect of LQ treatment in inhibiting ongoing MS/EAE disease progression.

PIMD: 24349280

Disconnection mechanism and regional cortical atrophy contribute to impaired processing of facial expressions and theory of mind in multiple sclerosis: a structural MRI study.

Successful socialization requires the ability of understanding of others' mental states. This ability called as mentalization (Theory of Mind) may become deficient and contribute to everyday life difficulties in multiple sclerosis. We aimed to explore the impact of brain pathology on mentalization performance in multiple sclerosis. Mentalization performance of 49 patients with multiple sclerosis was compared to 24 age- and gender matched healthy controls. T1- and T2-weighted three-dimensional brain MRI images were acquired at 3Tesla from patients with multiple sclerosis and 18 gender- and age matched healthy controls. We assessed overall brain cortical thickness in patients with multiple sclerosis and the scanned healthy controls, and measured the total and regional T1 and T2 white matter lesion volumes in patients with multiple sclerosis. Performances in tests of recognition of mental states and emotions from facial expressions and eye gazes correlated with both total T1-lesion load and regional T1-lesion load of association fiber tracts interconnecting cortical regions related to visual and emotion processing (genu and splenium of corpus callosum, right inferior longitudinal fasciculus, right inferior fronto-occipital fasciculus, uncinate fasciculus). Both of these tests showed correlations with specific cortical areas involved in emotion recognition from facial expressions (right and left fusiform face area, frontal eye filed), processing of emotions (right entorhinal cortex) and socially relevant information (left temporal pole). Thus, both disconnection mechanism due to white matter lesions and cortical thinning of specific brain areas may result in cognitive deficit in multiple sclerosis affecting emotion and mental state processing from facial expressions and contributing to everyday and social life difficulties of these patients.

PIMD: 24304574

Stable gastric pentadecapeptide BPC 157 heals cysteamine-colitis and colon-colon-anastomosis and counteracts cuprizone brain injuries and motor disability.

Stable gastric pentadecapeptide BPC 157 was suggested to link inflammatory bowel disease and multiple sclerosis, and thereby, shown to equally counteract the models of both of those diseases. For colitis, cysteamine (400 mg/kg intrarectally (1 ml/rat)) and colon-colon anastomosis (sacrifice at day 3, 5, 7, and 14) were used. BPC 157 (10 μg/kg, 10 ng/kg) was applied either intraperitoneally once time daily (first application immediately after surgery, last at 24 hours before sacrifice) or per-orally in drinking water (0.16 μg/ml/12 ml/day till the sacrifice) while controls simultaneously received an equivolume of saline (5 ml/kg) intraperitoneally or drinking water only (12 ml/day). A multiple sclerosis suited toxic rat model, cuprizone (compared with standard, a several times higher regimen, 2.5% of diet regimen + 1 g/kg intragastrically/day) was combined with BPC 157 (in drinking water 0.16 μg or 0.16 ng/ml/12 ml/day/rat + 10 μg or 10 ng/kg intragastrically/day) till the sacrifice at day 4. In general, the controls could not heal cysteamine colitis and colon-colon anastomosis. BPC 157 induced an efficient healing of both at the same time. Likewise, cuprizone-controls clearly exhibited an exaggerated and accelerated damaging process; nerve damage appeared in various brain areas, with most prominent damage in corpus callosum, laterodorsal thalamus, nucleus reunions, anterior horn motor neurons. BPC 157-cuprizone rats had consistently less nerve damage in all damaged areas, especially in those areas that otherwise were most affected. Consistently, BPC 157 counteracted cerebellar ataxia and impaired forelimb function. Thereby, this experimental evidence advocates BPC 157 in both inflammatory bowel disease and multiple sclerosis therapy.

PIMD: 24274741

Encephalopathic Susac's Syndrome associated with livedo racemosa in a young woman before the completion of family planning.

Susac's Syndrome (SS) consists of the triad of encephalopathy, branch retinal artery occlusions (BRAO) and hearing loss (HL). Histopathologically, SS is characterised by a microangiopathy, and some observations suggest that an immune-mediated damage of endothelial cells might play a role. These findings also implicate a similarity between SS and other autoimmune diseases, most notably juvenile dermatomyositis (JDM). However, SS and JDM are commonly thought to affect distinct and non-overlapping sets of organs, and it is currently not clear how these specificities arise. Moreover, in the absence of clinical trials, some authors suggest that therapeutic approaches in SS should rely on the model of other autoimmune diseases such as JDM.Here, we report a case of SS in a 32-year-old pregnant woman. She initially was admitted to the hospital with subacute severe encephalopathy and multifocal neurologic signs. As cranial magnetic resonance imaging (MRI) revealed multifocal white matter lesions including the corpus callosum, erroneously a diagnosis of multiple sclerosis (MS) was made, and intravenous methylprednisolone (IVMP) therapy was initiated. A few days later, an exanthema appeared on the trunk and extremities, which was diagnosed as livedo racemosa (LR). Several weeks later, the patient was readmitted to the clinic with an obscuration of her left visual hemifield and a bilateral HL. Ophthalmologic examination revealed extensive ischemic damage to both retinae. Now the correct diagnosis of SS was established, based on the above triad of clinical symptoms in conjunction with typical MRI and fundoscopic findings. When SS was diagnosed, the standard therapy with intravenous cyclophosphamide (IVCTX) was not instituted because of a significant risk of permanent infertility. Instead, sustained control of disease activity could be achieved with a therapeutic regime combining prednisolone, intravenous immunoglobulins (IVIG), mycophenylate mofetil (MM), and methotrexate (MTX).An association with LR has only been described in very few cases of SS before and further underlines the pathogenetic relationship between SS and other autoimmune diseases such as JDM. In young women with SS and the desire for a child the combination of MM and MTX may represent a reasonable alternative to IVCTX.

PIMD: 24192684

An unusual case of neurobrucellosis presenting as demyelination disorder.

Brucellosis is a public health problem in most countries in the Mediterranean. Involvement of the central nervous system is seen in 4-13% of patients with brucellosis. A 13-year-old girl was admitted because of gait disturbance, diplopia, and dizziness. Her complaints began about 1.5 years ago. The second symptomatic episode repeated about three months ago and the third two months ago. In total, attacks repeated 3 times over 1.5 years. The magnetic resonance imaging (MRI) and the clinical features mimicked multiple sclerosis. The patient was given pulse steroid treatments. After steroid treatment, her gait disturbance and diplopia improved over the short term. Following positive developments, her symptoms recurred. The tests were repeated; the MRI showed increasingly high signal abnormalities, and Brucella melitensis was grown in cerebrospinal fluid. The patient was started on an oral combination of rifampin, doxycycline, and ciprofloxacin. MRI findings improved markedly after nine months of treatment. Although neurobrucellosis is associated rarely with demyelination in adults, this finding has not been reported previously in children or adolescents. Additionally, this case is the first in terms of involvement of the corpus callosum in neurobrucellosis. In this article, we present an unusual case of neurobrucellosis.

PIMD: 24148569

Mobilization of progenitors in the subventricular zone to undergo oligodendrogenesis in the Theiler's virus model of multiple sclerosis: implications for remyelination at lesions sites.

Remyelination involves the generation of new myelin sheaths around axons, as occurs spontaneously in many multiple sclerosis (MS) lesions and other demyelinating diseases. When considering repairing a diseased brain, the adult mouse subventricular zone (SVZ) is of particular interest since the stem cells in this area can migrate and differentiate into the three major cell types in the central nervous system (CNS). In Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD), we assessed the relative contribution of the SVZ to the remyelination in the corpus callosum at preclinical stages in this MS model. CNPase, MBP and Luxol Fast Blue staining revealed prominent demyelination 35days post-infection (dpi), concomitant with a strong staining in GFAP(+) type B astrocytes in the SVZ and the increased proliferation in this area. The migration of oligodendrocyte progenitors from the SVZ contributed to the remyelination observed at 60 dpi, evident through the number of APC(+)/BrdU(+) mature oligodendrocytes in the corpus callosum of infected animals. These data suggest that the inflammation induced by the Theiler's virus not only provokes strong preclinical demyelination but also, it is correlated with oligodendrocyte generation in the adult SVZ, cells that along with resident progenitor cells contribute to the prompt remyelination observed in the corpus callosum.

PIMD: 24139243

[Cavitary lesions in multiple sclerosis: multicenter study on twenty patients].

Cavitary white matter changes are mainly described in leukodystrophies and especially in vanishing white matter disease. Large cavitary lesions are not typical for multiple sclerosis (MS).We studied MS patients with large cavitary brain lesions. Patient characteristics, disease onset/duration/subtype, expanded disability status scale (EDSS), mini mental state (MMS), vanishing white matter disease genetic analysis, and MRI characteristics of the cavitary lesions were analyzed.Twenty patients were analyzed (6 men and 14 women). Mean age at disease onset was 37.6 (range 17-58). Mean disease duration was 10 years (range 2-20). Five patients had initial relapsing-remitting MS and nine patients had primary-progressive MS. Mean EDSS was 5.5 (range 2-8). Mean MMS was 20/30. Vanishing white matter disease genetic analysis was performed and negative in seven patients. Inferior corpus callosum lesions were seen in all patients with available sagittal FLAIR sequences. Cavitary lesions were strictly supratentorial, and located inside the diffuse leukoencephalopathy, with often a posterior predominance.MS patients with large cavitary lesions seem to represent a MS subgroup, predominantly women, with relatively late disease onset, predominantly primary-progressive type, relatively high EDSS scores, and severe cognitive dysfunction.

PIMD: 24137109

Effects of intraventricular methotrexate administration on Cuprizone-induced demyelination in mice.

We previously showed that intrathecal administration of methotrexate slowed disability progression in multiple sclerosis (MS) patients with progressive disease. In general MS patients with progressive disease respond poorly to anti-inflammatory therapies. In order to better understand the mechanism by which methotrexate is protective in progressive MS, we analyzed its impact on the non-inflammatory cuprizone-induced demyelination model. When low-dose methotrexate was administered intracerebroventricularly it reduced demyelination and accumulation of GFAP+ reactive astrocytes in the corpus callosum. Administration of methotrexate after the withdrawal of cuprizone neither delayed remyelination nor influenced the number of astrocytes in the corpus callosum suggesting that methotrexate does not interfere with repair processes in the CNS. Moreover, methotrexate increased the expression of IGF1 in vitro and in vivo, a factor known to protect oligodendrocytes and limit the activation of astrocytes. Our studies show that methotrexate has an impact on pathogenic process in a demyelination model whose pathophysiological basis is not primarily related to inflammatory mechanisms, similar to neurodegenerative mechanisms associated with progressive MS. The pronounced inhibitory influence of methotrexate on the accumulation of astrocytes in the corpus callosum suggests that intrathecal methotrexate modulates astroglial activation in progressive MS possibly by promoting CNS production of IGF1.

PIMD: 24070676

Enhanced accumulation of Kir4.1 protein, but not mRNA, in a murine model of cuprizone-induced demyelination.

Two channel proteins, inwardly rectifying potassium channel 4.1 (Kir4.1) and water channel aquaporin-4 (AQP4), were recently identified as targets of an autoantibody response in patients with multiple sclerosis and neuromyelitis optica, respectively. In the present study, we examined the expression patterns of Kir4.1 and AQP4 in a mouse model of demyelination induced by cuprizone, a copper chelator. Demyelination was confirmed by immunohistochemistry using an anti-proteolipid protein antibody in various brain regions, including the corpus callosum, of cuprizone-fed mice. Activation of microglial and astroglial cells was also confirmed by immunohistochemistry, using an anti-ionized calcium binding adapter molecule and a glial fibrillary acidic protein antibody. Western blot analysis revealed the induction of Kir4.1 protein, but not AQP4, in the cortex of cuprizone-fed mice. Immunohistochemical analysis confirmed the Kir4.1 protein induction in microvessels of the cerebral cortex. Real-time polymerase chain reaction analysis revealed that mRNA levels of Kir4.1 and AQP4 in the cortex did not change during cuprizone administration. These findings suggest that enhanced accumulation of Kir4.1 protein in the brain with an inflammatory condition facilitates the autoantibody formation against Kir4.1 in patients with multiple sclerosis.

PIMD: 24037007

Segmented corpus callosum diffusivity correlates with the Expanded Disability Status Scale score in the early stages of relapsing-remitting multiple sclerosis.

The aim of this study was to characterize the microscopic damage to the corpus callosum in relapsing-remitting multiple sclerosis (RRMS) with diffusion tensor imaging and to investigate the correlation of this damage with disability. The diffusion tensor imaging parameters of fractional anisotropy and mean diffusivity provide information about the integrity of cell membranes, offering two more specific indices, namely the axial and radial diffusivities, which are useful for discriminating axon loss from demyelination.Brain magnetic resonance imaging exams of 30 relapsing-remitting multiple sclerosis patients and 30 age- and sex-matched healthy controls were acquired in a 3T scanner. The axial diffusivities, radial diffusivities, fractional anisotropy, and mean diffusivity of five segments of the corpus callosum, correlated to the Expanded Disability Status Scale score, were obtained.All corpus callosum segments showed increased radial diffusivities and mean diffusivity, as well as decreased fractional anisotropy, in the relapsing-remitting multiple sclerosis group. The axial diffusivity was increased in the posterior midbody and splenium. The Expanded Disability Status Scale scores correlated more strongly with axial diffusivities and mean diffusivity, with an isolated correlation with radial diffusivities in the posterior midbody of the corpus callosum. There was no significant correlation with lesion loads.Neurological dysfunction in relapsing-remitting multiple sclerosis can be influenced by commissural disconnection, and the diffusion indices of diffusion tensor imaging are potential biomarkers of disability that can be assessed during follow-up.

PIMD: 24032544

The Notch signaling pathway: its role in focal CNS demyelination and apotransferrin-induced remyelination.

Oligodendroglial damage and demyelination are common pathological features characterizing white matter and neurodegenerative disorders. Identifying the signaling pathways involved in myelin repair through oligodendroglial progenitor maturation is essential for the development of new therapies. This article investigated the role of the Notch signaling pathway in CNS demyelination and apotransferrin-induced remyelination in a focal lysolecithin-induced demyelination model in rats. Notch was found activated in Nestin-expressing neural progenitor cells and in NG2-expressing oligodendroglial precursor cells in the subventricular zone and corpus callosum of lysolecithin-demyelinated rats. Notch activation seemed to be driven by Jagged1, which led to a high expression of downstream gene Hes5 in the subventricular zone of demyelinated rats. Apotransferrin injection induced remyelination, while the injection of the γ-secretase inhibitor reversed this effect. In addition, 24 h after apotransferrin injection, evidence showed Notch activation concomitantly with an increase in F3/contactin levels and the up-regulation of the myelin-associated glycoprotein gene in the subventricular zone and corpus callosum of demyelinated rats. Collected evidence supports the participation of both canonical and non-canonical Notch signaling pathways in demyelination/remyelination. Notch activation was found to trigger Hes5 expression as a consequence of focal demyelination, which might promote oligodendroglial precursor cell proliferation. During apotransferrin-induced remyelination, Notch activation seemed to be mediated by the expression of F3/contactin, which might induce apotransferrin-mediated oligodendroglial maturation. Evidence of the participation of Notch signaling in the demyelination/remyelination process will help further understand demyelinating disorders such as Multiple Sclerosis and the use of aTf should be taken into consideration as a possible therapeutic intervention.

PIMD: 23959709

The relationship between total and regional corpus callosum atrophy, cognitive impairment and fatigue in multiple sclerosis patients.

The objective of this paper is to investigate the relationship between total and regional corpus callosum (CC) atrophy, neuropsychological test performance and fatigue in multiple sclerosis (MS) patients.We conducted a cross-sectional study in 113 MS patients: mean age 48 ± 11 years, 75/113 women, 84/113 relapsing-remitting MS, mean disease duration 21 ± 9 years, mean Expanded Disability Status Scale (EDSS) score 3.2 ± 1.7. All patients underwent brain magnetic resonance imaging, standardised neurological assessment and comprehensive cognitive testing including assessments for fatigue and depression. Total and regional CC atrophy was assessed using the corpus callosum index (CCI).CCI correlated more strongly with T2- and T1-lesion volume and whole brain volume than with disease duration or EDSS score. CCI correlated strongly with the verbal fluency test (VFT), Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT). Multivariate regression analysis revealed that atrophy of the posterior CC segment was significantly associated with poor outcome in the PASAT, VFT and SDMT. In contrast, atrophy of the anterior CC segment was significantly associated with fatigue severity and poor outcome in the long-term memory test.Atrophy of the CC is associated with cognitive impairment and fatigue. Regional CCI results indicate that these associations are partially spatially segregated.

PIMD: 23943390

Quantitative MRI and ultrastructural examination of the cuprizone mouse model of demyelination.

The cuprizone mouse model of demyelination was used to investigate the influence that white matter changes have on different magnetic resonance imaging results. In vivo T2 -weighted and magnetization transfer images (MTIs) were acquired weekly in control (n = 5) and cuprizone-fed (n = 5) mice, with significant increases in signal intensity in T2 -weighted images ($p < 0.001$) and lower magnetization transfer ratio ($p < 0.001$) in the corpus callosum of the cuprizone-fed mice starting at 3 weeks and peaking at 4 and 5 weeks, respectively. Diffusion tensor imaging (DTI), quantitative MTI (qMTI), and T1/T2 measurements were used to analyze freshly excised tissue after 6 weeks of cuprizone administration. In multicomponent T2 analysis with 10 ms echo spacing, there was no visible myelin water component associated with the short T2 value. Quantitative MTI metrics showed significant differences in the corpus callosum and external capsule of the cuprizone-fed mice, similar to previous studies of multiple sclerosis in humans and animal models of demyelination. Fractional anisotropy was significantly lower and mean, axial, and radial diffusivity were significantly higher in the cuprizone-fed mice. Cellular distributions measured in electron micrographs of the corpus callosum correlated strongly to several different quantitative MRI metrics. The largest Spearman correlation coefficient varied depending on cellular type: T1 versus the myelinated axon fraction ($\rho = -0.90$), the bound pool fraction (f) versus the myelin sheath fraction ($\rho = 0.93$), and axial diffusivity versus the non-myelinated cell fraction ($\rho = 0.92$). Using Pearson's correlation coefficient, f was strongly correlated to the myelin sheath fraction ($r = 0.98$) with a linear equation predicting myelin content ($5.37f - 0.25$). Of the calculated MRI metrics, f was the strongest indicator of myelin content, while longitudinal relaxation rates and diffusivity measurements were the strongest indicators of changes in tissue structure.

PIMD: 23937696

Multiple sclerosis presenting initially with a worsening of migraine symptoms.

Multiple sclerosis (MS) is a chronic autoimmune disease that targets myelinated axons in the central nervous system. Headache has been reported as a subtle symptom of the onset of MS, with a variable frequency of 1.6-28.5%; however, it remains unclear whether headache is a true symptom of MS onset. Here, we report the case of a female patient who had a history of migraine without aura and experienced worsening of migraine-headache symptoms as the initial manifestation of MS. Three similar cases were reported previously; however, unlike this case, those cases had no history of migraine without aura. In our case, we excluded factors that could trigger migraine attacks, such as changes in weather, drugs, alcohol, caffeine withdrawal, stress, fatigue, lack of sleep, hormonal therapy, diet, and hunger. The patient had one episode of MS attack with the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions, including hyperintense lesions in the bilateral periventricular white matter, body of the corpus callosum, and periaqueductal grey matter, as observed on the T2-weighted images obtained at the first brain magnetic resonance imaging. In addition, after the injection of gadolinium contrast, ring enhancement over these lesions was noted in T1-weighted images, which was suggestive of active demyelination. MS was diagnosed according to the McDonald criteria (2010 revision). We conclude that MS with periaqueductal grey matter involvement may present with worsening migraine. It is important to be cautious if any secondary causes exist, especially when the patient has a history of migraine without aura. MS should be one of the differential diagnoses in young women showing a change in headache pattern or poor clinical drug response to migraine treatment accompanied by episodes of focal neurological deficit. Failure to recognize MS may lead to inappropriate treatment and worse prognosis; early diagnosis in patients with MS is essential to improve their clinical outcomes and quality of life.

PIMD: 23933305

Multimodal imaging of subventricular zone neural stem/progenitor cells in the cuprizone mouse model reveals increased neurogenic potential for the olfactory bulb pathway, but no contribution to remyelination of the corpus callosum.

Multiple sclerosis is a devastating demyelinating disease of the central nervous system (CNS) in which endogenous remyelination, and thus recovery, often fails. Although the cuprizone mouse model allowed elucidation of many molecular factors governing remyelination, currently very little is known about the spatial origin of the oligodendrocyte progenitor cells that initiate remyelination in this model. Therefore, we here investigated in this model whether subventricular zone (SVZ) neural stem/progenitor cells (NSPCs) contribute to remyelination of the splenium following cuprizone-induced demyelination. Experimentally, from the day of in situ NSPC labeling, C57BL/6J mice were fed a 0.2% cuprizone diet during a 4-week period and then left to recover on a normal diet for 8weeks. Two in situ labeling strategies were employed: (i) NSPCs were labeled by intraventricular injection of micron-sized iron oxide particles and then followed up longitudinally by means of magnetic resonance imaging (MRI), and (ii) SVZ NSPCs were transduced with a lentiviral vector encoding the eGFP and Luciferase reporter proteins for longitudinal monitoring by means of in vivo bioluminescence imaging (BLI). In contrast to preceding suggestions, no migration of SVZ NSPC towards the demyelinated splenium was observed using both MRI and BLI, and further validated by histological analysis, thereby demonstrating that SVZ NSPCs are unable to contribute directly to remyelination of the splenium in the cuprizone model. Interestingly, using longitudinal BLI analysis and confirmed by histological analysis, an increased migration of SVZ NSPC-derived neuroblasts towards the olfactory bulb was observed following cuprizone treatment, indicative for a potential link between CNS inflammation and increased neurogenesis.

PIMD: 23907269

Topography of brain sodium accumulation in progressive multiple sclerosis.

Sodium accumulation is involved in neuronal injury occurring in multiple sclerosis (MS). We aimed to assess sodium accumulation in progressive MS, known to suffer from severe neuronal injury.3D-(23)Na-MRI was obtained on a 3T-MR-scanner in 20 progressive MS patients [11 primary-progressive (PPMS) and nine secondary-progressive (SPMS)] and 15 controls. Total sodium concentrations (TSC) within grey matter (GM), normal-appearing white matter (WM) and lesions were extracted. Statistical mapping analyses of TSC abnormalities were also performed.Progressive MS patients presented higher GM-TSC values (48.8 ± 3.1 mmol/l wet tissue vol, $p < 0.001$) and T2lesions-TSC values (50.9 ± 2.2 mmol/l wet tissue vol, $p = 0.01$) compared to GM and WM of controls. Statistical mapping analysis showed TSC increases in PPMS patients confined to motor and somatosensory cortices, prefrontal cortices, pons and cerebellum. In SPMS, TSC increases were associated with areas involving: primary motor, premotor and somatosensory cortices; prefrontal, cingulate and visual cortices; the corpus callosum, thalami, brainstem and cerebellum. Anterior prefrontal and premotor cortices TSC were correlated with disability.Sodium accumulation is present in progressive MS patients, more restricted to the motor system in PPMS and more widespread in SPMS. Local brain sodium accumulation appears as a promising marker to monitor patients with progressive MS.

PIMD: 23890807

Distribution of oligodendrocyte loss and mitochondrial toxicity in the cuprizone-induced experimental demyelination model.

Cuprizone is a copper-chelating mitochondrial toxin that causes oligodendrocyte apoptosis and demyelination preferentially in the corpus callosum (CC) and the superior cerebellar peduncles, but not in the spinal cord (SC) of C57BL/6 mice. Here we aimed to determine the activities of copper-containing enzymes in correlation with the distribution of demyelination during exposure to cuprizone. The study revealed mitochondrial complex IV and superoxide dismutase activity alterations in both the pathology-affected CC and the non-affected SC. This observation raises the possibility that regionally different subcellular molecular interactions lead to the selective oligodendrocyte loss induced by the nonselective mitochondrial toxin, cuprizone.

PIMD: 23862116

Promotion of remyelination by adipose mesenchymal stem cell transplantation in a cuprizone model of multiple sclerosis.

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS). Stem cell transplantation is a new therapeutic approach for demyelinating diseases such as MS which may promote remyelination. In this study, we evaluate the remyelinating potential of adipose mesenchymal stem cells (ADSCs) and their effect on neural cell composition in the corpus callosum in an experimental model of MS.This experimental study used adult male C57BL/6 mice. Cultured ADSCs were confirmed to be CD73(+),CD90(+), CD31(-),CD45(-), and labeled by PKH26. Animals were fed with 0.2% w/w cuprizone added to ground breeder chow ad libitum for six weeks. At day 0 after cuprizone removal, mice were randomly divided into two groups: the ADSCs-transplanted group and the control vehicle group (received medium alone). Some mice of the same age were fed with their normal diet to serve as healthy control group. Homing of ADSCs in demyelinated lesions was examined by fluorescent microscope. At ten days after transplantation, the mice were euthanized and their cells analyzed by luxol fast blue staining (LFB), transmission electron microscopy and flow cytometry. Results were analyzed by one-way analysis of variance (ANOVA).According to fluorescent cell labeling, transplanted ADSCs appeared to survive and exhibited homing specificity. LFB staining and transmission electron microscope evaluation revealed enhanced remyelination in the transplanted group compared to the control vehicle group. Flow cytometry analysis showedan increase in Olig2 and O4 cells and a decrease in GFAP and Iba-1 cells in the transplanted group.Our results indicate that ADSCs may provide a feasible, practical way for remyelination in diseases such as MS.

PIMD: 23845898

Diffuse cauda equina enhancement in a middle aged male with Susac syndrome and symptomatic cauda equina syndrome.

Susac syndrome is a rare neurologic disorder first described by Susac et al. in 1979. Clinically, Susac syndrome consists of a triad including encephalopathy, branch retinal artery occlusions and sensorineural hearing loss. All three components of the triad usually do not present at the same time, thus delaying time to diagnosis. MRI studies often show characteristic punched out lesions of the central fibers of the corpus callosum. Intracranial leptomeningeal enhancement may be seen, however, cauda equina involvement has not been described to our knowledge. We present a case of Susac syndrome in a middle-aged male with symptoms of cauda equina syndrome, and spinal MRI showing diffuse enhancement of the nerve roots of the cauda equina.

PIMD: 23832594

Astrogliopathy and oligodendrogliopathy are early events in CNS demyelination.

We examined the phenotypic composition of cells and the underlying mechanisms of demyelination following injection of lipopolysaccharide (LPS) into the corpus callosum of rats. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay showed fragmented DNA, which co-localized with oligodendrocytes in areas of demyelination following intracerebral injection with LPS. Immunostaining showed the presence of caspase 3 in cells which expressed the oligodendrocyte markers, suggesting activation of the apoptotic pathway. Commensurate reduction in glial fibrillary acid protein (GFAP)+/ gap junction protein connexin43+ (Cx43) cells, was also seen in the corpus callosum prior to histochemical evidence of demyelination. Expression of mRNA for proinflammatory cytokines was maximal 3 day postinjection, at a time when the numbers of TUNEL positive cells in the corpus callosum were declining and the total number of CD68+ cells peaked at day 14 postinjection. Our studies suggest that death of oligodendrocytes is an early event in LPS model of demyelination. We believe that the innate immune model of oligodendrocyte death will be useful in the development of neuroprotective agents capable of rescuing oligodendrocytes from apoptosis.

PIMD: 23777468

The relationship between executive functioning, processing speed, and white matter integrity in multiple sclerosis.

The primary purpose of the current study was to examine the relationship between performance on executive tasks and white matter integrity, assessed by diffusion tensor imaging (DTI) in multiple sclerosis (MS). A second aim was to examine how processing speed affects the relationship between executive functioning and fractional anisotropy (FA). This relationship was examined in two executive tasks that rely heavily on processing speed: the Color-Word Interference Test and the Trail Making Test (Delis-Kaplan Executive Function System). It was hypothesized that reduced FA is related to poor performance on executive tasks in MS, but that this relationship would be affected by the statistical correction of processing speed from the executive tasks. A total of 15 healthy controls and 25 persons with MS participated. Regression analyses were used to examine the relationship between executive functioning and FA, both before and after processing speed was removed from the executive scores. Before processing speed was removed from the executive scores, reduced FA was associated with poor performance on the Color-Word Interference Test and Trail Making Test in a diffuse network including corpus callosum and superior longitudinal fasciculus. However, once processing speed was removed, the relationship between executive functions and FA was no longer significant on the Trail Making Test, and significantly reduced and more localized on the Color-Word Interference Test.

PIMD: 23761899

Loss of branched O-mannosyl glycans in astrocytes accelerates remyelination.

In demyelinating diseases such as multiple sclerosis, a critical problem is failure of remyelination, which is important for protecting axons against degeneration and restoring conduction deficits. However, the underlying mechanism of demyelination/remyelination remains unclear. N-acetylglucosaminyltransferase-IX (GnT-IX; also known as GnT-Vb) is a brain-specific glycosyltransferase that catalyzes the branched formation of O-mannosyl glycan structures. O-Mannosylation of α-dystroglycan is critical for its function as an extracellular matrix receptor, but the biological significance of its branched structures, which are exclusively found in the brain, is unclear. In this study, we found that GnT-IX formed branched O-mannosyl glycans on receptor protein tyrosine phosphatase β (RPTPβ) in vivo. Since RPTPβ is thought to play a regulatory role in demyelinating diseases, GnT-IX-deficient mice were subjected to cuprizone-induced demyelination. Cuprizone feeding for 8 weeks gradually promoted demyelination in wild-type mice. In GnT-IX-deficient mice, the myelin content in the corpus callosum was reduced after 4 weeks of treatment, but markedly increased at 8 weeks, suggesting enhanced remyelination under GnT-IX deficiency. Furthermore, astrocyte activation in the corpus callosum of GnT-IX-deficient mice was significantly attenuated, and an oligodendrocyte cell lineage analysis indicated that more oligodendrocyte precursor cells differentiated into mature oligodendrocytes. Together, branched O-mannosyl glycans in the corpus callosum in the brain are a necessary component of remyelination inhibition in the cuprizone-induced demyelination model, suggesting that modulation of O-mannosyl glycans is a likely candidate for therapeutic strategies.

PIMD: 23739972

Ascl1/Mash1 promotes brain oligodendrogenesis during myelination and remyelination.

Oligodendrocytes are the myelin-forming cells of the CNS. They differentiate from oligodendrocyte precursor cells (OPCs) that are produced from progenitors throughout life but more actively during the neonatal period and in response to demyelinating insults. An accurate regulation of oligodendrogenesis is required to generate oligodendrocytes during these developmental or repair processes. We hypothesized that this regulation implicates transcription factors, which are expressed by OPCs and/or their progenitors. Ascl1/Mash1 is a proneural transcription factor previously implicated in embryonic oligodendrogenesis and operating in genetic interaction with Olig2, an essential transcriptional regulator in oligodendrocyte development. Herein, we have investigated the contribution of Ascl1 to oligodendrocyte development and remyelination in the postnatal cortex. During the neonatal period, Ascl1 expression was detected in progenitors of the cortical subventricular zone and in cortical OPCs. Different genetic approaches to delete Ascl1 in cortical progenitors or OPCs reduced neonatal oligodendrogenesis, showing that Ascl1 positively regulated both OPC specification from subventricular zone progenitors as well as the balance between OPC differentiation and proliferation. Examination of remyelination processes, both in the mouse model for focal demyelination of the corpus callosum and in multiple sclerosis lesions in humans, indicated that Ascl1 activity was upregulated along with increased oligodendrogenesis observed in remyelinating lesions. Additional genetic evidence indicated that remyelinating oligodendrocytes derived from Ascl1(+) progenitors/OPCs and that Ascl1 was required for proper remyelination. Together, our results show that Ascl1 function modulates multiple steps of OPC development in the postnatal brain and in response to demyelinating insults.

PIMD: 23711509

Regional regulation of glutamate signaling during cuprizone-induced demyelination in the brain.

Glutamate excitotoxicity is associated with a wide range of neurodegenerative disorders and also seems to be involved in the pathology of demyelinating disorders such as multiple sclerosis (MS). Cuprizone-induced toxic demyelination shows clear characteristics of MS such as demyelination and axonal damage without the involvement of the innate immune system. In this study, we have evaluated glutamate signaling during cuprizone-induced demyelination in the white and gray matter of mouse brain by studying the expression of ionotropic and metabotropic glutamate-receptors and -transporters by Affymetrix gene array analysis, followed by real-time PCR and western blot analysis. Cellular localization of glutamate transporters was investigated by fluorescence double-labeling experiments. Comparing white and gray matter areas, the expression of glutamate receptors was region-specific. Among NMDA receptor subunits, NR2A was up-regulated in the demyelinated corpus callosum (CC), whereas the metabotropic glutamate receptor mGluR2 was down-regulated in demyelinated gray matter. Glutamate-aspartate transporter (GLAST) co-localizing with GFAP(+) astrocytes was increased in both demyelinated CC and telencephalic cortex, whereas Slc1a4 transporter was up-regulated only in CC. Our data indicate that cuprizone treatment affects glutamate-receptors and -transporters differently in gray and white matter brain areas revealing particularly regulation of GLAST and Slc1a4 compared with other genes. This might have an important influence on brain-region selective sensitivity to neurotoxic compounds and the progression of demyelination as has been reported for MS and other demyelinating neurological diseases.

PIMD: 23696802

Assessing the correlation between grey and white matter damage with motor and cognitive impairment in multiple sclerosis patients.

Multiple sclerosis (MS) is characterized by demyelinating and degenerative processes within the central nervous system. Unlike conventional MRI,new advanced imaging techniques improve pathological specificity and better highlight the relationship between anatomical damage and clinical impairment.To investigate the relationship between clinical disability and both grey (GM) and white matter (WM) regional damage in MS patients.Thirty-six relapsing remitting-MS patients and 25 sex- and age-matched controls were enrolled. All patients were clinically evaluated by the Expanded Disability Status Scale and the Multiple Sclerosis Functional Composite (MSFC) scale, which includes the 9-hole peg test (9HPT), the timed 25-feet walking test (T25FW) and the paced auditory serial addition test (PASAT). All subjects were imaged by a 3.0 T scanner: dual-echo fast spin-echo, 3DT1-weighted and diffusion-tensor imaging (DTI) sequences were acquired. Voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) analyses were run for regional GM and WM assessment, respectively. T2 lesion volumes were also calculated, by using a semi-automated technique.Brain volumetric assessment of GM and DTI measures revealed significant differences between patients and controls. In patients, different measures of WM damage correlated each-other ($p<0.0001$), whereas none of them correlated with GM volume. In patients, focal GM atrophy and widespread WM damage significantly correlated with clinical measures. In particular, VBM analysis revealed a significant correlation ($p<0.05$) between GM volume and 9HPT in cerebellum and between GM volume and PASAT in orbito-frontal cortex. TBSS showed significant correlations between DTI metrics with 9HPT and PASAT scores in many WM bundles ($p<0.05$), including corpus callosum, internal capsule, posterior thalamic radiations, cerebral peduncles.Selective GM atrophy and widespread WM tracts damage are associated with functional impairment of upper-limb motion and cognition. The combined analysis of volumetric and DTI data may help to better understand structural alterations underlying physical and cognitive dysfunction in MS.

PIMD: 23684572

FGF2 and FGFR1 signaling regulate functional recovery following cuprizone demyelination.

In demyelinating diseases, such as multiple sclerosis, remyelination offers the potential to recover function of viable denuded axons by restoring saltatory conduction and/or protecting from further damage. Mice with genetic reduction of fibroblast growth factor 2 (Fgf2) or Fgf receptor 1 (Fgfr1) exhibit dramatically improved remyelination following experimental demyelination with cuprizone. The current studies are the first to test neurobehavioral outcomes with these gene deletions that improved remyelination. The cuprizone protocols used did not produce overt abnormalities but did reduce bilateral sensorimotor coordination (complex wheel task) and increase sociability (two chamber apparatus with novel mouse). A significant effect of genotype was observed on the complex wheel task but not in the sociability apparatus. Specifically, complex wheel velocities for Fgf2 nulls improved significantly after removal of cuprizone from the diet. This improvement in Fgf2 null mice occurred following either acute (6 weeks) or chronic (12 weeks) demyelination. Plp/CreERT:Fgfr1(fl/fl) mice administered tamoxifen at 10 weeks of cuprizone treatment to induce Fgfr1 knockdown also showed improved recovery of running velocities on the complex wheels. Therefore, constitutive deletion of Fgf2 or Fgfr1 knockdown in oligodendrocyte lineage cells is sufficient to overcome impairment of sensorimotor coordination after cuprizone demyelination.

PIMD: 23681354

Early white matter changes in childhood multiple sclerosis: a diffusion tensor imaging study.

Loss of integrity in nonlesional white matter occurs as a fundamental feature of multiple sclerosis in adults. The purpose of our study was to evaluate DTI-derived measures of white matter microstructure in children with MS compared with age- and sex-matched controls by using tract-based spatial statistics.Fourteen consecutive pediatric patients with MS (11 female/3 male; mean age, 15.1 ± 1.6 years; age range, 12-17 years) and age- and sex-matched healthy subjects (11 female/3 male; mean age, 14.8 ± 1.7 years) were included in the study. After we obtained DTI sequences, data processing was performed by using tract-based spatial statistics.Compared with healthy age- and sex-matched controls, children with multiple sclerosis showed a global decrease in mean fractional anisotropy ($P \leq .001$), with a concomitant increase in mean ($P < .001$), radial ($P < .05$), and axial diffusivity ($P < .001$). The most pronounced fractional anisotropy value decrease in patients with MS was found in the splenium of the corpus callosum ($P < .001$). An additional decrease in fractional anisotropy was identified in the right temporal and right and left parietal regions ($P < .001$). Fractional anisotropy of the white matter skeleton was related to disease duration and may, therefore, serve as a diagnostic marker.The microstructure of white matter is altered early in the disease course in childhood multiple sclerosis.

PIMD: 23650566

Investigation of sequential growth factor delivery during cuprizone challenge in mice aimed to enhance oligodendrogliogenesis and myelin repair.

Repair in multiple sclerosis involves remyelination, a process in which axons are provided with a new myelin sheath by new oligodendrocytes. Bone morphogenic proteins (BMPs) are a family of growth factors that have been shown to influence the response of oligodendrocyte progenitor cells (OPCs) in vivo during demyelination and remyelination in the adult brain. We have previously shown that BMP4 infusion increases numbers of OPCs during cuprizone-induced demyelination, while infusion of Noggin, an endogenous antagonist of BMP4 increases numbers of mature oligodendrocytes and remyelinated axons following recovery. Additional studies have shown that insulin-like growth factor-1 (IGF-1) promotes the survival of OPCs during cuprizone-induced demyelination. Based on these data, we investigated whether myelin repair could be further enhanced by sequential infusion of these agents firstly, BMP4 to increase OPC numbers, followed by either Noggin or IGF-1 to increase the differentiation and survival of the newly generated OPCs. We identified that sequential delivery of BMP4 and IGF-1 during cuprizone challenge increased the number of mature oligodendrocytes and decreased astrocyte numbers following recovery compared with vehicle infused mice, but did not alter remyelination. However, sequential delivery of BMP4 and Noggin during cuprizone challenge did not alter numbers of oligodendrocytes or astrocytes in the corpus callosum compared with vehicle infused mice. Furthermore, electron microscopy analysis revealed no change in average myelin thickness in the corpus callosum between vehicle infused and BMP4-Noggin infused mice. Our results suggest that while single delivery of Noggin or IGF-1 increased the production of mature oligodendrocytes in vivo in the context of demyelination, only Noggin infusion promoted remyelination. Thus, sequential delivery of BMP4 and Noggin or IGF-1 does not further enhance myelin repair above what occurs with delivery of Noggin alone.

PIMD: 23647102

Minocycline reduces remyelination by suppressing ciliary neurotrophic factor expression after cuprizone-induced demyelination.

Remyelination is disrupted in demyelinating diseases such as multiple sclerosis, but the underlying pathogenetic mechanisms are unclear. In this study, we employed the murine cuprizone model of demyelination, in which remyelination occurs after removal of the toxin from the diet, to examine the cellular and molecular changes during demyelination and remyelination. Microglia accumulated in the corpus callosum during weeks 2-4 of the cuprizone diet, and these cells remained activated 2 weeks after the change to the normal diet. To examine the role of microglia in remyelination, mice were treated with minocycline to inactivate these cells after cuprizone-induced demyelination. Minocycline treatment reduced the number of CC1-positive oligodendrocytes, as well as levels of myelin basic protein (MBP) and CNPase in the remyelination phase. The expression of CNTF mRNA in the corpus callosum increased after 4 weeks on the cuprizone diet and remained high 2 weeks after the change to the normal diet. Minocycline suppressed CNTF expression during the remyelination phase on the normal diet. Primary culture experiments showed that CNTF was produced by microglia in addition to astrocytes. In vitro, CNTF directly affected the differentiation of oligodendrocytic cells. These findings suggest that minocycline reduces remyelination by suppressing CNTF expression by microglia after cuprizone-induced demyelination.

PIMD: 23643443

Tract-specific white matter correlates of fatigue and cognitive impairment in benign multiple sclerosis.

Although benign multiple sclerosis (BMS) is traditionally defined by the presence of mild motor involvement decades after disease onset, symptoms of fatigue and cognitive impairment are very common.To investigate the association between micro-structural damage in the anterior thalamic (AT) tracts and in the corpus callosum (CC), as measured by diffusion tensor imaging (DTI) tractography, and fatigue and cognitive deficits.DTI data were acquired from 26 BMS patients and 24 sex- and age-matched healthy controls.General and mental fatigue scores were significantly impaired in patients compared with controls ($p \leq 0.05$ for both) and 38% of patients resulted cognitively impaired. Mean diffusivity (MD) of the AT and CC tracts was significantly higher and fractional anisotropy (FA) was lower in patients compared with controls ($p < 0.001$ for all). Fatigue was associated with increased MD ($p = 0.01$) of the AT tracts whereas deficit of executive functions and verbal learning were associated with decreased FA in the body ($p = 0.004$) and genu ($p = 0.008$) of the CC. Deficits in processing speed and attention were associated with the T2 lesion volume of the AT tracts ($p < 0.01$ for all).These findings suggest that fatigue and cognitive impairment are quite frequent in BMS patients and are, at least in part, related to micro-structural damage and T2LV of WM tracts connecting the brain cortical and sub-cortical regions of the two hemispheres.

PIMD: 23616276

A novel approach with "skeletonised MTR" measures tract-specific microstructural changes in early primary-progressive MS.

We combined tract-based spatial statistics (TBSS) and magnetization transfer (MT) imaging to assess white matter (WM) tract-specific short-term changes in early primary-progressive multiple sclerosis (PPMS) and their relationships with clinical progression. Twenty-one PPMS patients within 5 years from onset underwent MT and diffusion tensor imaging (DTI) at baseline and after 12 months. Patients' disability was assessed. DTI data were processed to compute fractional anisotropy (FA) and to generate a common WM "skeleton," which represents the tracts that are "common" to all subjects using TBSS. The MT ratio (MTR) was computed from MT data and co-registered with the DTI. The skeletonization procedure derived for FA was applied to each subject's MTR image to obtain a "skeletonised" MTR map for every subject. Permutation tests were used to assess (i) changes in FA, principal diffusivities, and MTR over the follow-up, and (ii) associations between changes in imaging parameters and changes in disability. Patients showed significant decreases in MTR over one year in the corpus callosum (CC), bilateral corticospinal tract (CST), thalamic radiations, and superior and inferior longitudinal fasciculi. These changes were located both within lesions and the normal-appearing WM. No significant longitudinal change in skeletonised FA was found, but radial diffusivity (RD) significantly increased in several regions, including the CST bilaterally and the right inferior longitudinal fasciculus. MTR decreases, RD increases, and axial diffusivity decreases in the CC and CST correlated with a deterioration in the upper limb function. We detected tract-specific multimodal imaging changes that reflect the accrual of microstructural damage and possibly contribute to clinical impairment in PPMS. We propose a novel methodology that can be extended to other diseases to map cross-subject and tract-specific changes in MTR.

PIMD: 23589195

Investigating the role of the corpus callosum in regulating motor overflow in multiple sclerosis.

The corpus callosum (CC) is commonly affected in multiple sclerosis (MS), however, sensitive behavioral measures of MS-related CC pathology are lacking. The CC is considered a key structure in the mediation of a type of involuntary movement known as motor overflow. In this study, we sought to characterize the impact of CC damage on motor overflow in MS. Twenty MS participants and 20 controls performed a unilateral force production task. Motor overflow (involuntary force) in the non-active hand was measured while the active hand performed the task. CC volume and lesion load were calculated for MS participants using T2-weighted MRI. We found no group differences in motor overflow; however, motor overflow correlated significantly with MS disease severity [Expanded disability status scale (EDSS)]. CC damage (lesions and decreased volume) did not correlate with motor overflow. This study suggests that CC damage may not directly lead to changes in the regulation of motor overflow. Rather, findings support the notion that a wider network of structures may mediate the production and suppression of motor overflow.

PIMD: 23575354

Multiple sclerosis susceptibility loci do not alter clinical and MRI outcomes in clinically isolated syndrome.

It has not yet been established whether genetic predictors of multiple sclerosis (MS) susceptibility also influence disease severity and accumulation of disability. Our aim was to evaluate associations between 16 previously validated genetic susceptibility markers and MS phenotype. Patients with clinically isolated syndrome verified by positive magnetic resonance imaging (MRI) and cerebrospinal fluid findings (n=179) were treated with interferon-β. Disability and volumetric MRI parameters were evaluated regularly for 2 years. Sixteen single-nucleotide polymorphisms (SNPs) previously validated as predictors of MS susceptibility in our cohort and their combined weighted genetic risk score (wGRS) were tested for associations with clinical (conversion to MS, relapses and disability) and MRI disease outcomes (whole brain, grey matter and white matter volumes, corpus callosum cross-sectional area, brain parenchymal fraction, T2 and T1 lesion volumes) 2 years from disease onset using mixed-effect models. We have found no associations between the tested SNPs and the clinical or MRI outcomes. Neither the combined wGRS predicted MS activity and progression over 2-year follow-up period. Power analyses confirmed 90% power to identify clinically relevant changes in all outcome variables. We conclude that the most important MS susceptibility loci do not determine MS phenotype and disease outcomes.

PIMD: 23468546

Cognitive impairment in MS: impact of white matter integrity, gray matter volume, and lesions.

To investigate whether extent and severity of white matter (WM) damage, as measured with diffusion tensor imaging (DTI), can distinguish cognitively preserved (CP) from cognitively impaired (CI) multiple sclerosis (MS) patients.Conventional MRI and DTI data were acquired from 55 MS patients (35 CP, 20 CI) and 30 healthy controls (HC). Voxelwise analyses were used to investigate fractional anisotropy (FA), mean diffusivity, radial diffusivity, and axial diffusivity of a WM skeleton. Regional gray matter volume was quantified and lesion probability maps were generated.Compared to HCs, decreased FA was found in 49% of the investigated WM skeleton in CP patients and in 76% of the investigated WM in CI patients. Several brain areas that showed reduced FA in both patient groups were significantly worse in CI patients, i.e, corpus callosum, superior and inferior longitudinal fasciculus, corticospinal tracts, forceps major, cingulum, and fornices. In CI patients, WM integrity damage was additionally seen in cortical brain areas, thalamus, uncinate fasciculus, brainstem, and cerebellum. These findings were independent of lesion location and regional gray matter volume, since no differences were found between the groups.CI patients diverged from CP patients only on DTI metrics. WM integrity changes were found in areas that are highly relevant for cognition in the CI patients but not in the CP patients. These WM changes are therefore thought to be related to the cognitive deficits and suggest that DTI might be a powerful tool when monitoring cognitive impairment in MS.

PIMD: 23456519

17β-Estradiol enhances the efficacy of adipose-derived mesenchymal stem cells on remyelination in mouse model of multiple sclerosis.

Previous studies have demonstrated the potential of monotherapy with either mesenchymal stem cells (MSCs) or estrogen in autoimmune and cuprizone models of multiple sclerosis (MS). The aim of this study was to examine the effects of co-administration of 17β-estradiol (E2) and adipose-derived mesenchymal stem cells (ADSCs) on remyelination of corpus callosum axons in a cuprizone model of MS. Forty eight male C57BL/6 mice were fed cuprizone (0.2%) for 6 weeks. At day 0 after cuprizone removal, animals were randomly divided into four groups. The E2 monotherapy, ADSCs monotherapy, E2/ADSCs combined therapy and vehicle control. Some mice of the same age were fed with their normal diet to serve as healthy control group. E2 pellets, designed to release 5.0 mg E2 over 10 days, were implanted subcutaneously. 10(6) PKH26 labeled ADSCs were transplanted into lateral tail. The extent of demyelination, remyelination, and cell type's composition of host brain were examined at 10 days post-transplantation in the body of the corpus callosum. Transplanted cells migrated to the corpus callosum injury. Histological examination revealed efficacy of intravenous ADSCs transplantation in remyelination of mouse cuprizone model of MS can be significantly enhanced by E2 administration. Flow cytometry showed that the mean percentages of expression of Iba-1, Olig2 and O4 were significantly increased in E2/ADSCs combined therapy in comparison with ADSCs monotherapy. In conclusion, the findings of this study revealed that E2 administration enhanced efficacy of intravenous ADSCs transplantation in remyelination of corpus callosum axons in mouse cuprizone model of MS.

PIMD: 23432650

A 63 year old woman with white matter lesions and pachymeningeal inflammation.

We describe the case of a 63-year-old woman with CNS Rosai-Dorfman disease, presenting with diffuse dural infiltration, mimicking idiopathic hypertrophic pachymeningitis, and right vertebral artery dissection. Her symptoms included a progressive 11-month history of vertigo, gait ataxia, and right thalamic stroke. A diagnosis of CNS Rosai-Dorfman disease was made following open dural biopsy, and later confirmed on autopsy studies. The autopsy demonstrated widespread dural infiltration by inflammatory cells, principally large histiocytes, many of which exhibited emperipolesis, a characteristic finding in Rosai-Dorfman disease. A second pathological finding on autopsy was the presence of multiple demyelinating plaques (with preservation of axons), located in the corpus callosum, periventricular white matter, and multiple brainstem segments. These were consistent with a diagnosis of multiple sclerosis. This case description serves to remind clinicians that CNS Rosai-Dorfman disease—although uncommon—may present as a focal, dural-based, hemispheric mass lesion, or as diffuse pachymeningeal inflammation. Our case was also unusual due to the co-existence of CNS Rosai-Dorfman disease, multiple sclerosis, and polycythemia vera (all rare diseases) in a single patient. Although the overlap of disorders may have been co-incidental, one could raise the question whether all three disorders were triggered by the same underlying dysimmune state.

PIMD: 23365232

The antiaging protein Klotho enhances oligodendrocyte maturation and myelination of the CNS.

We have previously shown that myelin abnormalities characterize the normal aging process of the brain and that an age-associated reduction in Klotho is conserved across species. Predominantly generated in brain and kidney, Klotho overexpression extends life span, whereas loss of Klotho accelerates the development of aging-like phenotypes. Although the function of Klotho in brain is unknown, loss of Klotho expression leads to cognitive deficits. We found significant effects of Klotho on oligodendrocyte functions, including induced maturation of rat primary oligodendrocytic progenitor cells (OPCs) in vitro and myelination. Phosphoprotein analysis indicated that Klotho's downstream effects involve Akt and ERK signal pathways. Klotho increased OPC maturation, and inhibition of Akt or ERK function blocked this effect on OPCs. In vivo studies of Klotho knock-out mice and control littermates revealed that knock-out mice have a significant reduction in major myelin protein and gene expression. By immunohistochemistry, the number of total and mature oligodendrocytes was significantly lower in Klotho knock-out mice. Strikingly, at the ultrastructural level, Klotho knock-out mice exhibited significantly impaired myelination of the optic nerve and corpus callosum. These mice also displayed severe abnormalities at the nodes of Ranvier. To decipher the mechanisms by which Klotho affects oligodendrocytes, we used luciferase pathway reporters to identify the transcription factors involved. Together, these studies provide novel evidence for Klotho as a key player in myelin biology, which may thus be a useful therapeutic target in efforts to protect brain myelin against age-dependent changes and promote repair in multiple sclerosis.

PIMD: 23365093

Targeting ASIC1 in primary progressive multiple sclerosis: evidence of neuroprotection with amiloride.

Neurodegeneration is the main cause for permanent disability in multiple sclerosis. The effect of current immunomodulatory treatments on neurodegeneration is insufficient. Therefore, direct neuroprotection and myeloprotection remain an important therapeutic goal. Targeting acid-sensing ion channel 1 (encoded by the ASIC1 gene), which contributes to the excessive intracellular accumulation of injurious Na(+) and Ca(2+) and is over-expressed in acute multiple sclerosis lesions, appears to be a viable strategy to limit cellular injury that is the substrate of neurodegeneration. While blockade of ASIC1 through amiloride, a potassium sparing diuretic that is currently licensed for hypertension and congestive cardiac failure, showed neuroprotective and myeloprotective effects in experimental models of multiple sclerosis, this strategy remains untested in patients with multiple sclerosis. In this translational study, we tested the neuroprotective effects of amiloride in patients with primary progressive multiple sclerosis. First, we assessed ASIC1 expression in chronic brain lesions from post-mortem of patients with progressive multiple sclerosis to identify the target process for neuroprotection. Second, we tested the neuroprotective effect of amiloride in a cohort of 14 patients with primary progressive multiple sclerosis using magnetic resonance imaging markers of neurodegeneration as outcome measures of neuroprotection. Patients with primary progressive multiple sclerosis underwent serial magnetic resonance imaging scans before (pretreatment phase) and during (treatment phase) amiloride treatment for a period of 3 years. Whole-brain volume and tissue integrity were measured with high-resolution T(1)-weighted and diffusion tensor imaging. In chronic brain lesions of patients with progressive multiple sclerosis, we demonstrate an increased expression of ASIC1 in axons and an association with injury markers within chronic inactive lesions. In patients with primary progressive multiple sclerosis, we observed a significant reduction in normalized annual rate of whole-brain volume during the treatment phase, compared with the pretreatment phase ($P = 0.018$, corrected). Consistent with this reduction, we showed that changes in diffusion indices of tissue damage within major clinically relevant white matter (corpus callosum and corticospinal tract) and deep grey matter (thalamus) structures were significantly reduced during the treatment phase ($P = 0.02$, corrected). Our results extend evidence of the contribution of ASIC1 to neurodegeneration in multiple sclerosis and suggest that amiloride may exert neuroprotective effects in patients with progressive multiple sclerosis. This pilot study is the first translational study on neuroprotection targeting ASIC1 and supports future randomized controlled trials measuring neuroprotection with amiloride in patients with multiple sclerosis.

PIMD: 23325589

Anatomical brain connectivity can assess cognitive dysfunction in multiple sclerosis.

Brain disconnection plays a major role in determining cognitive disabilities in multiple sclerosis (MS). We recently developed a novel diffusion-weighted magnetic resonance imaging (DW-MRI) tractography approach, namely anatomical connectivitity mapping (ACM), that quantifies structural brain connectivity.Use of ACM to assess structural connectivity modifications in MS brains and ascertain their relationship with the patients' Paced-Auditory-Serial-Addition-Test (PASAT) scores.Relapsing-remitting MS (RRMS) patients (n = 25) and controls (n = 25) underwent MRI at 3T, including conventional images, T1-weighted volumes and DW-MRI. Volumetric scans were coregistered to fractional anisotropy (FA) images, to obtain parenchymal FA maps for both white and grey matter. We initiated probabilistic tractography from all parenchymal voxels, obtaining ACM maps by counting the number of streamlines passing through each voxel, then normalizing by the total number of streamlines initiated. The ACM maps were transformed into standard space, for statistical use.RRMS patients had reduced grey matter volume and FA, consistent with previous literature. Also, we showed reduced ACM in the thalamus and in the head of the caudate nucleus, bilaterally. In our RRMS patients, ACM was associated with PASAT scores in the corpus callosum, right hippocampus and cerebellum.ACM opens a new perspective, clarifying the contribution of anatomical brain disconnection to clinical disabilities in MS.

PIMD: 23286059

Extracting quantitative measures from EAP: a small clinical study using BFOR.

The ensemble average propagator (EAP) describes the 3D average diffusion process of water molecules, capturing both its radial and angular contents, and hence providing rich information about complex tissue microstructure properties. Bessel Fourier orientation reconstruction (BFOR) is one of several analytical, non-Cartesian EAP reconstruction schemes employing multiple shell acquisitions that have recently been proposed. Such modeling bases have not yet been fully exploited in the extraction of rotationally invariant q-space indices that describe the degree of diffusion anisotropy/restrictivity. Such quantitative measures include the zero-displacement probability (P(o)), mean squared displacement (MSD), q-space inverse variance (QIV), and generalized fractional anisotropy (GFA), and all are simply scalar features of the EAP. In this study, a general relationship between MSD and q-space diffusion signal is derived and an EAP-based definition of GFA is introduced. A significant part of the paper is dedicated to utilizing BFOR in a clinical dataset, comprised of 5 multiple sclerosis (MS) patients and 4 healthy controls, to estimate P(o), MSD, QIV, and GFA of corpus callosum, and specifically, to see if such indices can detect changes between normal appearing white matter (NAWM) and healthy white matter (WM). Although the sample size is small, this study is a proof of concept that can be extended to larger sample sizes in the future.

PIMD: 23281138

G protein-coupled receptor 30 contributes to improved remyelination after cuprizone-induced demyelination.

Estrogen exerts neuroprotective and promyelinating actions. The therapeutic effect has been shown in animal models of multiple sclerosis, in which the myelin sheath is specifically destroyed in the central nervous system. However, it remains unproven whether estrogen is directly involved in remyelination via the myelin producing cells, oligodendrocytes, or which estrogen receptors are involved. In this study, we found that the membrane-associated estrogen receptor, the G protein-coupled receptor 30 (GPR30), also known as GPER, was expressed in oligodendrocytes in rat spinal cord and corpus callosum. Moreover, GPR30 was expressed throughout oligodendrocyte differentiation and promyelinating stages in primary oligodendrocyte cultures derived from rat spinal cords and brains. To evaluate the role of signaling via GPR30 in promyelination, a specific agonist for GPR30, G1, was administered to a rat model of demyelination induced by cuprizone treatment. Histological examination of the corpus callosum with oligodendrocyte differentiation stage-specific markers showed that G1 enhanced oligodendrocyte maturation in corpus callosum of cuprizone-treated animals. It also enhanced oligodendrocyte ensheathment of dorsal root ganglion (DRG) neurons in co-culture and myelination in cuprizone-treated animals. This study is the first evidence that GPR30 signaling promotes remyelination by oligodendrocytes after demyelination. GPR30 ligands may provide a novel therapy for the treatment of multiple sclerosis.

PIMD: 23223533

Location of brain lesions predicts conversion of clinically isolated syndromes to multiple sclerosis.

To assess in a large population of patients with clinically isolated syndrome (CIS) the relevance of brain lesion location and frequency in predicting 1-year conversion to multiple sclerosis (MS).In this multicenter, retrospective study, clinical and MRI data at onset and clinical follow-up at 1 year were collected for 1,165 patients with CIS. On T2-weighted MRI, we generated lesion probability maps of white matter (WM) lesion location and frequency. Voxelwise analyses were performed with a nonparametric permutation-based approach ($p < 0.05$, cluster-corrected).In CIS patients with hemispheric, multifocal, and brainstem/cerebellar onset, lesion probability map clusters were seen in clinically eloquent brain regions. Significant lesion clusters were not found in CIS patients with optic nerve and spinal cord onset. At 1 year, clinically definite MS developed in 26% of patients. The converting group, despite a greater baseline lesion load compared with the nonconverting group (7 ± 8.1 cm3 vs. 4.6 ± 6.7 cm3, $p < 0.001$), showed less widespread lesion distribution (18% vs. 25% of brain voxels occupied by lesions). High lesion frequency was found in the converting group in projection, association, and commissural WM tracts, with larger clusters being in the corpus callosum, corona radiata, and cingulum.Higher frequency of lesion occurrence in clinically eloquent WM tracts can characterize CIS subjects with different types of onset. The involvement of specific WM tracts, in particular those traversed by fibers involved in motor function and near the corpus callosum, seems to be associated with a higher risk of clinical conversion to MS in the short term.

PIMD: 23166826

Volumetric MRI markers and predictors of disease activity in early multiple sclerosis: a longitudinal cohort study.

To compare clinical and MRI parameters between patients with clinically isolated syndrome and those converting to clinically definite multiple sclerosis within 2 years, to identify volumetric MRI predictors of this conversion and to assess effect of early relapses.The SET study comprised 220 patients with clinically isolated syndrome treated with interferon beta (mean age, 29 years; Expanded Disability Status Scale, 1.5). Three patients with missing data were excluded from the analysis. Physical disability, time to clinically definite multiple sclerosis and volumetric MRI data were recorded for 2 years.Patients reaching clinically definite multiple sclerosis showed impaired recovery of neurological function, faster decrease in corpus callosum cross-sectional area, higher T2 lesion volume and more contrast-enhancing lesions. Six-month decrease in corpus callosum cross-sectional area (≥ 1%) and baseline T2 lesion volume (≥ 5 cm(3)) predicted clinically definite multiple sclerosis within 2 years (hazard ratios 2.5 and 1.8, respectively). Of 22 patients fulfilling both predictive criteria, 83% reached clinically definite multiple sclerosis (hazard ratio 6.5). More relapses were associated with poorer recovery of neurological function and accelerated brain atrophy.Neurological impairment is more permanent, brain atrophy is accelerated and focal inflammatory activity is greater in patients converting to clinically definite multiple sclerosis. Six-month corpus callosum atrophy and baseline T2 lesion volume jointly help predict individual risk of clinically definite multiple sclerosis. Early relapses contribute to permanent damage of the central nervous system.

PIMD: 23144775

Relevance of brain lesion location to cognition in relapsing multiple sclerosis.

To assess the relationship between cognition and brain white matter (WM) lesion distribution and frequency in patients with relapsing-remitting multiple sclerosis (RR MS).MRI-based T2 lesion probability map (LPM) was used to assess the relevance of brain lesion location for cognitive impairment in a group of 142 consecutive patients with RRMS. Significance of voxelwise analyses was $p<0.05$, cluster-corrected for multiple comparisons. The Rao Brief Repeatable Battery was administered at the time of brain MRI to categorize the MS population into cognitively preserved (CP) and cognitively impaired (CI).Out of 142 RRMS, 106 were classified as CP and 36 as CI. Although the CI group had greater WM lesion volume than the CP group ($p=0.001$), T2 lesions tended to be less widespread across the WM. The peak of lesion frequency was almost twice higher in CI (61% in the forceps major) than in CP patients (37% in the posterior corona radiata). The voxelwise analysis confirmed that lesion frequency was higher in CI than in CP patients with significant bilateral clusters in the forceps major and in the splenium of the corpus callosum ($p<0.05$, corrected). Low scores of the Symbol Digit Modalities Test correlated with higher lesion frequency in these WM regions.Overall these results suggest that in MS patients, areas relevant for cognition lie mostly in the commissural fiber tracts. This supports the notion of a functional (multiple) disconnection between grey matter structures, secondary to damage located in specific WM areas, as one of the most important mechanisms leading to cognitive impairment in MS.

PIMD: 23074847

Selective ultrastructural vulnerability in the cuprizone-induced experimental demyelination.

It has been reported that multiple sclerosis has four different neuropathological subtypes, and two of them (type III and IV) are characterized by primary oligodendrocyte loss. However, the exact pathomechanism that lead to oligodendrocyte apoptosis in human demyelinating diseases is still elusive. The copper chelator cuprizone induces primary oligodendrocyte apoptosis and consequent demyelination in well defined areas of the mouse brain. Nevertheless, the precise subcellular events that result in oligodendrocyte cell death in the cuprizone model are still unknown. We aimed to study the ultrastructural alterations that might induce oligodendrocyte apoptosis in the cuprizone experimental demyelination model.C57BL/6 mice were given cuprizone for two, 21 and 35 days to induce demyelination to investigate early pathological events, and different stages of demyelination. In addition, mice were given cuprizone for 35 days and were allowed to recover for two or 14 days to study early and late remyelination. After the cuprizone treatment, mice were sacrificed and the corpus callosum, the superior cerebellar peduncle, the optic nerve and the sciatic nerve were studied by electron microscopy.The ultrastructural analysis revealed that cuprizone induced oligodendrocyte apoptosis is accompanied by the formation of giant mitochondria in the affected cells in the corpus callosum and in the superior cerebellar peduncle. Apoptosis of the myelin producing cells was present through the whole cuprizone challenge. Severe demyelination occurred after three weeks of cuprizone administration associated with massive macrophage infiltration and astrocytosis of the demyelinated areas. Axons and neurons remained unaffected.The formation of giant mitochondria in myelin producing oligodendrocytes is the first pathological sign in the cuprizone experimental demyelination. Mitochondrium pathology in the cuprizone challenge might serve as a useful model to study the pathomechanism of multiple sclerosis subtypes (III and IV) characterized by primary oligodendrocyte degeneration.

PIMD: 23054589

Regional heterogeneity of cuprizone-induced demyelination: topographical aspects of the midline of the corpus callosum.

The cuprizone model is a suitable animal model of de- and remyelination secondary to toxin-induced oligodendrogliopathy. From a pharmaceutical point of view, the cuprizone model is a valuable tool to study the potency of compounds which interfere with toxin-induced oligodendrocyte cell death or boost/inhibit remyelinating pathways and processes. The aim of this study was to analyze the vulnerability of neighboring white mater tracts (i.e., the fornix and cingulum) next to the midline of the corpus callosum which is the region of interest of most studies using this model. Male mice were fed cuprizone for various time periods. Different white matter areas were analyzed for myelin (anti-PLP), microglia (anti-IBA1), and astrocyte (anti-GFAP) responses by means of immunohistochemistry. Furthermore, Luxol fast blue-periodic acid Schiff stains were performed to validate loss of myelin-reactive fibers in the different regions. Cuprizone induced profound demyelination of the midline of the corpus callosum and medial parts of the cingulum that was paralleled by a significant astrocyte and microglia response. In contrast, lateral parts of the corpus callosum and the cingulum, as well as the fornix region which is just beneath the midline of the corpus callosum appeared to be resistant to cuprizone exposure. Furthermore, resistant areas displayed reduced astrogliosis and microgliosis. This study clearly demonstrates that neighboring white matter tracts display distinct vulnerability to toxin-induced demyelination. This important finding has direct relevance for evaluation strategies in this frequently used animal model for multiple sclerosis.

PIMD: 23027402

Determinants of central nervous system adult neurogenesis are sex, hormones, mouse strain, age, and brain region.

Multiple sclerosis is a sexually dimorphic (SD) disease that causes oligodendrocyte death, but SD of glial cells is poorly studied. Here, we analyze SD of neural progenitors in 6-8 weeks and 6-8 months normal C57BL/6, SJL/J, and BALB/c mice in the subventricular zone (SVZ), dorsolateral horn (DLC), corpus callosum (CC), and parenchyma. With a short 2-h bromodeoxyuridine (BrdU) pulse, no gender and strain differences are present at 6-8 weeks. At 6-8 months, the number of BrdU(+) cells decreases twofold in each sex, strain, and region, indicating that a common aging mechanism regulates BrdU incorporation. Strikingly, 2× more BrdU(+) cells are found in all brain regions in 6-8 months C57BL/6 females versus males, no gender differences in 6-8 months SJL/J, and fewer BrdU(+) cells in females versus males in BALB/cs. The number of BrdU(+) cells modestly fluctuates throughout the estrous cycle in C57BL/6 and SJLs. Castration causes a dramatic increase in BrdU(+) cells in SVZ and DLC. These findings indicate that testosterone is a major regulator of adult neural proliferation. At 6-8 months, the ratio of PDGFRα(+) cells in the CC to BrdU(+) cells in the DLC of both strains, sexes, estrous cycle, and castrated mice was essentially the same, suggesting that BrdU(+) cells in the DLC differentiate into CC oligodendrocytes. The ratio of TUNEL(+) to BrdU(+) cells does not match proliferation, indicating that these events are differentially regulated. Differential regulation of these two processes leads to the variation in glial numbers between gender and strain. Explanations of neural proliferation based upon data from one sex or strain may be very misleading.

PIMD: 23025787

Astrogliosis during acute and chronic cuprizone demyelination and implications for remyelination.

In multiple sclerosis, microglia/macrophage activation and astrocyte reactivity are important components of the lesion environment that can impact remyelination. The current study characterizes these glial populations relative to expression of candidate regulatory molecules in cuprizone demyelinated corpus callosum. Importantly, periods of recovery after acute or chronic cuprizone demyelination are examined to compare conditions of efficient versus limited remyelination, respectively. Microglial activation attenuates after early demyelination. In contrast, astrocyte reactivity persists throughout demyelination and a 6-week recovery period following either acute or chronic demyelination. This astrocyte reaction is characterized by (a) early proliferation, (b) increased expression of GFAP (glial fibrillary acidic protein), Vim (vimentin), Fn1 (fibronectin) and CSPGs (chondroitin sulphate proteoglycans) and (c) elaboration of a dense network of processes. Glial processes elongated in the axonal plane persist throughout lesion areas during both the robust remyelination that follows acute demyelination and the partial remyelination that follows chronic demyelination. However, prolonged astrocyte reactivity with chronic cuprizone treatment does not progress to barrier formation, i.e. dense compaction of astrocyte processes to wall off the lesion area. Multiple candidate growth factors and inflammatory signals in the lesion environment show strong correlations with GFAP across the acute cuprizone demyelination and recovery time course, yet there is more divergence across the progression of chronic cuprizone demyelination and recovery. However, differential glial scar formation does not appear to be responsible for differential remyelination during recovery in the cuprizone model. The astrocyte phenotype and lesion characteristics in this demyelination model inform studies to identify triggers of non-remyelinating sclerosis in chronic multiple sclerosis lesions.

PIMD: 22988936

Callosal atrophy in multiple sclerosis is related to cognitive speed.

Long-term changes regarding corpus callosum area (CCA) and information processing speed in cognitive and sensory-motor tasks have rarely been studied in multiple sclerosis (MS).Information processing speed in cognitive (Symbol Digit Modalities Test, SDMT), sensory (visual and auditory reaction time) and motor (finger-tapping speed, FT; right and left hand) tasks as well as auditory inter-hemispheric transfer (verbal dichotic listening, VDL) was related to CCA, measured by MRI at baseline and at follow-up after nine years in 22 patients with MS. Possible confounding by demographic (age, gender and education), clinical (symptom onset, duration, severity of disease) and relative brain volume (RBV) as well as T2 lesion load was taken into account.The smaller the CCA at baseline, the slower was SDMT performance at baseline. In a similar way, CCA at follow-up was associated with poor SDMT result at follow-up. Furthermore, the higher the annual rate of change in CCA, the poorer was performance in VDL on the left ear and the more pronounced was the right ear advantage. A positive relationship between performance in VDL right ear and annual rate of change in RBV was also seen. Sensory-motor tests were not significantly associated with CCA. T2 lesion load at baseline was associated with FT performance at baseline. Demographic, clinical and radiological (RBV and T2 lesion load) characteristics did not confound the significant relation between CCA and SDMT.CCA unlike RBV and T2 lesion load was associated with SDMT, which indicated a marked cognitive rather than perceptual-motor component.

PIMD: 22987661

Diffusion tensor imaging based network analysis detects alterations of neuroconnectivity in patients with clinically early relapsing-remitting multiple sclerosis.

Although it is inarguable that conventional MRI (cMRI) has greatly contributed to the diagnosis and assessment of multiple sclerosis (MS), cMRI does not show close correlation with clinical findings or pathologic features, and is unable to predict prognosis or stratify disease severity. To this end, diffusion tensor imaging (DTI) with tractography and neuroconnectivity analysis may assist disease assessment in MS. We, therefore, attempted this pilot study for initial assessment of early relapsing-remitting MS (RRMS). Neuroconnectivity analysis was used for evaluation of 24 early RRMS patients within 2 years of presentation, and compared to the network measures of a group of 30 age-and-gender-matched normal control subjects. To account for the situation that the connections between two adjacent regions may be disrupted by an MS lesion, a new metric, network communicability, was adopted to measure both direct and indirect connections. For each anatomical area, the brain network communicability and average path length were computed and compared to characterize the network changes in efficiencies. Statistically significant ($P < 0.05$) loss of communicability was revealed in our RRMS cohort, particularly in the frontal and hippocampal/parahippocampal regions as well as the motor strip and occipital lobes. Correlation with the 25-foot Walk test with communicability measures in the left superior frontal ($r = -0.71$) as well as the left superior temporal gyrus ($r = -0.43$) and left postcentral gyrus ($r = -0.41$) were identified. Additionally identified were increased communicability between the deep gray matter structures (left thalamus and putamen) with the major interhemispheric and intrahemispheric white matter tracts, the corpus callosum, and cingulum, respectively. These foci of increased communicability are thought to represent compensatory changes. The proposed DTI-based neuroconnectivity analysis demonstrated quantifiable, structurally relevant alterations of fiber tract connections in early RRMS and paves the way for longitudinal studies in larger patient groups.

PIMD: 22978568

White matter volume is decreased in the brain of patients with neuromyelitis optica.

Neuromyelitis optica (NMO) is an inflammatory disease involving predominantly the spinal cord and optic nerves. Whether patients with NMO have a loss in white or grey matter (GM) volumes remains to be determined.Thirty patients with NMO, 30 healthy subjects matched for age and gender, 21 patients with multiple sclerosis (MS) and 20 patients with a clinically isolated syndrome (CIS) were studied. We applied a SIENAX post-treatment software. We compared white matter (WM) and GM volumes between groups and explored correlations of changes in NMO patients with age, gender, duration, disease severity, visual acuity and T2 hyperintensities. We also performed a voxel-based morphometry (VBM) analysis to identify the regions affected by loss of volume.White matter volume was significantly reduced in patients with NMO (764.4 ± 58.3 cm(3)) compared to healthy subjects (843.1 ± 49.3 cm(3)) ($P < 0.001$), whereas no difference was observed for the GM. Patients with CIS also presented an elective atrophy of WM and MS an atrophy of both WM and GM. We did not find any predictive factors of brain atrophy. The decrease in WM volume in NMO was noted even in the absence of visible MRI hypersignals. The VBM analysis found a few regions of WM atrophy (corpus callosum and optic radiations, $P < 0.005$, uncorrected) and a few regions of GM atrophy (thalamus and prefrontal cortex, $P < 0.001$, uncorrected).These results suggest a significant brain involvement in NMO, especially an involvement of WM which appears not to be limited to secondary degeneration after spinal cord and optic nerve damage.

PIMD: 22933014

Astrocyte TNFR2 is required for CXCL12-mediated regulation of oligodendrocyte progenitor proliferation and differentiation within the adult CNS.

Multiple sclerosis (MS) is characterized by episodes of inflammatory demyelination with progressive failure of remyelination. Prior studies using murine models of MS indicate that remyelination within the adult central nervous system (CNS) requires the expression and activity of TNFR2 and CXCR4 by oligodendrocyte progenitor cells (OPCs), promoting their proliferation and differentiation into mature oligodendrocytes. Here, we extend these studies by examining the role of TNFR2 in the expression of the CXCR4 ligand, CXCL12, within the corpus callosum (CC) during cuprizone (CPZ) intoxication and by demonstrating that lentiviral-mediated gene delivery of CXCL12 to the demyelinated CC improves OPC proliferation and myelin expression during remyelination. Activated astrocytes and microglia express both TNFR1 and TNFR2 within the demyelinated CC. However, CPZ intoxicated TNFR2-/- mice exhibit loss of up-regulation of CXCL12 in astrocytes with concomitant decreases in numbers of CXCR4+ NG2+ OPCs within the CC. While CXCR4 antagonism does not affect OPC migration from subventricular zones into the CC, it decreases their proliferation and differentiation within the CC. Stereotactic delivery of lentivirus expressing CXCL12 protein into the CC of acutely demyelinated TNFR2-/- mice increases OPC proliferation and expression of myelin. In contrast, chronically demyelinated wild-type mice, which exhibit significant loss of astrocytes and OPCs, are unable to be rescued via CXCL12 lentivirus alone but instead required engraftment of CXCL12-expressing astrocytes for increased myelin expression. Our results show that TNFR2 activation induces CXCL12 expression in the demyelinated CC via autocrine signaling specifically within astrocytes, which promotes OPC proliferation and differentiation. In addition, gene delivery of critical pro-myelinating proteins might be a feasible approach for the treatment of remyelination failure in MS.

PIMD: 22931739

Monosymptomatic clinically isolated syndrome with sudden sensorineural hearing loss: case report and critical review of the literature.

Isolated cranial nerve involvement is rare in patients with multiple sclerosis (10.4%) and extremely rare is an eighth nerve palsy, especially in the context of a clinically isolated syndrome (<1%).A 34-year-old male presented with a history of left-sided tinnitus and sudden sensorineural hearing loss (SSNHL). Magnetic resonance imaging of the brain revealed >9, nonenhancing periventricular and corpus callosum lesions. Brainstem auditory evoked potentials were abnormal, ipsilateral to the affected ear, consistent with the presumed underlying demyelinating pathology. Visual evoked potentials showed bilateral prolonged P100 latencies. Oligoclonal bands were not detected in the cerebrospinal fluid, but IgG index was marginally elevated. After administration of corticosteroids, the patient recovered auditory function over a several month period.This report describes a case of SSNHL in the context of magnetic resonance imaging of the brain and electrophysiological findings consistent with a demyelinating etiology. SSNHL is a rare and possibly underrecognized manifestation of clinically isolated syndrome.

PIMD: 22907640

Clinical and radiological characteristics in multiple sclerosis patients with large cavitary lesions.

Large cavitary lesions are not typical for multiple sclerosis (MS). Cavitary white matter changes may be seen in megalencephalic leukoencephalopathy with subcortical cysts, Alexander disease, mitochondrial leukoencephalopathies, vanishing white matter disease, leukoencephalopathy with calcifications and cysts, cytomegalovirus infection, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.To analyze clinical and radiological characteristics in MS patients with large cavitary lesions.We studied MS patients with large cavitary brain lesions. Patient characteristics, disease onset/duration/subtype, expanded disability status scale (EDSS), mini mental state (MMS), corpus callosum lesions, history of segmental myelitis, CSF oligoclonal bands (OCB), visual evoked potentials (VEP), vanishing white matter disease genetic analysis, and characteristics of the cavitary lesions were analyzed.Nine patients were analyzed, 1 man and 8 women. Mean age of disease onset was 38.5 years. Mean disease duration was 9 years. Three patients had initial relapsing-remitting MS and 6 patients had primary-progressive MS. Mean EDSS was 4.5. Mean MMS was 20/30. Segmental myelitis was present in 6 cases. OCB were found in 6 patients. VEP was performed in 6 patients, and pathological in all but one. Vanishing white matter disease genetic analysis was performed and negative in 5 patients. Inferior corpus callosum lesions were seen in all patients with available sagittal FLAIR sequences. Cavitary lesions were strictly supratentorial, and located inside the diffuse leukoencephalopathy, with often a posterior predominance.MS patients with large cavitary lesions seem to represent an MS subgroup, predominantly women, with relatively late disease onset, predominantly primary-progressive type, relatively high EDSS scores, and severe cognitive dysfunction.

PIMD: 22896934

Sudden sensorineural hearing loss: when ophthalmology meets otolaryngology.

Sudden sensorineural hearing loss is a perplexing entity in otology. Susac's syndrome (also called retinocochleocerebral vasculopathy) is a rare disorder that consists of microangiopathy of the brain, retina, and inner ear, and usually affects women in young adulthood. We describe the clinical aspects, radiographic findings, and management of one such case.A 30-year-old woman was admitted to the hospital because of sudden onset of bilateral deafness and headache. During her hospitalization, she developed discrete right hemiparesis and hypoesthesia.Magnetic resonance imaging revealed multiple signal hyperintensities and atrophy of the corpus callosum. The differential diagnosis was a myelinating condition, such as multiple sclerosis or acute demyelinating encephalomyelitis.Retinal fluorescein angiography helped the diagnosis of Susac's syndrome.

PIMD: 22886062

Tract-specific quantitative MRI better correlates with disability than conventional MRI in multiple sclerosis.

Although diffusion tensor imaging (DTI) and the magnetization transfer ratio (MTR) have been extensively studied in multiple sclerosis (MS), it is still unclear if they are more effective biomarkers of disability than conventional MRI. MRI scans were performed on 117 participants with MS in addition to 26 healthy volunteers. Mean values were obtained for DTI indices and MTR for supratentorial brain and three white matter tracts of interest. DTI and MTR values were tested for correlations with measures of atrophy and lesion volume and were compared with these more conventional indices for prediction of disability. All DTI and MTR values correlated to an equivalent degree with lesion volume and cerebral volume fraction (CVF). Thalamic volumes correlated with all indices in the optic radiations and with mean and perpendicular diffusivity in the corpus callosum. Nested model regression analysis demonstrated that, compared with CVF, DTI indices in the optic radiations were more strongly correlated with Expanded Disability Status Scale and were also more strongly correlated than both CVF and lesion volume with low-contrast visual acuity. Abnormalities in DTI and MTR are equivalently linked with brain atrophy and inflammatory lesion burden, suggesting that for practical purposes they are markers of multiple aspects of MS pathology. Our findings that some DTI and MTR indices are more strongly linked with disability than conventional MRI measures justifies their potential use as targeted, functional system-specific clinical trial outcomes in MS.

PIMD: 22848007

Sex-related differences of cAMP-specific PDE4B3 mRNA in oligodendrocytes following systemic inflammation.

Sex-related differences have been observed in the incidence and severity of several neurological diseases and in sepsis in humans. Cyclic adenosine monophosphate (cAMP) has been shown to play an important role in modulating the inflammatory environment during neuroinflammation and importantly in protecting myelin from excitotoxic cell death. Considering the sexual dimorphism in the functional properties of oligodendrocytes and the importance of a systemic inflammation in the progression of multiple sclerosis, we focused on identifying possible sex-related differences in the alterations previously reported for the two phosphodiesterase4B (PDE4B) splice-variants (PDE4B2 and PDE4B3) mRNA expression during innate neuroinflammation. PDE4A, PDE4B, and PDE4D are present in oligodendrocytes and we have previously reported that PDE4B3 mRNA is readily expressed in both oligodendrocytes and neurons. In this study, we analyzed the influence of an intraperitoneal lipopolysaccharide injection on the distribution pattern and expression levels of the PDE4B mRNA splicing variants in both male and female mice brains. Clear differences were observed in PDE4B2 and PDE4B3 mRNA expression levels in males compared with females in a time-dependent manner. Furthermore, we observed that the clear downregulation of PDE4B3 mRNA was reflected in a lower percentage of oligodendrocytes positive for this transcript which correlated with a decrease in inducible cAMP early repressor expression in female corpus callosum.

PIMD: 22820857

Metallic gold slows disease progression, reduces cell death and induces astrogliosis while simultaneously increasing stem cell responses in an EAE rat model of multiple sclerosis.

Multiple sclerosis (MS) is the most common neurodegenerative disease in the Western world affecting younger, otherwise healthy individuals. Today no curative treatment exists. Patients suffer from recurring attacks caused by demyelination and underlying neuroinflammation, ultimately leading to loss of neurons. Recent research shows that bio-liberation of gold ions from metallic gold implants can ameliorate inflammation, reduce apoptosis and promote proliferation of neuronal stem cells (NSCs) in a mouse model of focal brain injury. Based on these findings, the present study investigates whether metallic gold implants affect the clinical signs of disease progression and the pathological findings in experimental autoimmune encephalomyelitis (EAE), a rodent model of MS. Gold particles 20-45 μm suspended in hyaluronic acid were bilaterally injected into the lateral ventricles (LV) of young Lewis rats prior to EAE induction. Comparing gold-treated animals to untreated and vehicle-treated ones, a statistically significant slowing of disease progression in terms of reduced weight loss was seen. Despite massive inflammatory infiltration, terminal deoxynucleotidyl transferase dUTP nick end labeling staining revealed reduced apoptotic cell death in disease foci in the brain stem of gold-treated animals, alongside an up-regulation of glial fibrillary acidic protein-positive reactive astrocytes near the LV and in the brain stem. Cell counting of frizzled-9 and nestin-stained cells showed statistically significant up-regulation of NSCs migrating from the subventricular zone. Additionally, the neuroprotective proteins Metallothionein-1 and -2 were up-regulated in the corpus callosum. In conclusion, this study is the first to show that the presence of small gold implants affect disease progression in a rat model of MS, increasing the neurogenic response and reducing the loss of cells in disease foci. Gold implants might thus improve clinical outcome for MS patients and further research into the long-term effects of such localized gold treatment is warranted.

PIMD: 22809881

Diffuse and heterogeneous T2-hyperintense lesions in the splenium are characteristic of neuromyelitis optica.

Callosal lesions in multiple sclerosis (MS) are usually focal, involving the inferior aspect of the corpus callosum on brain magnetic resonance imaging (MRI), but little is known about callosal lesions in neuromyelitis optica (NMO).To clarify MRI abnormalities in callosal lesions of NMO.Japanese patients with NMO (n=28) or MS (n=22) were assessed. The distributions and appearances of callosal lesions were evaluated on a brain mid-sagittal T2-weighted image (T2WI) or a fluid-attenuated inversion recovery image with a 1.5T MRI scanner. Logistic regression analysis identified which characteristics of the callosal lesions were useful for discriminating NMO from MS.Callosal lesions were present in 79% of NMO and 82% of MS patients. Callosal abnormalities of NMO, including splenial lesions (57% in NMO versus 27% in MS, odds ratio (OR)=4.23, p=0.04), diffusely spreading lesions from the lower to upper edges of the corpus callosum (71% versus 23%, OR=7.18, p=0.0024), and heterogeneous T2 hyperintense lesions (71% versus 9%, OR=44.3, p=0.0006), were feasible for discriminating NMO from MS.Diffuse and heterogeneous T2 hyperintense splenial lesions were characteristic of NMO. These findings could help distinguish NMO from MS on MRI.

PIMD: 22805669

Differences in diffusion tensor imaging-derived metrics in the corpus callosum of patients with multiple sclerosis without and with gadolinium-enhancing cerebral lesions.

To analyze differences in corpus callosum diffusion tensor imaging metrics among patients with relapsing-remitting multiple sclerosis (MS) (RRMS) and secondary progressive MS (SPMS) with enhancing and nonenhancing cerebral lesions.One-way analysis of variance and multiple linear regression models were used to assess the relationship between MS subtype, the presence of enhancing lesions, and fractional anisotropy (FA)/mean diffusivity (MD) values of the genu, body, and splenium of the corpus callosum from 22 patients with RRMS and 25 patients with SPMS.Analyses of variance: The subjects with SPMS with enhancing lesions had significantly lower genu and body FA values than those with nonenhancing SPMS and significantly lower genu, body, and splenium FA values than those with RRMS. Regression models: Enhancement was associated with decreased genu FA ($P = 0.014$). Secondary progressive MS was associated with decreased genu ($P = 0.002$) and splenium FA ($P < 0.001$) and significantly increased MD values.Patients with SPMS with enhancing lesions may be at increased risk for neuronal damage compared to nonenhancing SPMS and RRMS subtypes.

PIMD: 22779688

The cuprizone model: regional heterogeneity of pathology.

The cuprizone model is a model of de- and remyelination secondary to oligodendrocyte death, likely to be mediated by an inhibition of mitochondrial function. The aim of this study was to characterize histopathological changes associated with de/remyelination in grey and white matter at different disease stages in C57Bl/6 mice after per oral administration of cuprizone. Oligodendrocyte loss, astrocytosis and complement activation was detected in areas of demyelination. Demyelination, astrocytosis and complement activation occurred earlier in the cerebral cortex than in the corpus callosum. There was no perivascular lymphocyte infiltration. Microglia- and macrophage activation was observed in the corpus callosum, but not in the cerebral cortex. After cuprizone exposure was stopped, remyelination was extensive in the corpus callosum, but scarce in the cortex. In conclusion, cortical demyelination and oligodendrocyte loss in the cuprizone model may be due to a direct effect on oligodendrocyte mitochondrial function, as it occurs in the absence of microglial activation. The histopathology of de/remyelination in the cuprizone treated mice show regional heterogeneities which suggest differences in the underlying pathophysiology. Cuprizone-induced demyelination is a relevant model for the study of regional heterogeneity of demyelination and lesion pathology in multiple sclerosis.

PIMD: 22711711

Lesion morphology at 7 Tesla MRI differentiates Susac syndrome from multiple sclerosis.

Although an orphan disease with still obscure aetiopathogenesis, Susac syndrome has to be considered as differential diagnosis in multiple sclerosis (MS), since its clinical presentation and paraclinical features including routine magnetic resonance imaging (MRI) findings partially overlap.We aimed to study a potential benefit of 7T MRI for (i) the differentiation between Susac syndrome and MS and (ii) the clarification of pathogenesis of Susac syndrome.Five patients suffering from Susac syndrome, 10 sex- and age-matched patients with relapsing-remitting MS (median Expanded Disability Status Scale (EDSS) score 1.5) and 15 matching healthy controls were investigated at 7 Tesla MRI. The protocol included T1-weighted MPRAGE, T2*-weighted FLASH, and TIRM sequences.Almost all T2* FLASH lesions in patients with MS were centred by a small central vein (325 lesions; 92%) and often showed a small hypointense rim (145 lesions; 41%). In contrast, white matter lesions in Susac syndrome exhibited a perivascular setting significantly less frequently (148 lesions; 54%, p=0.002), and very rarely exhibited a hypointense rim (12 lesions; 4%, p=0.004). Furthermore, in addition to callosal atrophy, Susac patients showed cerebrospinal fluid-isointense lesions within the central part of corpus callosum that are not commonly seen in MS.At 7T MRI, plaques in MS patients and patients with Susac syndrome differed substantially with respect to morphology and pattern. Thus, lesion morphology at 7T (i) may serve as a marker to distinguish Susac syndrome from MS and (ii) reflects a different pathophysiological mechanism underlying Susac syndrome, for example microinfarction rather than demyelination.

PIMD: 22699909

IL-17-induced Act1-mediated signaling is critical for cuprizone-induced demyelination.

Cuprizone inhibits mitochondrial function and induces demyelination in the corpus callosum, which resembles pattern III lesions in multiple sclerosis patients. However, the molecular and cellular mechanism by which cuprizone induces demyelination remains unclear. Interleukin-17 (IL-17) secreted by T helper 17 cells and γδT cells are essential in the development of experimental autoimmune encephalomyelitis. In this study, we examined the importance of IL-17 signaling in cuprizone-induced demyelination. We found that mice deficient in IL-17A, IL-17 receptor C (IL-17RC), and adaptor protein Act1 (of IL-17R) all had reduced demyelination accompanied by lessened microglial and polydendrocyte cellular reactivity compared with that in wild-type mice in response to cuprizone feeding, demonstrating the essential role of IL-17-induced Act1-mediated signaling in cuprizone-induced demyelination. Importantly, specific deletion of Act1 in astrocytes reduced the severity of tissue injury in this model, indicating the critical role of CNS resident cells in the pathogenesis of cuprizone-induced demyelination. In cuprizone-fed mice, IL-17 was produced by CNS CD3(+) T cells, suggesting a source of IL-17 in CNS upon cuprizone treatment.

PIMD: 22689449

Myelin debris regulates inflammatory responses in an experimental demyelination animal model and multiple sclerosis lesions.

In multiple sclerosis (MS), gray matter pathology is characterized by less pronounced inflammation when compared with white matter lesions. Although regional differences in the cytoarchitecture may account for these differences, the amount of myelin debris in the cortex during a demyelinating event might also be contributory. To analyze the association between myelin debris levels and inflammatory responses, cortical areas with distinct and sparse myelination were analyzed for micro- and astrogliosis before and after cuprizone-induced demyelination in mice. In postmortem tissue of MS patients, leucocortical lesions were assessed for the type and level of inflammation in the cortical and white matter regions of the lesion. Furthermore, mice were injected intracerebrally with myelin-enriched debris, and the inflammatory response analyzed in white and grey matter areas. Our studies show that the magnitude of myelin loss positively correlates with microgliosis in the cuprizone model. In MS, the number of MHC class II expressing cells is higher in the white compared with the grey matter part of leucocortical lesions. Finally, direct application of myelin debris into the corpus callosum or cortex of mice induces profound and comparable inflammation in both regions. Our data suggest that myelin debris is an important variable in the inflammatory response during demyelinating events. Whether myelin-driven inflammation affects neuronal integrity remains to be clarified.

PIMD: 22677920

Corpus callosum atrophy--a simple predictor of multiple sclerosis progression: a longitudinal 9-year study.

To determine whether corpus callosum atrophy predicts future clinical deterioration in multiple sclerosis.In 39 multiple sclerosis patients the area of corpus callosum in the sagittal plane, T2 and T1 lesion volumes, brain parenchymal fraction and brain atrophy were determined at baseline and 1 year after treatment initiation. Non-parametric and multiple regression models were built to identify the most reliable predictors of disability and of its changes over 9 years.Corpus callosum atrophy during the first year of treatment was the best predictor of disability (r = -0.56) and of its increase at 9 years (r = 0.65). Corpus callosum atrophy of at least 2% predicted increase in disability with 93% sensitivity and 73% specificity (odds ratio = 35).Corpus callosum atrophy is a simple and accurate predictor of future disability accumulation and is feasible for routine clinical practice.

PIMD: 22675841

Multiple sclerosis in Israeli children: incidence, an clinical, cerebrospinal fluid and magnetic resonance imaging findings.

Multiple sclerosis (MS) occurs in young adults and infrequently appears in childhood.To determine the incidence of MS and describe the clinical, cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings at onset of MS in children in Israel.Incidence and case-specific data were obtained through the MS Center Database and Israeli Health Statistics Census Data over 15 years, from 1995 to 2009, and compared between patients with childhood (< 12 years), juvenile (> or = 12 years, < or = 18 years) and adult (> 18 years) MS onset.Of 1129 eligible MS patients, we identified 10 (0.89%) with childhood-onset MS, 74 (6.55%) with juvenile-onset MS, and 1045 (92.56%) with adult-onset MS. There were 0 to 3 incident childhood cases/year, leading to an annual incidence of 0.1/100,000 among Israeli children; the incidence of juvenile and adult MS was 2.6 and 5.4/100,000, respectively. Neurological presentation among children with MS was optic neuritis, motor weakness or brainstem involvement. CSF oligoclonal immunoglobulin (IgG) were positive in 62.5%. The most frequent MRI finding was the occurrence of > or = 3 periventricular white matter lesions followed by corpus callosum lesions, with 71% co-occurrence. Cervical and thoracic lesions occurred in 33% and 43%, respectively. Time to second neurological event ranged from 0.3 to 4.2 years and none of the patients with childhood MS reached EDSS = 6.0 within a mean follow-up period of 8.4 years.Childhood-onset MS is rare, with an incidence of 0.1/100,000 Israeli children. Childhood MS does not differ significantly from juvenile and adult-onset MS in terms of clinical, laboratory and imaging findings.

PIMD: 22641299

Non-lesional white matter changes in pediatric multiple sclerosis and monophasic demyelinating disorders.

To analyze diffusion tensor imaging (DTI) derived metrics between patients with childhood onset multiple sclerosis (MS), monophasic demyelinating illnesses, and healthy controls.Monophasic demyelinating illnesses can be indistinguishable clinically and radiologically, utilizing standard MRI studies. DTI studies in adults implicate the involvement of normal-appearing white matter (NAWM) in MS.Subjects with DTI studies (15 directions, 1.5 Tesla (GE), 3x3x3 mm, interpolated to 1.5x1.5x3 mm) were retrospectively identified. We studied three groups: childhood onset MS (n=18), monophasic illness (eight with acute disseminated encephalomyelitis (ADEM), seven with clinically isolated syndrome (CIS)) and age-matched controls. DTI had been obtained within one month of symptom onset for patients with ADEM and within a median of 20 months for the MS group. DTI measures were determined using a semi-automated method from standardized regions of interest (ROI) containing central fibers of the corpus callosum genu and internal capsule.The MS group had significantly lower fractional anisotropy (FA) values compared to controls ($p<0.001$), with increased radial diffusivity (RD) and decreased axial diffusivity (AD). In the monophasic group FA was smaller than the controls ($p=0.01$) with increased RD and no difference in AD.This retrospective analysis provides evidence that NAWM is affected in pediatric MS and monophasic demyelinating disease, with a potentially novel pattern demonstrating reduced AD in pediatric MS. Further larger scale confirmatory studies are needed to address whether the demonstrated DTI changes could be used as a biomarker in pediatric patients presenting with an initial demyelinating event.

PIMD: 22626631

MRI mean diffusivity detects widespread brain degeneration in multiple sclerosis.

We investigated the magnetic resonance imaging (MRI) findings of 32 multiple sclerosis (MS) patients using voxel-based morphometry (VBM) and voxel-based analysis of white matter fluid-attenuated inversion recovery image (FLAIR) high-intensity lesions and diffusion tensor imaging (DTI). Compared with 18 healthy controls, MS patients showed gray matter volume reduction in the thalamus, hypothalamus, caudate, limbic lobe, and frontal lobe. A marked volume reduction of white matter was evident along the ventriculus lateralis and corpus callosum. FLAIR high-intensity lesions were observed beside the ventriculus lateralis. DTI revealed reduced fractional anisotropy areas similar to those of the FLAIR high-intensity lesions. Changes in the volume of increased mean diffusivity (MD) were the most widespread and extended to normal-appearing white matter ($p<0.001$). Multiple regression analysis revealed that MD values were significantly correlated with both disease duration ($r=0.381$, $p=0.032$) and expanded disability status scale scores (EDSS) ($r=0.393$, $p=0.026$). This study demonstrated that combined voxel-based analysis for volumetry, FLAIR high-intensity lesions, and DTI could reveal widespread brain abnormalities in MS patients. Furthermore, DTI, especially MD, showed far more widespread brain degeneration than other MRI parameters, and was significantly correlated with both severity and disease duration.

PIMD: 22606347

Influence of corpus callosum damage on cognition and physical disability in multiple sclerosis: a multimodal study.

Corpus callosum (CC) is a common target for multiple sclerosis (MS) pathology. We investigated the influence of CC damage on physical disability and cognitive dysfunction using a multimodal approach.Twenty-one relapsing-remitting MS patients and 13 healthy controls underwent structural MRI and diffusion tensor of the CC (fractional anisotropy; mean diffusivity, MD; radial diffusivity, RD; axial diffusivity). Interhemisferic transfer of motor inhibition was assessed by recording the ipsilateral silent period (iSP) to transcranial magnetic stimulation. We evaluated cognitive function using the Brief Repeatable Battery and physical disability using the Expanded Disability Status Scale (EDSS) and the MS Functional Composite (MSFC) z-score.The iSP latency correlated with physical disability scores (r ranged from 0.596 to 0.657, P values from 0.004 to 0.001), and with results of visual memory (r=-0.645, P=0.002), processing speed (r=-0.51, P=0.018) and executive cognitive domain tests (r=-0.452, P=0.039). The area of the rostrum correlated with the EDSS (r=-0.442, P=0.045). MD and RD correlated with cognitive performance, mainly with results of visual and verbal memory tests (r ranged from -0.446 to -0.546, P values from 0.048 to 0.011). The iSP latency correlated with CC area (r=-0.345, P=0.049), volume (r=-0.401, P=0.002), MD (r=0.404, P=0.002) and RD (r=0.415, P=0.016).We found evidence for structural and microstructural CC abnormalities associated with impairment of motor callosal inhibitory conduction in MS. CC damage may contribute to cognitive dysfunction and in less extent to physical disability likely through a disconnection mechanism.

PIMD: 22585536

Shape analysis of the corpus callosum and cerebellum in female MS patients with different clinical phenotypes.

The aim of this study was to investigate the shape differences in the corpus callosum (CC) and cerebellum of female relapsing-remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS) patients compared with healthy controls. This study was conducted using the magnetic resonance imaging scans of 15 control subjects, 26 RRMS, and 14 SPMS patients. The data obtained from the landmark coordinates were analyzed with statistical shape analysis. The landmarks that were chosen to determine the shape differences of the CC and cerebellum have been identified and used in previous studies. In addition to these landmarks, constructed landmarks were determined and used to assess regional shape differences better. The shapes of the CC and cerebellum showed statistically significant differences from the controls when compared with both the RRMS and SPMS patients. It was found that the deformation observed from controls to SPMS was greater than the deformation from controls to RRMS, both for the CC and cerebellum. In conclusion, this study revealed CC and cerebellar shape change in RRMS and SPMS, and showed that deformations both in CC and cerebellum advances with the disease progression.

PIMD: 22573688

Investigating axonal damage in multiple sclerosis by diffusion tensor spectroscopy.

Sensitive and specific in vivo measures of axonal damage, an important determinant of clinical status in multiple sclerosis (MS), might greatly benefit prognostication and therapy assessment. Diffusion tensor spectroscopy (DTS) combines features of diffusion tensor imaging and magnetic resonance spectroscopy, allowing measurement of the diffusion properties of intracellular, cell-type-specific metabolites. As such, it may be sensitive to disruption of tissue microstructure within neurons. In this cross-sectional pilot study, diffusion of the neuronal metabolite N-acetylaspartate (NAA) was measured in the human normal-appearing corpus callosum on a 7 tesla MRI scanner, comparing 15 MS patients and 14 healthy controls. We found that NAA parallel diffusivity is lower in MS ($p = 0.030$) and inversely correlated with both water parallel diffusivity ($p = 0.020$) and clinical severity ($p = 0.015$). Interpreted in the context of previous experiments, our findings provide preliminary evidence that DTS can distinguish axonopathy from other processes such as inflammation, edema, demyelination, and gliosis. By detecting reduced diffusion of NAA parallel to axons in white matter, DTS may thus be capable of distinguishing axonal disruption in MS in the setting of increased parallel diffusion of water, which is commonly observed in MS but pathologically nonspecific.

PIMD: 22528463

Inflammatory response and chemokine expression in the white matter corpus callosum and gray matter cortex region during cuprizone-induced demyelination.

Brain inflammation plays a central role in multiple sclerosis (MS). Besides lymphocytes, the astroglia and microglia mainly contribute to the cellular composition of the inflammatory infiltrate in MS lesions. Several studies were able to demonstrate that cortical lesions are characterized by lower levels of inflammatory cells among activated microglia/macrophages. The underlying mechanisms for this difference, however, remain to be clarified. In the current study, we compared the kinetics and extent of microglia and astrocyte activation during early and late cuprizone-induced demyelination in the white matter tract corpus callosum and the telencephalic gray matter. Cellular parameters were related to the expression profiles of the chemokines Ccl2 and Ccl3. We are clearly able to demonstrate that both regions are characterized by early oligodendrocyte stress/apoptosis with concomitant microglia activation and delayed astrocytosis. The extent of microgliosis/astrocytosis appeared to be greater in the subcortical white matter tract corpus callosum compared to the gray matter cortex region. The same holds true for the expression of the key chemokines Ccl2 and Ccl3. The current study defines a model to study early microglia activation and to investigate differences in the neuroinflammatory response of white vs. gray matter.

PIMD: 22492966

Demyelination reduces brain parenchymal stiffness quantified in vivo by magnetic resonance elastography.

The detection of pathological tissue alterations by manual palpation is a simple but essential diagnostic tool, which has been applied by physicians since the beginnings of medicine. Recently, the virtual "palpation" of the brain has become feasible using magnetic resonance elastography, which quantifies biomechanical properties of the brain parenchyma by analyzing the propagation of externally elicited shear waves. However, the precise molecular and cellular patterns underlying changes of viscoelasticity measured by magnetic resonance elastography have not been investigated up to date. We assessed changes of viscoelasticity in a murine model of multiple sclerosis, inducing reversible demyelination by feeding the copper chelator cuprizone, and correlated our results with detailed histological analyses, comprising myelination, extracellular matrix alterations, immune cell infiltration and axonal damage. We show firstly that the magnitude of the complex shear modulus decreases with progressive demyelination and global extracellular matrix degradation, secondly that the loss modulus decreases faster than the dynamic modulus during the destruction of the corpus callosum, and finally that those processes are reversible after remyelination.

PIMD: 22483341

Tumefactive multiple sclerosis requiring emergent biopsy and histological investigation to confirm the diagnosis: a case report.

Tumefactive multiple sclerosis is a demyelinating disease that demonstrates tumor-like features on magnetic resonance imaging. Although diagnostic challenges without biopsy have been tried by employing radiological studies and cerebrospinal fluid examinations, histological investigation is still necessary for certain diagnosis in some complicated cases.A 37-year-old Asian man complaining of mild left leg motor weakness visited our clinic. Magnetic resonance imaging demonstrated high-signal lesions in bilateral occipital forceps majors, the left caudate head, and the left semicentral ovale on fluid-attenuated inversion recovery and T2-weighted imaging, and these lesions were enhanced by gadolinium-dimeglumin. Tumefactive multiple sclerosis was suspected because the enhancement indistinctly extended along the corpus callosum on magnetic resonance imaging and scintigraphy showed a low malignancy of the lesions. But oligoclonal bands were not detected in cerebrospinal fluid. In a few days, his symptoms fulminantly deteriorated with mental confusion and left hemiparesis, and steroid pulse therapy was performed. In spite of the treatment, follow-up magnetic resonance imaging showed enlargement of the lesions. Therefore, emergent biopsy was performed and finally led to the diagnosis of demyelinating disease. The enhanced lesion on magnetic resonance imaging disappeared after one month of prednisolone treatment, but mild disorientation and left hemiparesis remained as sequelae.Fulminant aggravation of the disease can cause irreversible neurological deficits. Thus, an early decision to perform a biopsy is necessary for exact diagnosis and appropriate treatment if radiological studies and cerebrospinal fluid examinations cannot rule out the possibility of brain tumors.

PIMD: 22461009

Diosgenin promotes oligodendrocyte progenitor cell differentiation through estrogen receptor-mediated ERK1/2 activation to accelerate remyelination.

Differentiation of oligodendrocyte progenitor cells (OPCs) into mature oligodendrocytes is a prerequisite for remyelination after demyelination, and impairment of this process is suggested to be a major reason for remyelination failure. Diosgenin, a plant-derived steroid, has been implicated for therapeutic use in many diseases, but little is known about its effect on the central nervous system. In this study, using a purified rat OPC culture model, we show that diosgenin significantly and specifically promotes OPC differentiation without affecting the viability, proliferation, or migration of OPC. Interestingly, the effect of diosgenin can be blocked by estrogen receptor (ER) antagonist ICI 182780 but not by glucocorticoid and progesterone receptor antagonist RU38486, nor by mineralocorticoid receptor antagonist spirolactone. Moreover, it is revealed that both ER-alpha and ER-beta are expressed in OPC, and diosgenin can activate the extracellular signal-regulated kinase 1/2 (ERK1/2) in OPC via ER. The pro-differentiation effect of diosgenin can also be obstructed by the ERK inhibitor PD98059. Furthermore, in the cuprizone-induced demyelination model, it is demonstrated that diosgenin administration significantly accelerates/enhances remyelination as detected by Luxol fast blue stain, MBP immunohistochemistry and real time RT-PCR. Diosgenin also increases the number of mature oligodendrocytes in the corpus callosum while it does not affect the number of OPCs. Taking together, our results suggest that diosgenin promotes the differentiation of OPC into mature oligodendrocyte through an ER-mediated ERK1/2 activation pathway to accelerate remyelination, which implicates a novel therapeutic usage of this steroidal natural product in demyelinating diseases such as multiple sclerosis (MS).

PIMD: 22454097

Voxelwise analysis of conventional magnetic resonance imaging to predict future disability in early relapsing-remitting multiple sclerosis.

The ability of conventional magnetic resonance imaging (MRI) to predict subsequent physical disability and cognitive deterioration after a clinically isolated syndrome (CIS) is weak.We aimed to investigate whether conventional MRI changes over 1 year could predict cognitive and physical disability 5 years later in CIS. We performed analyses using a global approach (T(2) lesion load, number of T(2) lesions), but also a topographic approach.This study included 38 patients with a CIS. At inclusion, 10 out of 38 patients fulfilled the 2010 revised McDonald's criteria for the diagnosis of multiple sclerosis. Expanded Disability Status Scale (EDSS) evaluation was performed at baseline, year 1 and year 5, and cognitive evaluation at baseline and year 5. T(2)-weighted MRI was performed at baseline and year 1. We used voxelwise analysis to analyse the predictive value of lesions location for subsequent disability.Using the global approach, no correlation was found between MRI and clinical data. The occurrence or growth of new lesions in the brainstem was correlated with EDSS changes over the 5 years of follow-up. The occurrence or growth of new lesions in cerebellum, thalami, corpus callosum and frontal lobes over 1 year was correlated with cognitive impairment at 5 years.The assessment of lesion location at the first stage of multiple sclerosis may be of value to predict future clinical disability.

PIMD: 22445592

MR imaging findings of the corpus callosum region in the differentiation between multiple sclerosis and neuromyelitis optica.

To evaluate MR imaging findings in corpus callosum region for the discrimination between opticospinal multiple sclerosis (OSMS) and neuromyelitis optica (NMO).Forty-two definite OSMS with seronegative NMO-IgG and 23 NMO with seropositive NMO-IgG, and 27 age-matched normal controls (NC) were recruited. Sagittal T2-FLAIR images with 2-mm slice thickness were obtained. Subcallosal dot-dash (SCDD) sign and subcallosal striations (SCS) sign were reviewed.SCDD was more commonly detected in OSMS (28 of 42 patients) than in NMO (5 of 23 patients) ($P<0.05$). SCS showed no difference between OSMS (31 of 42 patients) and NMO (12 of 23 patients) ($P>0.05$). For comparing ROC analysis among SCDD, SCS, and SCDD+SCS for predicted probability through binary logistic regression analysis, SCDD+SCS had the largest area under ROC curve (0.777) than SCDD (0.725) and SCS (0.608).SCDD may be helpful in distinguishing OSMS from NMO. The regression equation may also be a simple and effective method of choice for the differentiation between OSMS and NMO.

PIMD: 22421533

Cuprizone-induced demyelination in the rat cerebral cortex and thyroid hormone effects on cortical remyelination.

Multiple Sclerosis (MS) is an inflammatory demyelinating disease of the Central Nervous System which is characterized by multifocal demyelinated lesions dispersed throughout the brain. Although white matter lesions have been the most extensively studied, cortical demyelinaton lesions are also detected in MS brains. Cuprizone (CPZ)-induced demyelination in rodents has been widely used as a model for MS. Most of these studies focus on oligodendrocyte-rich structures, such as the corpus callosum (CC) and the cerebellar peduncles. However, it has been recently described that CPZ administration in mice also produces cortical demyelination, resembling some of the lesions found in MS patients. In this work we used CPZ-demyelinating model in Wistar rats to study demyelination in cortical forebrain areas. At the ultrastructural level, demyelination in the cortex was observed before detectable myelin loss in the subcortical white matter. During the course of CPZ intoxication Myelin Basic Protein immunodetection was decreased in cortical layers I-III due to a reduction in the number of cortical oligodendrocytes (OL). Oligodendroglial loss in CPZ-intoxicated rats correlated with an increase in the number of Glial Fibrillary Acidic Protein positive astrocytes and a shift in the location of Carbonic Anhydrase II from OL to astrocytes. After removal of CPZ from the diet, we evaluate intranasal Thyroid hormone (TH) effects on the progression of cortical lesions. As previously reported in the CC, TH treatment also accelerates remyelination rate in the cortex compared to rats undergoing spontaneous remyelination. Our results suggest that manipulation of TH levels could be considered as a strategy to promote remyelination process in the cortex and to prevent neuronal irreversible damage in patients suffering from MS.

PIMD: 22396019

Erythropoietin attenuates neurological and histological consequences of toxic demyelination in mice.

Erythropoietin (EPO) reduces symptoms of experimental autoimmune encephalomyelitis in rodents and shows neuroregenerative effects in chronic progressive multiple sclerosis. The mechanisms of action of EPO in these conditions with shared immunological etiology are still unclear. Therefore, we used a model of toxic demyelination allowing exclusion of T cell-mediated inflammation. In a double-blind (for food/injections), placebo-controlled, longitudinal four-arm design, 8-wk-old C57BL/6 mice (n = 26/group) were assigned to cuprizone-containing (0.2%) or regular food (ground chow) for 6 wks. After 3 wks, mice were injected every other day with placebo or EPO (5,000 IU/kg intraperitoneally) until the end of cuprizone feeding. Half of the mice were exposed to behavioral testing, magnetic resonance imaging (MRI) and histology immediately after treatment cessation, whereas the other half were allowed a 3-wk treatment-free recovery. Immediately after termination of cuprizone feeding, all toxin-exposed mice were compromised regarding vestibulomotor function/coordination, with EPO-treated animals performing better than placebo. Likewise, ventricular enlargement after cuprizone, as documented by MRI, was less pronounced upon EPO. After a 3-wk recovery, remarkable spontaneous improvement was observed in all mice with no measurable further benefit in the EPO group ("ceiling effect"). Histological analysis of the corpus callosum revealed attenuation by EPO of the cuprizone-induced increase in microglial numbers and amyloid precursor protein accumulations as a readout of inflammation and axonal degeneration. To conclude, EPO ameliorates neurological symptoms in the cuprizone model of demyelination, possibly by reduction of inflammation-associated axonal degeneration in white matter tracts. These findings underscore the value of future therapeutic strategies for multiple sclerosis based on EPO or EPO variants.

PIMD: 22366800

A representative cohort of patients with non-progressive multiple sclerosis at the age of normal life expectancy.

Multiple sclerosis may have a non-progressive symptomatology for decades; however, it is not clear whether the disease activity may abate completely. We identified a cohort of patients, resident in Gothenburg at the time of disease onset, between the years 1950-64 (n = 307). These geographical and temporal restrictions, along with favourable conditions for a 'spider' epidemiological study, were optimal for an unbiased selection; this 15-year incidence cohort was essentially followed prospectively for 37-59 years after onset. The shortest follow-up time for patients without primary or secondary progression was 45 years. For patients with an initial relapsing-remitting course and multiple sclerosis diagnosis according to the Poser criteria (n = 202), the probability of non-progressive disease after 40 years was 22% (standard error 3.0%), and after 50 years it was 14% (standard error 3.2%). For attack onset including patients with possible multiple sclerosis, the corresponding probabilities after 40 and 50 years were 35% (standard error 3.3%) and 28% (standard error 3.5%), respectively. At the last follow-up in 2009-10, when patients reached the average age of the Swedish population life expectancy, only 13 patients from the multiple sclerosis diagnosis cohort, according to the Poser criteria, remained alive and non-progressive. Their annualized attack frequency diminished with time from 0.29 to 0.015. These patients had been functioning well socially. Nine patients had an Expanded Disability Status Scale score of 0-2.5, and four patients had a score of 3 or 3.5, with deficits dating back to attacks decades ago. Eight patients participated in a complete neuropsychological examination, which showed a slight difference ($P < 0.01$) concerning verbal memory and executive function compared to an age and socially matched reference group, whereas results for five other cognitive domains were within the normal range. Magnetic resonance images fulfilled the Barkhof-Tintoré criteria for multiple sclerosis in 10 of 11 patients, with conspicuously few subcortical lesions relative to extensive periventricular lesions and lesions extending from the inferior midline aspect of the corpus callosum. Prediction of the non-progressive stage was possible with moderate hazard ratios and low sensitivity. Early features that predicted a non-progressive course were complete remission of the onset attack, low or moderate initial relapse frequency and-when the patients with possible multiple sclerosis were included-dominating afferent symptoms. The clinical disease activity had abated in these 13 patients, with the caveat that transition to secondary progression continued to occur after four decades, albeit with decreasing risk.

PIMD: 22328451

Corpus callosum damage predicts disability progression and cognitive dysfunction in primary-progressive MS after five years.

We aim to identify specific areas of white matter (WM) and grey matter (GM), which predict disability progression and cognitive dysfunction after five years in patients with primary-progressive multiple sclerosis (PPMS). Thirty-two patients with early PPMS were assessed at baseline and after five years on the Expanded Disability Status Scale (EDSS), and EDSS step-changes were calculated. At year five, a subgroup of 25 patients and 31 healthy controls underwent a neuropsychological assessment. Baseline imaging consisted of dual-echo (proton density and T2-weighted), T1-weighted volumetric, and diffusion tensor imaging. Fractional anisotropy (FA) maps were created, and fed into tract-based spatial statistics. To compensate for the potential bias introduced by WM lesions, the T1 volumes underwent a lesion-filling procedure before entering a voxel-based morphometry protocol. To investigate whether FA and GM volume predicted EDSS step-changes over five years and neuropsychological tests scores at five years, voxelwise linear regression analyses were performed. Lower FA in the splenium of the corpus callosum (CC) predicted a greater progression of disability over the follow-up. Lower FA along the entire CC predicted worse verbal memory, attention and speed of information processing, and executive function at five years. GM baseline volume did not predict any clinical variable. Our findings highlight the importance of damage to the interhemispheric callosal pathways in determining physical and cognitive disability in PPMS. Disruption of these pathways, which interconnect motor and cognitive networks between the two hemispheres, may result in a disconnection syndrome that contributes to long-term physical and cognitive disability.

PIMD: 22306550

Expression of retinoid X receptor β is induced in astrocytes during corpus callosum demyelination.

The experimental activation of retinoid receptors reduces pathological symptoms in animal models of multiple sclerosis. In order to assess the involvement of endogenous retinoid signaling during the process of demyelination we investigated retinoic acid synthesizing enzymes and nuclear receptors using the mouse model of cuprizone toxicity. The initiation of myelin degradation in the corpus callosum was accompanied with a local increase of retinaldehyde dehydrogenase (RALDH) immunoreactivity. On the level of receptors we observed a striking increase in protein expression of the retinoid X receptor (RXR)-β in the affected corpus callosum. The RXRβ immunoreactivity appeared exclusively in astrocytes, where it reached a maximum at five weeks of treatment, following the RALDH response. In the cerebral cortex and basal ganglia of affected mice RXRβ was also observed in neurons. Among nuclear receptor antigens RARα showed a cuprizone associated increase in the corpus callosum. Quantitative RT-PCR revealed strong basal expression of RXRβ and a significant, over 20-fold upregulation of the peroxisome proliferator-activated receptor-γ during demyelination. The results indicate that compensatory mechanisms during central demyelination may engage nuclear receptor dimers with an RXRβ partner.

PIMD: 22260974

[Case of NMO (neuromyelitis optica) spectum disorder triggered by interferon alpha, which involved extensive pyramidal tract lesion of the brain].

A 65-year-old woman developed left optic neuritis during the course of peg-interferon alpha (PEG-IFN-α) and ribavirin combination therapy for chronic hepatitis C. Brain T(2)W-MRI disclosed hyperintense lesions in the corpus callosum and white matter. We diagnosed neuromyelitis optica spectrum disorder (NMOSD) on the basis of anti-aquaporin-4 antibody seropositivity. PEG-IFN-α was discontinued, and she received steroid pulse therapy (intravenous high dose methylprednisolone). Two weeks later she also developed right optic neuritis. Repetitive steroid pulse therapy improved the left optic neuritis, but the upper half of the visual field of the right eye remained impaired. One month later she presented with mild dysarthria and mild left hemiparesis. Brain MRI disclosed an extensive pyramidal tract lesion from the right corona radiata to the pedunculus cerebri. This cerebral pyramidal tract lesion is associated with NMOSD. Our case corresponds to the past reports of optic neuritis or multiple sclerosis-like disease triggered by IFN-α. IFN-α may trigger NMOSD via a biological effect characteristic of Type I IFNs, a group that includes IFN-α and IFN-β.

PIMD: 22241681

Multi-modal quantitative MRI investigation of brain tissue neurodegeneration in multiple sclerosis.

To investigate the utility of multimodal quantitative MRI (qMRI) and atlas-based methods to identify characteristics of lesion-driven injury and neurodegeneration in relapsing remitting multiple sclerosis (RRMS).This work is health insurance portability and accountability act compliant. High resolution T1-weighted, dual echo, and fluid-attenuated inversion recovery and diffusion tensor MRI images were prospectively acquired on 68 RRMS patients (range, 25-58 years) and 68 age-matched controls. The data were analyzed using standardized human brain atlas-based tissue segmentation procedures to obtain regional volumes and their corresponding T2 relaxation times and DTI maps.Group-averaged brain atlas-based qMRI maps of T2, fractional anisotropy and diffusivities are visually presented and compared between controls and RRMS. The analysis shows a widespread injury in RRMS. Atrophy of the corpus callosum (CC) was substantial in RRMS. The qMRI attributes of the neocortex in combination with the CC such as T2 and diffusivities were elevated and correlated with disability.Using a standardized multimodal qMRI acquisition and analyses that accounted for lesion distribution we demonstrate that cerebral pathology is widespread in RRMS. Our analysis of CC and neocortex qMRI metrics in relation to disability points to a neurodegenerative injury component that is independent from lesions.

PIMD: 22172709

Developmental changes and subcellular location in inhibitor of DNA binding 2 (Id2) immunoreactivity in the rat Corpus callosum.

The mechanisms underlying oligodendrocyte differentiation and myelination are still unclear, but understanding them will be critical for the development of therapies for multiple sclerosis. Inhibitor of DNA binding 2 (Id2) is a transcription factor thought to inhibit oligodendrocyte differentiation, however, it is not known whether the developmental changes and subcellular localization of Id2 are related to myelination. Therefore, we investigated the developmental changes in and the subcellular localization of Id2 immunoreactivity in the rat Corpus callosum, at post-natal developmental stages P0, P7, P14, P21, P42 and P90, by immunohistochemistry. Id2 expression increased from P0 to a peak at P42, the late stage of myelination in the Corpus callosum. Id2 immunostaining decreased slightly, but still remained high at P90. Subcellular localization of Id2 changed from presence in cytoplasm at P14 to the nuclei at P42. Moreover, Id2 was mainly co-localized with CC-1-immunopositive mature oligodendrocytes at P42. These results may be consistent with Id2 inhibitory function in oligodendrocyte differentiation, at the end of myelination or in compaction of myelin in the Corpus callosum of postnatal rat brain.

PIMD: 22172647

Diffusion tensor imaging of normal-appearing white matter in neuromyelitis optica.

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system characterized by severe attacks of optic neuritis and myelitis. Brain was classically, unlike in multiple sclerosis (MS), spared. Nevertheless recent studies showed that brain lesions can be seen with MRI. We studied the diffusion characteristics of normal-appearing white matter (NAWM) and abnormal white matter in NMO patients compared with NAWM in healthy subjects.Diffusion tensor imaging (DTI) scans of the brain and spinal cord were obtained from 25 patients with NMO and 20 age- and gender-matched healthy subjects. Region of interest (ROI) analysis of the apparent diffusivity coefficient (ADC) and fractional anisotropy (FA) was performed in brain NAWM (optic radiations, corpus callosum [CC] and anterior and posterior limbs of the internal capsule [IC]) and in spinal cord NAWM and in lesions.ADC was increased and FA decreased in NMO patients in the posterior limb of the IC in the optic radiations and in spinal cord NAWM. FA was lower in spinal cord lesions. In contrast, there was no difference between the two groups in the anterior limb of the IC nor in the CC.These results suggest that DTI abnormalities are very severe in NMO spinal cord lesions. In our study, DTI abnormalities in NAWM were restricted to optic radiations and cortico-spinal tracts, suggesting secondary Wallerian degeneration. In contrast, NAWM outside these tracts (CC and anterior IC) remained normal suggesting that, unlike what is observed in MS, there is no infra-lesional abnormality in NMO.

PIMD: 22171354

Quantification of increased cellularity during inflammatory demyelination.

Multiple sclerosis is characterized by inflammatory demyelination and irreversible axonal injury leading to permanent neurological disabilities. Diffusion tensor imaging demonstrates an improved capability over standard magnetic resonance imaging to differentiate axon from myelin pathologies. However, the increased cellularity and vasogenic oedema associated with inflammation cannot be detected or separated from axon/myelin injury by diffusion tensor imaging, limiting its clinical applications. A novel diffusion basis spectrum imaging, capable of characterizing water diffusion properties associated with axon/myelin injury and inflammation, was developed to quantitatively reveal white matter pathologies in central nervous system disorders. Tissue phantoms made of normal fixed mouse trigeminal nerves juxtaposed with and without gel were employed to demonstrate the feasibility of diffusion basis spectrum imaging to quantify baseline cellularity in the absence and presence of vasogenic oedema. Following the phantom studies, in vivo diffusion basis spectrum imaging and diffusion tensor imaging with immunohistochemistry validation were performed on the corpus callosum of cuprizone treated mice. Results demonstrate that in vivo diffusion basis spectrum imaging can effectively separate the confounding effects of increased cellularity and/or grey matter contamination, allowing successful detection of immunohistochemistry confirmed axonal injury and/or demyelination in middle and rostral corpus callosum that were missed by diffusion tensor imaging. In addition, diffusion basis spectrum imaging-derived cellularity strongly correlated with numbers of cell nuclei determined using immunohistochemistry. Our findings suggest that diffusion basis spectrum imaging has great potential to provide non-invasive biomarkers for neuroinflammation, axonal injury and demyelination coexisting in multiple sclerosis.

PIMD: 22155618

Adult CNP::EGFP transgenic mouse shows pronounced hypomyelination and an increased vulnerability to cuprizone-induced demyelination.

CNP::EGFP transgenic mice, genetically engineered to express the enhanced green fluorescent protein (EGFP) under the control of the 2-3-cyclic nucleotide 3-phosphodiesterase (CNPase) promoter in oligodendroglial and Schwann cells, constitute a very important and widely used tool for the study of oligodendrocyte (OLG) development and function in young mice. Our results showed that CNP::EGFP mice were significantly more susceptible to CPZ-induced demyelination, as evaluated by MBP immunostaining, oligodendroglial progenitor cell (OPC) recruitment and astroglial, microglial and nestin response. This enhanced vulnerability was a consequence of their hypomyelination. CNP::EGFP control mice also displayed a significant decrease in corpus callosum (CC) thickness and MBP immunoreactivity. Morphometric analysis further showed a significant decrease in the frequency of myelinated axons, myelin turns (lamellae) and g-ratio carried out in the optic nerve (ON) and CC of CNP::EGFP, as compared to WT mice. Moreover, our results showed a decrease in the number of axons of small caliber, concomitantly with an increase in the number of axons of bigger size with more and enlarged mitochondria, which suggests a high energy demand. These findings and those displaying that MBP+ cells and NF200 staining in the CNP::EGFP cortex were more sparsely distributed provide evidence of axonal loss, which was supported by a decreased number of NeuN+ cells in the CA3 fields of the hippocampus. Transgenic mice also showed an increase in microglial and astroglial activation, accompanied by enhanced lipid peroxidation and recruitment of morphologically altered OPC. Finally, CNPase protein levels proved to be lower than MBP in the CC, which might indicate an altered pattern in myelin proteins with a CNPase deficiency. Behavioral analysis of adult CNP::EGFP transgenic mice supported our results, as it revealed a decrease in locomotion, exploratory activity and motor impairment, as compared to their WT littermates. Our data highlight the relevance of confronting results obtained in adult CNP::EGFP mice with those observed in WT mice. According to our findings, CNP::EGFP hypomyelination might be triggered by the cellular stress induced by the high level of EGFP expression in mature OLG. Adult CNP::EGFP mice could be considered a useful tool to evaluate future therapies for demyelinating diseases such as multiple sclerosis (MS), since these animals present chronic demyelination with axonal degeneration, a characteristic of such pathologies.

PIMD: 22155325

Myelin water imaging reflects clinical variability in multiple sclerosis.

Whilst MRI is routinely used for the assessment and diagnosis of multiple sclerosis, there is poor correspondence between clinical disability in primary progressive multiple sclerosis (PPMS) patients and conventional MRI markers of disease activity (e.g., number of enhancing lesions). As PPMS patients show diffuse and global myelin loss, the aim of this study was to evaluate the efficacy of whole-brain myelin water fraction (MWF) imaging in PPMS. Specifically, we sought to use full-brain analysis techniques to: 1) determine the reproducibility of MWF estimates in PPMS brain; 2) compare MWF values in PPMS brain to healthy controls; and 3) establish the relationship between MWF and clinical disability, regionally and globally throughout the brain. Seventeen PPMS patients and seventeen age-matched controls were imaged using a whole-brain multi-component relaxation imaging technique to measure MWF. Analysis of MWF reduction was performed on three spatial levels: 1) histogram; 2) white matter skeleton; and 3) voxel-wise at the single-subject level. From histogram analysis, PPMS patients had significantly reduced global normal appearing white matter MWF (6%, $p=0.04$) compared to controls. Focal lesions showed lower MWF values than white matter in controls (61%, $p<0.001$) and patients (59%, $p<0.001$). Along the white matter skeleton, MWF was diffusely reduced throughout the PPMS brain, with significant correlations between reduced MWF and increased clinical disability (more severe symptoms), as measured by the Expanded Disability Status Scale, within the corpus callosum and frontal, temporal, parietal and occipital white matter. Correlations with the more specific mental and sensory functional system scores were localized to clinically eloquent locations: reduced MWF was significantly associated with increased mental scores in anterior regions (i.e., frontal lobes and genu of the corpus callosum), and increased sensory scores in more posterior regions closer to the sensory cortex. Individual patient MWF maps were also compared to a normative population atlas, which highlighted areas of statistical difference between the individual patient and the population mean. A significant correlation was found between the volume of significantly reduced MWF and clinical disability ($p=0.008$, $R=0.58$). Our results show that clinical disability is reflected in particular regions of cerebral white matter that are consistent between subjects, and illustrates a method to examine tissue alteration throughout the brain of individual patients. These results strongly support the use of MWF imaging to evaluate disease activity in PPMS.

PIMD: 22108642

Diffusion tensor imaging characterization of occult brain damage in relapsing neuromyelitis optica using 3.0T magnetic resonance imaging techniques.

Studies of relapsing neuromyelitis optica (RNMO) using advanced MRI techniques are limited compared with those done on multiple sclerosis (MS). The present study used diffusion tensor imaging (DTI) to investigate whether occult brain damage exists in RNMO patients. DTI scans using a 3.0T MRI scanner were performed in 24 clinically confirmed RNMO patients whose conventional brain MRI results were normal, and also in 24 age- and sex-matched healthy control subjects. DTI data were processed to generate fractional anisotropy (FA) and mean diffusivity (MD) maps, and region of interest (ROI) analyses were performed to obtain these parameters in white matter (including medulla oblongata, cerebral peduncle, optic radiation, genu of corpus callosum, splenium of corpus callosum, and internal capsule) and gray matter (including thalamus and putamen). Regional measures from patients at stable and acute phases were compared with healthy controls. Both acute and stable NMO patients had a higher average FA in ROIs of the thalamus and putamen. Acute NMO patients had significantly higher average MDs than controls in the genu of corpus callosum and optic radiation, and significantly lower average MDs in the medulla oblongata. Stable NMO patients had increased MDs in the genu of corpus callosum and optic radiation, but lower MDs in the medulla oblongata, internal capsule and thalamus. The DTI findings confirm the presence of occult tissue damage in normal-appearance white and gray matter, especially deep gray matter, in RNMO patients. This study adds further to the evidence that DTI is suitable as a tool for characterizing subtle brain tissue damage.

PIMD: 22096634

Corpus callosum microstructural changes correlate with cognitive dysfunction in early stages of relapsing-remitting multiple sclerosis: axial and radial diffusivities approach.

The corpus callosum is the largest fiber bundle in the central nervous system and it takes part in several cognitive pathways. It can be affected by multiple sclerosis (MS) early in the disease. DTI is capable of infering the microstructural organization of the white matter. The vectorial analysis of the DTI offers the more specific indices of axial diffusivity (AD) and radial diffusivity (RD), which have shown to be useful to discriminate myelin damage from axon loss, respectively. This study presents DTI results (mean diffusivity (MD), fractional anisotropy (FA), RD, and AD) of 23 relapsing-remitting MS patients and its correlation with cognitive performance. There were 47.8% of cognitive impaired patients (MS CI). We found signs of demyelination, reflected by increased RD, and incipient axon loss, reflected by AD increase, which was slightly higher in the MS CI. The cognitive changes correlated with the DTI parameters, suggesting that loss of complexity in CC connections can impair neural conduction. Thus, cognitive impairment can be related to callosal disconnection, and DTI can be a promising tool to evaluate those changes.

PIMD: 22092885

Atlas-based versus individual-based fiber tracking of the corpus callosum in patients with multiple sclerosis: reliability and clinical correlations.

In multiple sclerosis (MS), the presence of lesions and normal-appearing white matter damage may affect the reliability of diffusion tensor (DT) magnetic resonance imaging (MRI)-based tractography. We compared the performance of an individual-based method for corpus callosum (CC) fiber tracking in MS with those of two atlas-based methods.Brain DT MRI scans were acquired from 35 patients with MS and 18 age-matched healthy volunteers (HV). DT-derived metrics from the CC-the mean diffusivity (MD) and fractional anisotropy (FA)-were calculated using an individual-based and two atlas-based methods with different types of subject registration (linear and nonlinear) to a CC atlas. Customized termination criteria were applied to stop the tracking algorithm when using the individual-based method.All the methods were able to distinguish between MS patients and HV. Using the individual-based method, stronger relationships were found between CC DT-derived metrics and the subjects' clinical condition.CC DT tractography using an individual-based method is more sensitive than the atlas-based ones to tract-specific alterations related to MS disability. An atlas-based method with nonlinear registration can be a valid alternative when an automated postprocessing is warranted, such as in the case of high volumes of data.

PIMD: 22084126

Brain involvement in neuromyelitis optica spectrum disorders.

Neuromyelitis optica spectrum disorders (NMOSDs) are severe inflammatory demyelinating disorders of the central nervous system. Brain involvement is increasingly recognized.To study brain involvement in NMOSDs among Hong Kong Chinese patients.Retrospective study of patients with NMOSDs.Tertiary medical center in Hong Kong. Patients Thirty-four Hong Kong Chinese patients with NMOSDs of 2 years or longer were recruited.Brain and spinal cord magnetic resonance imaging was performed during NMOSD attacks and was repeated yearly for the first 3 years.We evaluated clinical features of NMOSDs associated with brain involvement and brain lesions on magnetic resonance imaging.Among 34 patients with NMOSDs of 2 years or longer, 20 (59%) had brain involvement. The mean age at onset among these 20 patients was 45.6 years (age range, 19-67 years); 18 were women. Eleven patients (32% of all the patients with NMOSDs) had clinical manifestation of brain involvement, 19 patients (56%) had brain abnormalities on magnetic resonance imaging consistent with inflammatory demyelination, and 2 patients (6%) fulfilled criteria for multiple sclerosis. Clinical manifestation of brain involvement included the following: trigeminal neuralgia; vomiting, vertigo, ataxia, dysphagia, and tetraparesis from lesions around the third and fourth ventricles and aqueduct; homonymous hemianopia, aphasia, hemiparesis, and cognitive impairment from extensive hemispheric white matter lesions; and ataxia, diplopia, hiccups, facial sensory loss, internuclear ophthalmoplegia, hemisensory loss, and hemiparesis from other lesions in the midbrain, pons, cerebellar peduncles, and medulla. Eight patients (24%) developed brainstem encephalitis clinically, and brainstem encephalitis was the initial clinical manifestation in 6 patients (18%). Brain abnormalities on magnetic resonance imaging were detected in brainstem in 15 patients (44%), hemispheric periventricular white matter in 7 patients (21%), deep white matter in 7 patients (21%), corpus callosum in 4 patients (12%), subcortical white matter in 3 patients (9%), thalamus in 2 patients (6%), hypothalamus in 1 patient (3%), basal ganglia in 1 patient (3%), internal capsule in 1 patient (3%), periaqueductal gray matter in 1 patient (3%), and around the third and fourth ventricles in 1 patient (3%); large confluent lesions were detected in 2 patients (6%).Brain involvement manifesting clinically as brainstem encephalitis is common among Hong Kong Chinese patients with NMOSDs.

PIMD: 22072381

Identification of a microglia phenotype supportive of remyelination.

In multiple sclerosis, endogenous oligodendrocyte precursor cells (OPCs) attempt to remyelinate areas of myelin damage. During disease progression, however, these attempts fail. It has been suggested that modulating the inflammatory environment of the lesion might provide a promising therapeutic approach to promote endogenous remyelination. Microglia are known to play a central role in neuroinflammatory processes. To investigate the microglia phenotype that supports remyelination, we performed genome-wide gene expression analysis of microglia from the corpus callosum during demyelination and remyelination in the mouse cuprizone model, in which remyelination spontaneously occurs after an episode of toxin-induced primary demyelination. We provide evidence for the existence of a microglia phenotype that supports remyelination already at the onset of demyelination and persists throughout the remyelination process. Our data show that microglia are involved in the phagocytosis of myelin debris and apoptotic cells during demyelination. Furthermore, they express a cytokine and chemokine repertoire enabling them to activate and recruit endogenous OPCs to the lesion site and deliver trophic support during remyelination. This study not only provides a detailed transcriptomic analysis of the remyelination-supportive microglia phenotype but also reinforces the notion that the primary function of microglia is the maintenance of tissue homeostasis and the support of regeneration already at the earliest stages in the development of demyelinating lesions.

PIMD: 22062194

Multiple white matter tract abnormalities underlie cognitive impairment in RRMS.

Diffusion tensor imaging (DTI) is a sensitive tool for detecting microstructural tissue damage in vivo. In this study, we investigated DTI abnormalities in individuals with relapsing remitting multiple sclerosis (RRMS) and examined the relations between imaging-based measures of white matter injury and cognitive impairment. DTI-derived metrics using tract-based spatial statistics (TBSS) were compared between 37 individuals with RRMS and 20 healthy controls. Cognitive impairment was assessed with three standard tests: the Symbol Digit Modalities Test (SDMT), which measures cognitive processing speed and visual working memory, the Rey Auditory Verbal Learning Test (RAVLT), which examines verbal memory, and the Paced Auditory Serial Addition Test (PASAT), which assesses sustained attention and working memory. Correlations between DTI-metrics and cognition were explored in regions demonstrating significant differences between the RRMS patients and the control group. Lower fractional anisotropy (FA) was found in RRMS participants compared to controls across the tract skeleton (0.40 ± 0.03 vs. 0.43 ± 0.01, $p<0.01$). In areas of reduced FA, mean diffusivity was increased and was dominated by increased radial diffusivity with no significant change in axial diffusivity, an indication of the role of damage to CNS myelin in MS pathology. In the RRMS group, voxelwise correlations were found between FA reduction and cognitive impairment in cognitively-relevant tracts, predominantly in the posterior thalamic radiation, the sagittal stratum, and the corpus callosum; the strongest correlations were with SDMT measures, with contributions to these associations from both lesion and normal-appearing white matter. Moreover, results using threshold-free cluster enhancement (TFCE) showed more widespread white matter involvement compared to cluster-based thresholding. These findings indicate the important role for DTI in delineating mechanisms underlying MS-associated cognitive impairment and suggest that DTI could play a critical role in monitoring the clinical and cognitive effects of the disease.

PIMD: 22045260

White matter integrity and math performance in pediatric multiple sclerosis: a diffusion tensor imaging study.

Multiple sclerosis is associated with reduced white matter integrity and deficits in key cognitive processes important for arithmetic. This study examined the relationship between white matter microstructure and academic ability in 31 youths with multiple sclerosis (aged 11-19 years) and 34 demographically matched controls. Using diffusion tensor imaging, fractional anisotropy was calculated in corpus callosum and in lateralized hemispheric lobes. Difficulties with written arithmetic ability were observed in 26% of patients. Arithmetic ability correlated with fractional anisotropy values across all segments of the corpus callosum and in right frontal and parietal regions, controlling for age (r values >0.5, P<0.005). Findings highlight the functional impact of compromised white matter microstructure across diffuse regions of the brain on mathematical ability.

PIMD: 22036954

Immune cell NT-3 expression is associated with brain atrophy in multiple sclerosis patients.

While neurotrophins mediate cell survival and proliferation in the nervous system, they are also expressed within peripheral blood mononuclear cells (PBMCs) of the immunological system. In multiple sclerosis (MS) neurotrophins released from PBMCs might play a neuroprotective role, delaying neurodegeneration within central nervous system. We aimed for identifying the link between neurotrophins' PBMCs expression and brain atrophy markers in relapsing-remitting MS (RRMS) patients. We have found that neurotrophin-3 PBMCs concentration is strongly correlated with brain-parenchymal fraction and corpus callosum cross-sectional area, which are well-established brain atrophy measures. Thus, PBMC-derived neurotrophin-3 might exert a direct or indirect neuroprotective effect in MS.

PIMD: 22015947

Demyelination and remyelination in anatomically distinct regions of the corpus callosum following cuprizone intoxication.

Multiple sclerosis is a chronic demyelinating disease of the central nervous system. Spontaneous remyelination during early disease stages is thought to preserve and partially restore function. However, this process ceases in later stages despite the presence of pre-oligodendrocytes. Cuprizone-induced demyelination is a useful model with which to study the remyelination process. Previous studies have demonstrated heterogeneities in demyelination in individual animals. Here we investigated regional differences in demyelination and remyelination within the corpus callosum. C57BL/6 mice were fed 0.2% cuprizone for 5 weeks to induce demyelination. Remyelination was examined 2-5 weeks after cuprizone withdrawal. Immunohistochemistry and electron microscopy were used to quantify regional differences in demyelination, gliosis, and remyelination. We found that, while demyelination was limited in the rostral region of corpus callosum, nearly complete demyelination occurred in the caudal callosum, beginning at approximately -0.5mm from bregma. Astrogliosis and microgliosis were correlated with demyelination and differed between the rostral and caudal callosal structures. Remyelination upon cessation of cuprizone ensued at different rates with splenium remyelinating faster than dorsal hippocampal commissure. Our data show anatomical differences of cuprizone-induced demyelination and remyelination in the corpus callosum and the importance of examining specific callosal regions in myelin repair studies using this model.

PIMD: 21978603

Human brain atlas-based multimodal MRI analysis of volumetry, diffusimetry, relaxometry and lesion distribution in multiple sclerosis patients and healthy adult controls: implications for understanding the pathogenesis of multiple sclerosis and consolidation of quantitative MRI results in MS.

Multiple sclerosis (MS) is the most common immune-mediated disabling neurological disease of the central nervous system. The pathogenesis of MS is not fully understood. Histopathology implicates both demyelination and axonal degeneration as the major contributors to the accumulation of disability. The application of several in vivo quantitative magnetic resonance imaging (MRI) methods to both lesioned and normal-appearing brain tissue has not yet provided a solid conclusive support of the hypothesis that MS might be a diffuse disease. In this work, we adopted FreeSurfer to provide standardized macrostructure or volumetry of lesion free normal-appearing brain tissue in combination with multiple quantitative MRI metrics (T(2) relaxation time, diffusion tensor anisotropy and diffusivities) that characterize tissue microstructural integrity. By incorporating a large number of healthy controls, we have attempted to separate the natural age-related change from the disease-induced effects. Our work shows elevation in diffusivity and relaxation times and reduction in volume in a number of normal-appearing white matter and gray matter structures in relapsing-remitting multiple sclerosis patients. These changes were related in part with the spatial distribution of lesions. The whole brain lesion load and age-adjusted expanded disability status score showed strongest correlations in regions such as corpus callosum with qMRI metrics that are believed to be specific markers of axonal dysfunction, consistent with histologic data of others indicating axonal loss that is independent of focal lesions. Our results support that MS at least in part has a neurodegenerative component.

PIMD: 21972097

De- and remyelination in the CNS white and grey matter induced by cuprizone: the old, the new, and the unexpected.

The copper chelator cuprizone (bis-cyclohexanone oxaldihydrazone) was established as a neurotoxin in rodents in 1966 by Carlton. During the following years the usefulness of cuprizone feeding in mice to induce oligodendrocyte death with secondary demyelination of the superior cerebellar peduncles was described by Blakemore. In 1998 the cuprizone model experienced a renaissance as the group of Matsushima described the effects of cuprizone on the white matter of the cerebrum and focussed on demyelination in the corpus callosum, where the extent of demyelination could be scored more easily and consistently. Since then the toxic cuprizone model has been widely used to study experimental de- and remyelination in the corpus callosum. Recently, we and others have extended these studies and have shown several new aspects characteristic for this model. Many lessons can be learned from these recent findings that have implications for the basic understanding of remyelination and the design of remyelinating and neuroprotective strategies in demyelinating diseases of the CNS. Although the model is often mentioned in the context of multiple sclerosis, it must always be kept in mind that this model has a fundamentally different induction of demyelination. We highlight the important findings delineated from this model and critically discuss both the advantages and the shortcomings of cuprizone induced demyelination.

PIMD: 21881471

Acute disseminated encephalomyelitis after mixed malaria infection (Plasmodium falciparum and Plasmodium vivax) with MRI closely simulating multiple sclerosis.

Acute disseminated encephalomyelitis (ADEM) is a monophasic, inflammatory, immune-mediated disorder of the central nervous system. It is particularly difficult to distinguish between ADEM and an initial attack of multiple sclerosis (MS) clinically and based on magnetic resonance imaging (MRI) or cerebrospinal fluid. ADEM is quite rare after malaria infection. Our patient, although diagnosed provisionally of ADEM after mixed malaria infection, had neuroimaging closely simulating MS.We report a case of a woman with an adult type 2 diabetes presenting with fever and diagnosed by antigen assay to be suffering from mixed malaria infection (Plasmodium falciparum, Plasmodium vivax). While recovering with artesunate and doxycycline therapy, she developed acute onset bladder retention followed by paraparesis. On examination she had evidence of Upper Motor Neuron (UMN) signs in all the 4 limbs along with truncal sensory loss.Her MRI of spine showed T2 hyperintensities suggestive of resolving myelitis. MRI of the brain showed multifocal and confluent areas of demyelination mostly involving the corpus callosum and periventricular region. Lesions, particularly the callosal ones, closely simulated MS. In accordance with the McDonald Criteria and Barkhof's MRI Criteria, this patient did not fit into the diagnosis of MS. Our provisional diagnosis was ADEM.

PIMD: 21878451

Brain lesion location and clinical status 20 years after a diagnosis of clinically isolated syndrome suggestive of multiple sclerosis.

The objective of this study was to investigate associations between the spatial distribution of brain lesions and clinical outcomes in a cohort of people followed up 20 years after presentation with a clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS).Brain lesion probability maps (LPMs) of T1 and T2 lesions were generated from 74 people who underwent magnetic resonance imaging (MRI) and clinical assessment a mean of 19.9 years following a CIS. One-tailed t-test statistics were used to compare LPMs between the following groups: clinically definite (CD) MS and those who remained with CIS, with an abnormal MRI; people with MS and an Expanded Disability Status Scale (EDSS) ≤3 and >3; people with relapsing-remitting (RR) and secondary progressive (SP) MS. The probability of each voxel being lesional was analysed adjusting for age and gender using a multiple linear regression model.People with CDMS were significantly more likely than those with CIS and abnormal scan 20 years after onset to have T1 and T2 lesions in the corona radiata, optic radiation, and splenium of the corpus callosum (periventricularly) and T2 lesions in the right fronto-occipital fasciculus. People with MS EDSS >3, compared with those with EDSS ≤3, were more likely to have optic radiation and left internal capsule T2 lesions. No significant difference in lesion distribution was noted between RRMS and SPMS.This work demonstrates that lesion location characteristics are associated with CDMS and disability after long-term follow-up following a CIS. The lack of lesion spatial distribution differences between RRMS and SPMS suggests focal pathology affects similar regions in both subgroups.

PIMD: 21865884

Matrix metalloproteinases and their tissue inhibitors in cuprizone-induced demyelination and remyelination of brain white and gray matter.

Apart from their involvement in the pathogenesis of demyelinating diseases such as multiple sclerosis, there is emerging evidence that matrix metalloproteinases (MMPs) also promote remyelination. We investigated region-specific expression patterns of 11 MMPs and 4 tissueinhibitors of metalloproteinases (TIMPs) in the cuprizone murine demyelination model. Messenger RNA (mRNA) was extracted at different time points of exposure to cuprizone from microdissected samples of corpus callosum, cortex, and ex vivo isolated microglia and analyzedusing quantitative reverse transcription-polymerase chain reaction.Matrix metalloproteinase 12 and TIMP-1 mRNA were significantly upregulated versus age-matched controls in both areas during demyelination and remyelination. Matrix metalloproteinases 3, 11, and 14 mRNA were upregulated only in white matter during remyelination. Matrix metalloproteinase 24 mRNA was downregulated during both demyelination and remyelination. To identify potential cellular sources of the MMPs and TIMPs, we isolated microglia and detected high MMP-12and TIMP-2 mRNA upregulation at the peak of demyelination.By immunohistochemistry, MMP-3 protein was localized in astrocytes and MMP-12 was identified in microglia, astrocytes, and cells of oligodendrocyte lineage. These findings suggest that MMPs and TIMPs have roles in the regulation of demyelination and remyelination in thismodel. Moreover, differences in the expression levels of these genesbetween white and gray matter reveal region-specific molecularmechanisms.

PIMD: 21821263

Diffusion tensor imaging and cognitive speed in children with multiple sclerosis.

To compare white matter (WM) integrity in children with MS and healthy children using diffusion tensor imaging (DTI), and correlate DTI findings with disease activity, lesion burden, and cognitive processing speed.Fractional anisotropy (FA) and mean diffusivity (MD) in normal-appearing white matter (NAWM) were measured in four corpus callosum (CC), eight hemispheric regions, and the normal-appearing thalamus of 33 children and adolescents with MS and 30 age-matched healthy controls. Images were acquired on a GE LX 1.5T scanner. DTI parameters used were 25 directions, b = 1000 s/mm(2), and 5mm slice thickness. MS patients had T2 lesion volumes and Expanded Disability Status Scale (EDSS) scores were measured; all participants underwent two speeded cognitive tasks (Visual Matching and Symbol Digit Modalities Test (SDMT)).MS participants displayed lower FA values in the genu ($p<0.005$), splenium ($p<0.001$) and in NAWM of bilateral parietal, temporal, and occipital lobes ($p<0.001$) versus controls. FA and MD in the thalamus did not differ between groups. Higher lesion volumes correlated with reduced FA in CC and hemispheric NAWM. DTI metrics did not correlate with EDSS. FA values in CC regions correlated with Visual Matching ($p<0.001$) and SDMT ($p<0.005$) in MS participants only.DTI analyses indicate widespread NAWM disruption in children with MS-with the degree of abnormality correlating with impaired cognitive processing speed. These findings support an early onset tissue pathology in MS and illustrate its functional consequence.

PIMD: 21630352

Nonexponential T□ decay in white matter.

Visualizing myelin in human brain may help the study of diseases such as multiple sclerosis. Previous studies based on T(1) and T(2) relaxation contrast have suggested the presence of a distinct water pool that may report directly on local myelin content. Recent work indicates that T(2) contrast may offer particular advantages over T(1) and T(2) contrast, especially at high field. However, the complex mechanism underlying T(2) relaxation may render interpretation difficult. To address this issue, T(2) relaxation behavior in human brain was studied at 3 and 7 T. Multiple gradient echoes covering most of the decay curve were analyzed for deviations from mono-exponential behavior. The data confirm the previous finding of a distinct rapidly relaxing signal component (T(2) □ 6 ms), tentatively attributed to myelin water. However, in extension to previous findings, this rapidly relaxing component displayed a substantial resonance frequency shift, reaching 36 Hz in the corpus callosum at 7 T. The component's fractional amplitude and frequency shift appeared to depend on both field strength and fiber orientation, consistent with a mechanism originating from magnetic susceptibility effects. The findings suggest that T(2) contrast at high field may be uniquely sensitive to tissue myelin content and that proper interpretation will require modeling of susceptibility-induced resonance frequency shifts.

PIMD: 21600079

[The clinical and magnetic resonance imaging studies of brain damages in neuromyelitis optica].

To investigate the feature brain damage and clinical manifestations in neuromyelitis optica (NMO) patients; To investigate the relationship between serum NMO-IgG antibody and NMO brain damage.Clinical data of 37 NMO patients and their head and spinal cord MRI by 1.5T superconducting MR scanner, were analyzed; serum NMO-IgG antibody were measured by immunofluorescence.17 cases were found to have abnormal signals on MRI, which were mainly in the white matter, pons, medulla, ventricle, aqueduct, and around the corpus callosum; According to pathological changes, brain damage can be divided into scattered irregularity (13 cases), fusion (3 cases), multiple sclerosis-like (1 case), with scattered irregularity more common, 5 cases had clinical manifestations of brain damage: somnolence, vomiting, diplopia, visual rotation, 11 cases patients with brainstem damage show positive serum NMO-IgG antibodies.Brain damage can be seen in half of NMO patients, they often located in the high expression area of AQP4: brain white matter, periventricular, brainstem and so on. Clinical symptoms has nothing to do with the size of lesions but the location, they often occur when brainstem was involved. Serum NMO-IgG is helpful in differentiating NMO with brain damage and MS.

PIMD: 21594686

Fatigue and progression of corpus callosum atrophy in multiple sclerosis.

Fatigue is one of the most disabling symptoms in multiple sclerosis (MS) patients. There is no or only weak correlation between conventional magnetic resonance imaging (MRI) parameters and level of fatigue. The aim of this study was to investigate the relationship between progression of corpus callosum (CC) atrophy and fatigue in MS patients. This was a cohort study in 70 patients with relapsing form of MS (RRMS) and serial MRIs over a mean follow-up of 4.8 years [67% female, mean age 42 ± 11 years, mean disease duration 9.7 ± 7.6 years, mean Expanded Disability Status Scale (EDSS) 2.8 ± 1.6]. Fatigue was assessed by the Fatigue Severity Scale (FSS). CC size was measured with the CC index (CCI). In total, 40% of the patients suffered from fatigue (mean FSS score 5.3 ± 1.1) and 60% patients had no fatigue (mean FSS score of 2.1 ± 1). Patients with fatigue had higher EDSS scores ($p = 0.01$) and CC atrophy was more pronounced in patients with fatigue (-21.8 vs. -12.1%, $p = 0.005$). FSS correlated with CCI change over time ($r = -0.33$; $p = 0.009$) and EDSS ($p = 0.008$; $r = 0.361$). The association between annualized CCI change and FSS was independent from EDSS, disease duration, gender and age in a multivariate linear regression analysis ($p < 0.001$). Progression of CC atrophy may play a role in the evolution of MS-related fatigue.

PIMD: 21591539

Neurofibromatosis type I associated multiple sclerosis.

Neurofibromatosis (NF) type I is a common autosomal dominant disease that principally affects the skin and peripheral nervous system. Neurofibromatosis type I associated multiple sclerosis is a very rare condition. A 28-year old NF1 man developed progressive spastic-ataxic gait, left side dysmetria, right internuclear ophthalmoplegia, spastic dysarthria. MRI of the brain depicted Dawson finger appearance demyelination of the corpus callosum and other multifoci demyelinating lesions typical for MS. CSF revealed high CSF protein with negative oligoclonal band. Visual evoked potential showed prolonged P100 latency, abnormal waveform and temporal dispersion bilaterally. The syndrome partially responded and stabilized with corticosteroid. Six months later progression of the syndrome characterized by paraparesis, bilateral cerebellar hemispheric syndrome and bilateral internuclear ophthalmoplegia occurred. Repeated MRI revealed more extensive white matter lesions extended into centrum semiovale. The progressive syndrome did not respond to corticosteroid. Primary progressive multiple sclerosis was diagnosed. Only thirteen cases with NF1 and multiple sclerosis have been described in the literature. The association has been hypothesized to be related to mutations in the neurofibromin protein or oligodendrocyte-myelin glycoprotein (OMgp) gene.

PIMD: 21567135

Progressive decline in fractional anisotropy on serial DTI examinations of the corpus callosum: a putative marker of disease activity and progression in SPMS.

Clinical trials of secondary progressive multiple sclerosis (SPMS) is lacking reliable biomarkers or outcome measures that reflect tissue injury incurred within a 1- to 2-year observation period. Diffusion tensor imaging (DTI) is sensitive in detecting acute brain tissue damage. We monitored SPMS patients over 12 months for diffusion changes within the corpus callosum (CC).Bimonthly MRI examinations over a 1-year period were performed on 11 SPMS patients. The protocol included postcontrast T1-weighted images and DTI. Based on the appearance of T1 enhancing lesion(s) during the study period, the patients were divided into enhancing (five patients) and nonenhancing (six patients) groups. Fractional anisotropy (FA) and mean diffusivity (MD) of the genu, body, and splenium of the CC were measured and temporal changes in mean FA and MD were evaluated for each group as well as between groups. Immunology data from peripheral blood mononuclear cells were also collected on a monthly basis.The enhancing group showed significant, progressive decrease in FA in body ($p = 0.012$) and splenium ($p = 0.033$) of CC, and significantly higher lymphotoxin-β levels. No significant FA changes were seen in the nonenhancing group. Moreover, the FA decline in the enhancing group deviated significantly from the nonenhancing group, which remained essentially stable. Although MD increased slightly in both groups, there was no significant difference between the two groups.Based on the MR and immunology findings, the results of our study suggest that DTI undergo more rapid and longitudinal changes in SPMS patients with inflammatory activity.

PIMD: 21556863

Fractional anisotropy and mean diffusivity in the corpus callosum of patients with multiple sclerosis: the effect of physiotherapy.

Modulation of neurodegeneration by physical activity is an active topic in contemporary research. The purpose of this study was to investigate changes in the brain's microstructure in multiple sclerosis (MS) after facilitation physiotherapy.Eleven patients with MS were examined using motor and neuropsychological testing and multimodal MRI at the beginning of the study, with second baseline measurement after 1 month without any therapy, and after a 2-month period of facilitation physiotherapy. Eleven healthy controls were examined at the beginning of the study and after 1 month. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (λ (ax)), and radial diffusivity (λ (rad)) were calculated for the whole corpus callosum (CC) in the midsagittal slice of T1W 3D MPRAGE spatially normalized images. Data were analyzed using linear mixed-effect models, paired, and two-sample tests.At the baseline, patients with MS showed significantly lower values in FA ($p < 0.001$), and significantly higher values in MD ($p < 0.001$), λ (ax) ($p = 0.003$), and λ (rad) ($p < 0.001$) compared to control subjects. The FA, MD, λ (ax), and λ (rad) did not change between the first and second baseline examinations in either group. Differences 2 months after initiating facilitation physiotherapy were in FA, MD, and in λ (rad) significantly higher than differences in healthy controls ($p < 0.001$ for FA, $p = 0.02$ for MD, and $p = 0.002$ for λ (rad)). In MS patients, FA in the CC significantly increased ($p < 0.001$), MD and λ (rad) significantly decreased ($p = 0.014$ and $p = 0.002$), and thus approached the values in healthy controls.The results of the study show that facilitation physiotherapy influences brain microstructure measured by DTI.

PIMD: 21555210

Inhibition of 5-lipoxygenase activity in mice during cuprizone-induced demyelination attenuates neuroinflammation, motor dysfunction and axonal damage.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Increased expression of 5-lipoxygenase (5-LO), a key enzyme in the biosynthesis of leukotrienes (LTs), has been reported in MS lesions and LT levels are elevated in the cerebrospinal fluid of MS patients. To determine whether pharmacological inhibition of 5-LO attenuates demyelination, MK886, a 5-LO inhibitor, was given to mice fed with cuprizone. Gene and protein expression of 5-LO were increased at the peak of cuprizone-induced demyelination. Although MK886 did not attenuate cuprizone-induced demyelination in the corpus callosum or in the cortex, it attenuated cuprizone-induced axonal damage and motor deficits and reduced microglial activation and IL-6 production. These data suggest that during cuprizone-induced demyelination, the 5-LO pathway contributes to microglial activation and neuroinflammation and to axonal damage resulting in motor dysfunction. Thus, 5-LO inhibition may be a useful therapeutic treatment in demyelinating diseases of the CNS.

PIMD: 21549844

Impairment in explicit visuomotor sequence learning is related to loss of microstructural integrity of the corpus callosum in multiple sclerosis patients with minimal disability.

Sequence learning can be investigated by serial reaction-time (SRT) paradigms. Explicit learning occurs when subjects have to recognize a test sequence and has been shown to activate the frontoparietal network in both contralateral and ipsilateral hemispheres. Thus, the left and right superior longitudinal fasciculi (SLF), connecting the intra-hemispheric frontoparietal circuits, could have a role in explicit unimanual visuomotor learning. Also, as both hemispheres are involved, we could hypothesize that the corpus callosum (CC) has a role in this process. Pathological damage in both SLF and CC has been detected in patients with Multiple Sclerosis (PwMS), and microstructural alterations can be quantified by Diffusion Tensor Imaging (DTI). In light of these findings, we inquired whether PwMS with minimal disability showed impairments in explicit visuomotor sequence learning and whether this could be due to loss of white matter integrity in these intra- and inter-hemispheric white matter pathways. Thus, we combined DTI analysis with a modified version of SRT task based on finger opposition movements in a group of PwMS with minimal disability. We found that the performance in explicit sequence learning was significantly reduced in these patients with respect to healthy subjects; the amount of sequence-specific learning was found to be more strongly correlated with fractional anisotropy (FA) in the CC (r=0.93) than in the left (r=0.28) and right SLF (r=0.27) (p for interaction=0.005 and 0.04 respectively). This finding suggests that an inter-hemispheric information exchange between the homologous areas is required to successfully accomplish the task and indirectly supports the role of the right (ipsilateral) hemisphere in explicit visuomotor learning. On the other hand, we found no significant correlation of the FA in the CC and in the SLFs with nonspecific learning (assessed when stimuli are randomly presented), supporting the hypothesis that inter-hemispheric integrity is specifically relevant for explicit sequence learning.

PIMD: 21534686

MRI correlates of cognitive impairment in childhood-onset multiple sclerosis.

Brain MRI measures were correlated with neuropsychological function in 35 pediatric-onset multiple sclerosis (MS) patients and 33 age- and sex-matched healthy controls.Mean age of MS patients was 16.3 ± 2.3 years with average disease duration of 4.3 ± 3.1 years. Cortical gray matter, thalamic, and global brain volumes were calculated for all participants using a scaling factor computed using normalization of atrophy method to normalize total and regional brain volumes for head size. T1- and T2-weighted lesion volumes were calculated for MS patients.Cognitive impairment (CI) was identified in 29% of the MS cohort. Cognitive deficits predominantly involved attention and processing speed, expressive language, and visuomotor integration. Relative to controls, the MS group showed significantly lower thalamic volume ($p < .001$), total brain volume ($p < .008$), and gray matter volume ($p < .015$). Corpus callosum area and thalamic volume differentiated patients identified as having CI from those without CI ($p < .05$). Regression models controlling for disease duration and age indicated that thalamic volume accounted for significant incremental variance in predicting global IQ, processing speed, and expressive vocabulary ($\Delta R2$ ranging from .43 to .60) and was the most robust MRI predictor of cognition relative to other MRI metrics.The robust association between cognitive function and reduced size of thalamus and global brain volume in pediatric-onset MS patients implicate neurodegenerative processes early in the disease course, and suggest that plasticity of an immature central nervous system is not sufficient to protect patients from the deleterious consequences of MS on cognitive neural networks.

PIMD: 21531063

Perspectives on dichotic listening and the corpus callosum.

The present review summarizes historic and recent research which has investigated the role of the corpus callosum in dichotic processing within the context of audiology. Examination of performance by certain clinical groups, including split brain patients, multiple sclerosis cases, and other types of neurological lesions is included. Maturational, age related, and genetic factors are also discussed. Finally, some attention is given to recent trends in audiology research to develop improved diagnostic and rehabilitation tools for individuals with dichotic deficits potentially related to callosal dysfunction.

PIMD: 21516513

The hippocampal fimbria of cuprizone-treated animals as a structure for studying neuroprotection in multiple sclerosis.

It has been demonstrated that changes in the normal-appearing white matter (NAWM) in multiple sclerosis precede the appearance of classical lesions. The understanding of NAWM biology in an established disease model might help to clarify why some of them progress to active demyelinating lesions.C57BL6 male mice (19-21 g) were used in this study.Demyelination was induced by feeding mice a diet containing 0.2% cuprizone for up to 5 weeks.Routine stainings (luxol fast blue, and hematoxylin and eosin) and immunohistochemistry were performed to assess myelin status and the inflammatory infiltrate.We demonstrated that, in the toxic demyelination cuprizone model, the corpus callosum is severely demyelinated after a 5-week cuprizone challenge (acute demyelination) whereas the fimbria of the hippocampus appear normal in routine myelin stainings. Microgliosis but not astrogliosis is evident after acute demyelination in the fimbria. Interestingly, both regions, the fimbria and the corpus callosum, demonstrated early oligodendrocyte apoptosis as well as intense microglia accumulation and activation. However, only the corpus callosum progresses to actively demyelination lesions whereas the fimbria does not.The applied model appears suitable for elucidating pathways which promote progression of affected tissue to an active lesion.

PIMD: 21507085

Corticosteroids impair remyelination in the corpus callosum of cuprizone-treated mice.

Corticosteroids (CS) are effective in the treatment of many brain disorders, such as multiple sclerosis (MS) or traumatic brain injury. This has been scrutinised in different experimental animal models. However, neither the mechanisms, nor the site of CS action are fully understood. Short-term high-dose CS treatment improves MS symptoms and severity of clinical disability during an acute inflammatory exacerbation of disease. In the present study, we analysed the influence of CS on the expression of cellular and molecular markers of spontaneous endogenous remyelination in the toxic non-immune cuprizone animal model at early (9 days) and intermediate (21 days) remyelination, as well as steroidal effects in primary astrocytes and oligodendrocyte progenitor cultures. Dexamethasone (Dex) and methylprednisolone (MP) induced a higher expression of the differentiation markers myelin basic protein and proteolipid protein (PLP) in cultured oligodendrocyte progenitor cells (OPC). CS exposure of primary cultured astrocytes resulted in a greater expression of those genes involved in OPC proliferation [fibroblast growth factor 2 (FGF2) and platelet-derived growth factor (PDGF)-αα] and a reduced expression of the pro-maturation factor insulin-like growth factor 1. Pro-maturating effects of CS were completely blocked by FGF2 and PDGF-αα co-application in OPC cultures. MP treatment in vivo resulted in a reduced recovery of PLP-staining intensity, whereas the re-population of the demyelinated corpus callosum with adenomatous polyposis coli-expressing oligodendrocytes was not affected. The numbers of brain intrinsic inflammatory cells, microglia and astrocytes during remyelination were similar in placebo and MP-treated animals. Our findings suggest that treatment with CS might have, in addition to the well-known benefical effects on inflammatory processes, a negative influence on remyelination.

PIMD: 21495114

Motor callosal disconnection in early relapsing-remitting multiple sclerosis.

In relapsing-remitting multiple sclerosis (RRMS) the corpus callosum (CC) is often and early affected by macroscopic lesions when investigated by conventional MRI. We sought to determine to which extent microstructural and effective disconnection of the CC are already present in RRMS patients at the earliest stages of the disease prior to evidence of macroscopic CC lesion. We compared 16 very early RRMS patients (median expanded disability status scale (EDSS), 1.5; range, 0-2.0) to an age-matched group of healthy controls and focused analysis to the motor CC, i.e. that part of the CC relaying interhemispheric motor information. A combined functional magnetic resonance imaging/diffusion tensor imaging fiber-tracking procedure was applied to identify the callosal motor fibers (CMFs) connecting the hand areas of the primary motor cortices of the two hemispheres. Fractional anisotropy (FA) within the motor CC (FA-CC) assessed the CMF microstructural integrity. Bifocal paired transcranial magnetic stimulation (TMS) tested short-interval interhemispheric inhibition (S-IHI), an established measure of CMF effective connectivity. FA-CC and S-IHI were significantly reduced in early RRMS compared to healthy controls. Furthermore, a significant linear correlation between microstructure (FA-CC) and function (S-IHI) in the controls was broken down in the patients. These abnormalities were obtained in the absence of macroscopic CMF lesion in conventional MRI, and whilst motor hand/arm function in the nine-hole-peg test and corticospinal conduction time were normal. Findings suggest that reductions in FA and S-IHI may serve as surrogate markers of motor callosal disconnection at the earliest stages of RRMS prior to development of macroscopic lesion.

PIMD: 21447326

Microinjection of l-arginine into corpus callosum cause reduction in myelin concentration and neuroinflammation.

Role of nitric oxide (NO) in inflammationary diseases such as multiple sclerosis (MS) has been proposed previously. We sought to examine if NO plays centrally a key role in MS related phenomena; demyelination or neuroinflammation. Female Wistar rats (weighing 200-250 g) were mounted in a stereotaxic apparatus and received injections of l-arginine aimed at corpus callosum (AP: 1.2, L: ±1.8, V: 3.2). The drug (50-200 μg/rat) was microinjected intra-corpus callosum repeatedly (3-5 times/each per day). Control groups solely received saline (1 μg/rat) into the corpus callosum. The animals were tested for the novelty seeking behavior using the conditioning task. Memory impairment was examined using the shuttle box and Y-maze. l-NAME was pre-injected to l-arginine to involve the NO. All animals' brains were also processed for histological evaluation. l-arginine produced significant changes in the novelty seeking behavior but not in the memory formation, evidenced by passive avoidance and alternation behaviors. Pre-injection of l-NAME reversed the response to l-arginine. Present study further revealed a prominent inflammation as well as myelin elimination in the l-arginine treated rats' brains. These data suggest that the NO infusion in the myelin rich areas such as corpus callosum may lead to MS signs centrally.

PIMD: 21438010

Differentiation of induced pluripotent stem cells into functional oligodendrocytes.

The technology to generate autologous pluripotent stem cells (iPS cells) from almost any somatic cell type has brought various cell replacement therapies within clinical research. Besides the challenge to optimize iPS protocols to appropriate safety and GMP levels, procedures need to be developed to differentiate iPS cells into specific fully differentiated and functional cell types for implantation purposes. In this article, we describe a protocol to differentiate mouse iPS cells into oligodendrocytes with the aim to investigate the feasibility of IPS stem cell-based therapy for demyelinating disorders, such as multiple sclerosis. Our protocol results in the generation of oligodendrocyte precursor cells (OPCs) that can develop into mature, myelinating oligodendrocytes in-vitro (co-culture with DRG neurons) as well as in-vivo (after implantation in the demyelinated corpus callosum of cuprizone-treated mice). We report the importance of complete purification of the iPS-derived OPC suspension to prevent the contamination with teratoma-forming iPS cells.

PIMD: 21414412

Regional brain atrophy in children with multiple sclerosis.

We used cross-sectional tensor-based morphometry to visualize reduced volume in the whole brains of pediatric patients with multiple sclerosis, relative to healthy controls. As a marker of local volume difference, we used the Jacobian determinant of the deformation field that maps each subject to a standard space. To properly assess abnormal differences in volume in this age group, it is necessary to account for the normal, age-related differences in brain volume. This was accomplished by computing normalized z-score Jacobian determinant values at each voxel to represent the local volume difference (in standard deviations) between an individual subject and an age- and sex-matched healthy normal population. Compared with healthy controls, pediatric patients with multiple sclerosis exhibited significantly reduced volumes within the thalamus and the splenium of the corpus callosum and significant expansions in the ventricles. While T2-weighted lesion volume was correlated with reduced splenium volume, no correlation was found between T2-weighted lesion volume and reduced thalamic volume. Reduced volumes of the optic pathways, including that of the optic tracts and optic radiations, correlated with disease duration. Our results suggest that focal inflammatory lesions may play an important role in tract degeneration, including transsynaptic degeneration.

PIMD: 21393405

Voxelwise assessment of the regional distribution of damage in the brains of patients with multiple sclerosis and fatigue.

Fatigue affects up to 90% of patients with MS. We assessed the regional distribution of lesions and atrophy of the normal-appearing WM and GM in patients with RRMS with fatigue compared with HC and patients with similar characteristics, but without fatigue.From 14 patients with RRMS without fatigue, 10 with RRMS with fatigue, and 14 HC, we acquired brain dual-echo and high-resolution T1-weighted scans. Voxel-wise distributions of GM, WM damage, and T2 lesions were compared between patients with fatigued and nonfatigued MS by using SPM5 software. We report results at P < .05, FWE corrected.T2 lesion distribution and regional WM atrophy did not differ between patients with fatigued and nonfatigued MS. Compared with HC, patients with MS had significant WM atrophy in the posterior part of the corpus callosum and significant GM atrophy of the left superior frontal sulcus, left precentral gyrus, posterior cingulate cortex, right thalamus, and left middle frontal gyrus. No additional areas of atrophy were found in patients with nonfatigued MS compared with HC, whereas patients with fatigued MS also had atrophy of the left central sulcus. Atrophy in the left central sulcus and the precentral gyrus was more severe in patients with fatigued versus nonfatigued MS. In patients with MS, significant correlations were found between fatigue severity and GM atrophy in the left precentral gyrus (r = -0.73, P < .0001 uncorrected).Atrophy of the primary sensorimotor area is likely to contribute to MS-related fatigue.

PIMD: 21361672

Multimodal coherent anti-Stokes Raman scattering microscopy reveals microglia-associated myelin and axonal dysfunction in multiple sclerosis-like lesions in mice.

Myelin loss and axonal degeneration predominate in many neurological disorders; however, methods to visualize them simultaneously in live tissue are unavailable. We describe a new imaging strategy combining video rate reflectance and fluorescence confocal imaging with coherent anti-Stokes Raman scattering (CARS) microscopy tuned to CH(2) vibration of myelin lipids, applied in live tissue of animals with chronic experimental autoimmune encephalomyelitis (EAE). Our method allows monitoring over time of demyelination and neurodegeneration in brain slices with high spatial resolution and signal-to-noise ratio. Local areas of severe loss of lipid signal indicative of demyelination and loss of the reflectance signal from axons were seen in the corpus callosum and spinal cord of EAE animals. Even in myelinated areas of EAE mice, the intensity of myelin lipid signals is significantly reduced. Using heterozygous knock-in mice in which green fluorescent protein replaces the CX(3)CR1 coding sequence that labels central nervous system microglia, we find areas of activated microglia colocalized with areas of altered reflectance and CARS signals reflecting axonal injury and demyelination. Our data demonstrate the use of multimodal CARS microscopy for characterization of demyelinating and neurodegenerative pathology in a mouse model of multiple sclerosis, and further confirm the critical role of microglia in chronic inflammatory neurodegeneration.

PIMD: 21313900

Anatomical distribution of central nervous system plaques in multiple sclerosis: an Iranian experience.

Multiple Sclerosis (MS) begins most commonly in young adults and is characterized by multiple areas of Central Nervous System (CNS) white matter inflammation, demyelination and glial scarring. The most valuable laboratory aid for diagnosing MS is Magnetic Resonance Imaging (MRI). An advanced type of MRI that exploits molecular diffusion can detect acute and active lesions. Early diagnosis and onset of treatment help to hinder disease progression. The aim of this study was to compare the findings of conventional and Diffusion-Weighted (DW) MRI in assessing the cerebral lesions of MS patients. Thirty patients with clinically definite MS (mean age 32.76 +/- 8.79 years) and an age- and sex-matched control group of 30 healthy volunteers (mean age 32.75 +/- 9.23 years) were enrolled in this 12 month descriptive-prospective survey. Both groups were subjected to conventional and DW MRI and were compared in respect of the total number, morphology, location and the mean size of the intra-cerebral MS plaques. The sensitivities and specificities of both imaging methods in detecting these plaques were determined. The conventional method revealed significantly more plaques within the brain ($p < 0.05$) and showed more ovoid lesions. More lesions were detected by the conventional method in the periventricular area, centrum semiovale and corpus callosum. The minimum plaque size was significantly lower in the conventional method group. The sensitivity of both methods was 100%. The specificities of conventional and DW MRI were 86.6 and 96.6%, respectively, so DW MRI may detect lesions that are not obvious by routine methods.

PIMD: 21305597

Neural precursors exhibit distinctly different patterns of cell migration upon transplantation during either the acute or chronic phase of EAE: a serial MR imaging study.

As the complex pathogenesis of multiple sclerosis contributes to spatiotemporal variations in the trophic micromilieu of the central nervous system, the optimal intervention period for cell-replacement therapy must be systematically defined. We applied serial, 3D high-resolution magnetic resonance imaging to transplanted neural precursor cells (NPCs) labeled with superparamagnetic iron oxide nanoparticles and 5-bromo-2-deoxyuridine, and compared the migration pattern of NPCs in acute inflamed (n = 10) versus chronic demyelinated (n = 9) brains of mice induced with experimental allergic encephalomyelitis (EAE). Serial in vivo and ex-vivo 3D magnetic resonance imaging revealed that NPCs migrated 2.5 ± 1.3 mm along the corpus callosum in acute EAE. In chronic EAE, cell migration was slightly reduced (2.3 ± 1.3 mm) and only occurred in the lateral side of transplantation. Surprisingly, in 6/10 acute EAE brains, NPCs were found to migrate in a radial pattern along RECA-1(+) cortical blood vessels, in a pattern hitherto only reported for migrating glioblastoma cells. This striking radial biodistribution pattern was not detected in either chronic EAE or disease-free control brains. In both acute and chronic EAE brain, Iba1(+) microglia/macrophage number was significantly higher in central nervous system regions containing migrating NPCs. The existence of differential NPC migration patterns is an important consideration for implementing future translational studies in multiple sclerosis patients with variable disease.

PIMD: 21299379

Mesenchymal stem cells enhance the engraftment and myelinating ability of allogeneic oligodendrocyte progenitors in dysmyelinated mice.

Multiple sclerosis is an autoimmune disease characterized by demyelination and axonal loss throughout the central nervous system. No regenerative treatment exists for patients who fail to respond to conventional immunosuppressive and immunomodulating drugs. In this scenario, stem cell therapy poses as a rational approach for neurological regeneration. Transplantation of embryonic-derived oligodendrocyte progenitor cells (OPCs) has been shown to promote remyelination and ameliorate animal models of neurodegenerative diseases. However, its therapeutic application is limited due to potential transplant rejection. In multiple sclerosis, an added concern is that transplant rejection would be most pronounced at sites of previous lesions, exacerbating a hyperactive immune response which could prevent remyelination and precipitate additional demyelination. Routine systemic immunosuppression may not be sufficient to prevent transplant rejection-associated immune reactions in the cerebral microenvironment. Mesenchymal stem cells (MSCs), due to their homing properties and inherent immunosuppressive nature, are a promising tool for clinical application targeted toward immunosuppression at sites of injury. In this study, we used a co-transplantation strategy to investigate the effect of syngeneic MSCs on the survival and remyelination abilities of allogeneic OPCs in adult nonimmunosuppressed shiverer mice. At all time points examined, cotransplantation with MSCs increased OPC engraftment, migration, and maturation in myelinating oligodendrocytes, which produced widespread myelination in the host corpus callosum. In addition, MSCs reduced microglia activation and astrocytosis in the brain of transplanted animals as well as T-cell proliferation in vitro. These data suggest that combining the immunomodulatory and trophic properties of MSCs with the myelinating ability of OPCs might be a suitable strategy for promoting neurological regeneration in demyelinating diseases.

PIMD: 21248243

Neurobiological effects of sphingosine 1-phosphate receptor modulation in the cuprizone model.

Fingolimod (FTY720) is a sphingosine 1-phosphate (S1P) receptor modulator that regulates lymphocyte trafficking and exerts pleiotropic actions on oligodendrocytes (OLGs) and other neural cells. The purpose of this study was to investigate the role of S1P receptors in a non-T-cell model of demyelination, the cuprizone (cupr) model in C57BL/6 mice. Treatment with FTY720 (1 mg/kg) led to attenuated injury to OLGs, myelin, and axons in the corpus callosum (percentage of myelinated fibers was 44.7% in cupr-water and 63% in cupr-FTY720). Reactive astrogliosis and microgliosis were ameliorated when FTY720 was given from d 1, but astrogliosis was augmented when FTY720 was given from wk 4-9. FTY720 did not promote remyelination in this model. The protective effect of FTY720 was associated with decreased interleukin-1β and CCL2 transcripts in the corpus callosum, as well as altered S1P1 expression. Targeted deletion of S1P1 in OLG lineage cells did not lead to obvious clinical phenotype, but resulted in subtle abnormalities in myelin and an increased susceptibility to cupr-induced demyelination. We conclude that S1P receptors expressed by neuroglia are involved in regulating the response to injury, and CNS effects of FTY720 could contribute to its favorable therapeutic response in multiple sclerosis.

PIMD: 21248132

Genetically induced adult oligodendrocyte cell death is associated with poor myelin clearance, reduced remyelination, and axonal damage.

Loss of oligodendrocytes is a feature of many demyelinating diseases including multiple sclerosis. Here, we have established and characterized a novel model of genetically induced adult oligodendrocyte death. Specific primary loss of adult oligodendrocytes leads to a well defined and highly reproducible course of disease development that can be followed longitudinally by magnetic resonance imaging. Histological and ultrastructural analyses revealed progressive myelin vacuolation, in parallel to disease development that includes motor deficits, tremor, and ataxia. Myelin damage and clearance were associated with induction of oligodendrocyte precursor cell proliferation, albeit with some regional differences. Remyelination was present in the mildly affected corpus callosum. Consequences of acutely induced cell death of adult oligodendrocytes included secondary axonal damage. Microglia were activated in affected areas but without significant influx of B-cells, T-helper cells, or T-cytotoxic cells. Analysis of the model on a RAG-1 (recombination activating gene-1)-deficient background, lacking functional lymphocytes, did not change the observed disease and pathology compared with immune-competent mice. We conclude that this model provides the opportunity to study the consequences of adult oligodendrocyte death in the absence of primary axonal injury and reactive cells of the adaptive immune system. Our results indicate that if the blood-brain barrier is not disrupted, myelin debris is not removed efficiently, remyelination is impaired, and axonal integrity is compromised, likely as the result of myelin detachment. This model will allow the evaluation of strategies aimed at improving remyelination to foster axon protection.

PIMD: 21236446

Brain abnormalities in neuromyelitis optica.

Differentiating neuromyelitis optica (NMO) from multiple sclerosis (MS) is a real challenge in the clinical field. In the past, NMO (not MS), was inferred when abnormality was not detected in the brain magnetic resonance imaging (MRI). Recently, some studies have reported abnormalities in the brain MRIs of NMO, but only few among the Asian population. The aim of this study was to evaluate the frequency of brain MRI among Korean NMO patients and characterize findings that might be helpful to distinguish NMO from MS.Medical records, NMO-IgG, and brain MRI of 17 patients diagnosed with NMO by the revised diagnostic criteria of Wingerchuk et al. (2006) [6] from 2008 to 2010, were reviewed.11 out of 17 patients (64.7%) had abnormal MRI findings. More than two lesions were detected in most patients. The majority of patients with brain MRI abnormality showed nonspecific (5 patients) or atypical (6 patients) findings. Cerebral white matter was most frequently involved (58.8%). 3 patients (17.6%) involved corpus callosum, 4 (23.5%) with internal capsule, 2 (11.8%) with cerebellum, and 3 (17.6%) with brainstem. There were 5 (29.4%) patients who met the Paty et al. criteria (1988) [15] and 3 patients (35.3%) who met the multiple sclerosis (MS) spatial distribution diagnostic criteria of Barkhof et al. (1997) [14] in their brain MRI.Brain abnormalities have been frequently found among Korean NMO patients and the frequencies have been reported to be higher than that of Caucasians. Current MS spatial distribution criteria, such as Paty et al. (1988) [15] or Barkhof et al. (1997) [14], are not sufficient to discriminate NMO from MS in brain MRI findings. Our results will provide valuable information that would be useful in establishing future revising criteria for NMO.

PIMD: 21233178

11C-(R)-PK11195 PET imaging of microglial activation and response to minocycline in zymosan-treated rats.

We sought to advance methodology for studying microglial activation and putative therapeutic downregulation in response to minocycline by means of noninvasive in vivo imaging. A reproducible focal white matter lesion was used to reliably compare treatment conditions.The corpus callosum of female Sprague Dawley rats was injected with zymosan to promote microglial activation as confirmed by hematoxylin and eosin staining, (3)H-PK11195 autoradiography, and CD11b immunohistochemistry. A subset of subjects was treated systemically with minocycline to potentially alter microglial activation. Seven days after zymosan injection, subjects were imaged with PET using the radiotracer (11)C-(R)-PK11195. In vivo binding was evaluated using the distribution volume ratio (DVR) with respect to a reference region.At the lesion site, the observed (11)C-(R)-PK11195 DVR for each treatment was as follows: mean saline DVR ± SD, 1.17 ± 0.05 (n = 5); zymosan-only DVR, 1.96 ± 0.33 (n = 10); and zymosan with minocycline DVR, 1.58 ± 0.12 (n = 9). Therefore, compared with controls, zymosan increased binding (P = 0.0001, 2-tailed t test) and minocycline treatment reduced zymosan-induced binding by 46% (P = 0.004, 2-tailed t test).Zymosan-induced microglial activation and its response to minocycline can be quantitatively imaged in the rat brain using (11)C-(R)-PK11195 PET. The ability to detect a treatment effect in a focal white-matter lesion may be of use in studying therapies for multiple sclerosis (MS).

PIMD: 21220722

Longitudinal changes in diffusion tensor-based quantitative MRI in multiple sclerosis.

To estimate longitudinal changes in a quantitative whole-brain and tract-specific MRI study of multiple sclerosis (MS), with the intent of assessing the feasibility of this approach in clinical trials.A total of 78 individuals with MS underwent a median of 3 scans over 2 years. Diffusion tensor imaging indices, magnetization transfer ratio, and T2 relaxation time were analyzed in supratentorial brain, corpus callosum, optic radiations, and corticospinal tracts by atlas-based tractography. Linear mixed-effect models estimated annualized rates of change for each index, and sample size estimates for potential clinical trials were determined.There were significant changes over time in fractional anisotropy and perpendicular diffusivity in the supratentorial brain and corpus callosum, mean diffusivity in the supratentorial brain, and magnetization transfer ratio in all areas studied. Changes were most rapid in the corpus callosum, where fractional anisotropy decreased 1.7% per year, perpendicular diffusivity increased 1.2% per year, and magnetization transfer ratio decreased 0.9% per year. The T2 relaxation time changed more rapidly than diffusion tensor imaging indices and magnetization transfer ratio but had higher within-participant variability. Magnetization transfer ratio in the corpus callosum and supratentorial brain declined at an accelerated rate in progressive MS relative to relapsing-remitting MS. Power analysis yielded reasonable sample sizes (on the order of 40 participants per arm or fewer) for 1- or 2-year trials.Longitudinal changes in whole-brain and tract-specific diffusion tensor imaging indices and magnetization transfer ratio can be reliably quantified, suggesting that small clinical trials using these outcome measures are feasible.

PIMD: 21132325

Occurrence of neuronal dysfunction during the first 5 years of multiple sclerosis is associated with cognitive deterioration.

Brain neuronal injury is present in patients suffering from multiple sclerosis (MS) from the earliest stage of the disease; however, the functional counterpart of early neuronal injury is largely unknown. The goal of this study was to assess the potential impact of early neuronal dysfunction affecting white matter (WM), grey matter (GM), or the cerebellum on cognitive deterioration and/or EDSS progression during the first 5 years of MS. Magnetic resonance spectroscopic (MRS) examinations and neuropsychological assessments were performed in 23 patients included after the first clinical attack of MS and 24 healthy controls. The same protocol was performed in patients after a follow-up of 5 years. Metabolic neuronal function was assessed in WM (splenium of corpus callosum), GM (dorsal posterior cingulate cortex), and the cerebellum by evaluating N-acetylaspartate (NAA) levels. During follow-up, 39% of patients showed cognitive deterioration and 43% showed a deterioration in their EDSS. Patients with cognitive deterioration had greater NAA level reductions during follow-up in the cerebellum ($p = 0.003$) and WM ($p = 0.02$) compared to patients without cognitive deterioration. In addition, patients with cognitive deterioration had higher progression of T2 lesion load (T2LL) during the follow-up period compared to patients without cognitive deterioration ($p = 0.03$). No differences between patients with and without EDSS progression in terms of NAA levels or T2LL were observed. The present longitudinal study found evidence that, during the first 5 years of MS, cognitive deterioration is associated with the progression of neuronal dysfunction and tissue injury as assessed by MRS and T2LL, respectively.

PIMD: 21122007

Diffusion tensor imaging of corpus callosum integrity in multiple sclerosis: correlation with disease variables.

Corpus callosum (CC) is frequently involved in multiple sclerosis (MS). We aimed to investigate the relations between CC microstructure integrity as measured by diffusion tensor imaging (DTI) in relapsing-remitting MS patients with low neurological disability in comparison with age-matched healthy subjects and further to identify correlations between DTI-CC parameters and clinical variables of MS disease activity.CC volume was measured on 3.0T brain MRI by MS Analyze software. DTI metrics acquired along 31 independent directions were obtained and fractional anisotropy (FA), apparent diffusion coefficient (ADC), longitudinal (λ1) and transverse (λ 2, λ 3) diffusivities were measured in MS patients and healthy subjects. Disease activity was assessed by relapse rate and neurolgical disability by the Extended Disability Status Scale (EDSS).Thirty relapsing-remitting MS patients and 30 age- and sex-matched healthy subjects were studied. CC volume and DTI metrics differed significantly between MS patients and healthy subjects. In MS patients, all DTI parameters correlated with neurological disability. ADC, longitudinal and transverse diffusivity correlated with disease duration. ADC and the transverse diffusivity correlated with relapse rate.CC DTI parameters, especially ADC and transverse diffusivity correlated with disease variables especially with those associated with clinical activity.

PIMD: 21098009

Morphological and electrical properties of oligodendrocytes in the white matter of the corpus callosum and cerebellum.

In the central nervous system, electrical signals passing along nerve cells are speeded by cells called oligodendrocytes, which wrap the nerve cells with a fatty layer called myelin. This layer is important for rapid information processing, and is often lost in disease, causing mental or physical impairment in multiple sclerosis, stroke, cerebral palsy and spinal cord injury. The myelin speeds the information flow in two ways, by decreasing the capacitance of the nerve cell and by increasing its membrane resistance, but little is known about the latter aspect of myelin function. By recording electrically from oligodendrocytes and imaging their morphology we characterised the geometry and, for the first time, the resistance of myelin in the brain. This revealed differences between the properties of oligodendrocytes in two brain areas and established that the resistance of myelin is sufficiently high to prevent significant slowing of the nerve electrical signal by current leakage through the myelin.

PIMD: 21059507

Corpus callosum volume and interhemispheric transfer in multiple sclerosis.

The corpus callosum (CC) is frequently compromised in patients with multiple sclerosis (MS). Structural and functional measurements of the CC may be useful to monitor the progression of the disease. The aim of this pilot study was to determine if bimanual tactile temporal thresholds correlates with CC volume. A tactile temporal threshold is the longest temporal interval that separates the onsets of two tactile stimuli when they are judged by the observer as simultaneous. Judgments to bimanual stimulations require interhemispheric transfer via the CC.Thresholds were examined in MS patients and matched controls. Magnetic resonance (MR) images were acquired on a 3T MR system within 48 hours of clinical assessment and measurement of thresholds.Corpus callosum volume was assessed by using a semiautomatic livewire algorithm. The CC volume was smaller (by 21% on average, $p < 0.01$) and thresholds were higher (by 49% on average, $p < 0.03$) in MS patients when compared to controls. A significant correlation ($r = -0.66$, $p = 0.01$) between CC volume and thresholds emerged for the MS patients.Measuring treatment benefits of neuroprotective and repair therapies is a well recognized challenge in MS research. The overall findings of this study suggest that these measurements, which involve the transfer of information interhemispherically via the CC, may be promising outcome measures that warrant further scientific exploration to develop a model to measure recovery.

PIMD: 20859190

Is there evidence of brain white-matter abnormalities in obsessive-compulsive disorder?: a narrative review.

Although several studies have confirmed the occurrence of gray-matter abnormalities in obsessive-compulsive disorder (OCD), the literature on white matter in OCD is more limited. In this study, we reviewed the role of white-matter abnormalities in the pathophysiology of OCD.We reviewed the PubMed studies investigating white-matter integrity in patients with OCD between 1980 and 2010.Case studies of patients who developed obsessive-compulsive symptoms secondary to multiple sclerosis, cerebrovascular diseases, and paraneoplastic leucoencephalopathy and controlled studies of patients with OCD examined with neuroimaging techniques (eg, structural, diffusion, and spectroscopic magnetic resonance imaging) were all consistent with the existence of abnormalities in specific white-matter tracts (eg, internal capsule, cingulate bundle, and corpus callosum) of individuals with OCD.Our review emphasizes that the reported white-matter alterations in OCD complement the broader gray-matter abnormalities identified and may well suggest that OCD is associated with large-scale disruption in brain systems or networks, as opposed to being a consequence of disturbances in isolated brain regions.

PIMD: 20853437

Oligodendrocyte PTEN is required for myelin and axonal integrity, not remyelination.

Repair of myelin injury in multiple sclerosis may fail, resulting in chronic demyelination, axonal loss, and disease progression. As cellular pathways regulated by phosphatase and tensin homologue deleted on chromosome 10 (PTEN; eg, phosphatidylinositol-3-kinase [PI-3K]) have been reported to enhance axon regeneration and oligodendrocyte maturation, we investigated potentially beneficial effects of Pten loss of function in the oligodendrocyte lineage on remyelination.We characterized oligodendrocyte numbers and myelin sheath thickness in mice with conditional inactivation of Pten in oligodendrocytes, Olig2-cre, Pten(fl/fl) mice. Using a model of central nervous system demyelination, lysolecithin injection into the spinal cord white matter, we performed short- and long-term lesioning experiments and quantified oligodendrocyte maturation and myelin sheath thickness in remyelinating lesions.During development, we observed dramatic hypermyelination in the corpus callosum and spinal cord. Following white matter injury, however, there was no detectable improvement in remyelination. Moreover, we observed progressive myelin sheath abnormalities and massive axon degeneration in the fasciculus gracilis of mutant animals, as indicated by ultrastructure and expression of SMI-32, amyloid precursor protein, and caspase 6.These studies indicate adverse effects of chronic Pten inactivation (and by extension, activation PI-3K signaling) on myelinating oligodendrocytes and their axonal targets. We conclude that PTEN function in oligodendrocytes is required to regulate myelin thickness and preserve axon integrity. In contrast, PTEN is dispensable during myelin repair, and its inactivation confers no detectable benefit.

PIMD: 20844307

[AQP4 immunohistochemistry in neuromyelitis optica and multiple sclerosis: a neuropathological review].

We retrospectively analyzed and compared patterns of anti-aquaporin-4 (AQP4) immunoreactivity of autopsied brains of 2 patients with classical multiple sclerosis (MS) and 2 patients with neuromyelitis optica (NMO). Serological examination for NMO-IgG was not performed in all the cases. We confirmed that the expression of AQP4 is strongly inhibited in demyelinating lesions of NMO, accompanied by the loss of grial fibrillary acidic protein (GFAP) expression. The expression of AQP4 is preserved in MS lesions losing myelin basic protein (MBP) positivity. Therefore, AQP4 immunoreactivity may distinguish NMO from MS neuropathologically. NMO preferentially exhibited central lesions of the spinal cord with strongly necrotizing features and axonal injury. One NMO patient with oligoclonal band in the cerebrospinal fluid presented severe necrotizing lesions of the corpus callosum, cerebral white matter in addition to optic nerves and longitudinally extensive spinal cord lesions. Another patient with MS presented longitudinally extensive spinal cord lesions and a lesion in the medullary tegmentum in the floor of the fourth ventricle, which is reported to be one of the vulnerable lesions of NMO. We also reported a patient with NMO accompanied with Sjögren syndrome. These findings suggest that longitudinally extensive spinal cord lesions and medullary tegmentum lesion may be found in MS,and cerebral white matter lesion may be found in NMO. The distribution of lesions may overlap in MS and NMO although the immunoreactivity of AQP4 differs in these 2 conditions.

PIMD: 20833231

Remyelination after cuprizone induced demyelination is accelerated in mice deficient in the polysialic acid synthesizing enzyme St8siaIV.

Polysialic acid (PSA) is a carbohydrate polymer added post-translationally on the neural cell adhesion molecule (NCAM) affecting its adhesion properties. It has been suggested that the presence of PSA in demyelinated lesions in multiple sclerosis could prevent axon-glia interactions inhibiting spontaneous remyelination. The enzyme St8siaIV is one of the two polysialyltransferases responsible for PSA synthesis, and it is predominantly active during adult life. Here we treated 8-10-weeks old St8siaIV deficient and wild-type mice for 5 weeks with cuprizone, which is a reliable model for de- and remyelination in the corpus callosum and cortex. Developmental myelination of the St8siaIV knock-out mice was not disturbed and adult mice showed normal myelin protein expression. Demyelination did not differ between transgenic and wild-type mice but early myelin protein re-expression and thus remyelination were accelerated in St8siaIV knock-out mice during the first week after withdrawal of the toxin. This was mainly due to enhanced oligodendrocyte precursor cells (OPC) differentiation and to a lesser extent to OPC recruitment. These data are proof of principle that PSA expression interferes at least to some extent with remyelination in vivo.

PIMD: 20736006

Characterization of brain lesions in a mouse model of progressive multiple sclerosis.

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by damage to the neuronal myelin sheath, which results in different levels of muscle paralysis that can lead to neuronal death. In most MS mouse models, the neurologic damage mostly affects the spinal cord with limited damage to the brain, which cannot be monitored by magnetic resonance imaging (MRI) as used for humans. We show that immunization of non-obese diabetic (NOD) mice with myelin oligodendrocyte glycoprotein peptide 35-55 leads to the development of relapsing-remitting stages, evident from days 20 to 70, which then develops into a chronic progressive stage. This cycle is similar to MS stages found in humans. Brain MRI gadolinium-enhanced T1-weighted image analysis showed an increased blood-brain barrier permeability in brain gray and white matter specific to the corpus callosum, fimbria, and internal capsule as found in humans. MRI fractional anisotropy analysis showed demyelination and axonal damage in identical regions. Immunohistologic analysis supported the MRI data. No evidence of brain lesions was found in a common model of MS using C57BL/6 mice. We suggest that an increase in astrocyte toxicity in experimental autoimmune encephalomyelitis-induced NOD mice may be linked to brain lesion development. We suggest using NOD mice as a suitable model for studying MS using MRI methods toward future diagnostic and drug development.

PIMD: 20706041

Brain single photon emission computed tomography with Tc-99m MIBI or Tc-99m ECD in comparison to MRI in multiple sclerosis.

To evaluate whether or not brain single photon emission computed tomography (SPECT) with Tc-99m MIBI or Tc-99m ECD (ethyl cysteinate dimer) can detect any abnormality in patients with definite multiple sclerosis (MS). We then compared these values with the results of T1, T2, and fluid-attenuated inversion recovery in magnetic resonance imaging (MRI).A total of 16 patients with proved MS were enrolled in the study, and the MRI with and without gadolinium contrast and also brain SPECT with Tc-99m MIBI (8 cases) or Tc-99m ECD (8 other cases) were performed.MRI studies was performed in 16 patients (13 women and 3 men, aged 16-38 years) and an average of 10.47, 3.7, 5.3, 1.7, and 0.9 lesions was found in respect in periventricular white matter, juxtacortical white matter, corpus callosum, cerebellar peduncles, and brainstem, whereas brain SPECT with Tc-99m MIBI or Tc-99m ECD detected no abnormality. In addition, 6 cases had some degree of contrast enhancement.It seems that brain SPECT with Tc-99m MIBI or Tc-99m ECD would not improve this insufficiency. The small sizes of some plaques, particularly in chronic atrophic form of lesions, and the possibility of deeper anatomic positions of plaques can explain to some extent why the MS lesions were impossible to delineate on brain scan, although additional studies are needed.

PIMD: 20668697

Effects of fumaric acids on cuprizone induced central nervous system de- and remyelination in the mouse.

Fumaric acid esters (FAE) are a group of compounds which are currently under investigation as an oral treatment for relapsing-remitting multiple sclerosis. One of the suggested modes of action is the potential of FAE to exert a neuroprotective effect.We have investigated the impact of monomethylfumarate (MMF) and dimethylfumaric acid (DMF) on de- and remyelination using the toxic cuprizone model where the blood-brain-barrier remains intact and only scattered T-cells and peripheral macrophages are found in the central nervous system (CNS), thus excluding the influence of immunomodulatory effects on peripheral immune cells. FAE showed marginally accelerated remyelination in the corpus callosum compared to controls. However, we found no differences for demyelination and glial reactions in vivo and no cytoprotective effect on oligodendroglial cells in vitro. In contrast, DMF had a significant inhibitory effect on lipopolysaccharide (LPS) induced nitric oxide burst in microglia and induced apoptosis in peripheral blood mononuclear cells (PBMC).These results contribute to the understanding of the mechanism of action of fumaric acids. Our data suggest that fumarates have no or only little direct protective effects on oligodendrocytes in this toxic model and may act rather indirectly via the modulation of immune cells.

PIMD: 20607446

Glial amyloid precursor protein expression is restricted to astrocytes in an experimental toxic model of multiple sclerosis.

The amyloid precursor protein is rapidly induced in reactive glia in response to pathological stimuli and inflammation. In this study, we investigated its expression in an experimental multiple sclerosis animal model, the cuprizone mouse model which reveals massive myelin loss. Cuprizone intoxication for 5 weeks induced immense demyelination of the corpus callosum and resulted in hypertrophic and hyperplastic astrocytosis accompanied by microglia/macrophage invasion. Using double-immunofluorescence, real-time quantitative PCR and Western Blot, we observed that activated astrocytes are the main source of amyloid precursor protein during demyelination. In order to rule out astrocytes, in general, responding to inflammatory and toxic compounds by amyloid precursor protein expression, neonatal astroglia cultures were exposed to various stimuli. Under control conditions, astroglial amyloid precursor protein was only moderately expressed. None of the treatments had a significant effect on its expression in vitro. Our results suggest that amyloid precursor protein is specifically up-regulated under cuprizone-induced demyelination. It remains to be further elucidated whether amyloid precursor protein-positive astrocytes are directly implicated in the pathological mechanism of demyelination.

PIMD: 20535036

Rostrocaudal analysis of corpus callosum demyelination and axon damage across disease stages refines diffusion tensor imaging correlations with pathological features.

Noninvasive assessment of the progression of axon damage is important for evaluating disease progression and developing neuroprotective interventions in multiple sclerosis patients. We examined the cellular responses correlated with diffusion tensor imaging-derived axial (lambda(parallel)) and radial (lambda(perpendicular)) diffusivity values throughout acute (4 weeks) and chronic (12 weeks) stages of demyelination and after 6 weeks of recovery using the cuprizone demyelination of the corpus callosum model in C57BL/6 and Thy1-YFP-16 mice. The rostrocaudal progression of pathological alterations in the corpus callosum enabled spatially and temporally defined correlations of pathological features with diffusion tensor imaging measurements. During acute demyelination, microglial/macrophage activation was most extensive and axons exhibited swellings, neurofilament dephosphorylation, and reduced diameters. Axial diffusivity values decreased in the acute phase but did not correlate with axonal atrophy during chronic demyelination. In contrast, radial diffusivity increased with the progression of demyelination but did not correlate with myelin loss or astrogliosis. Unlike other animal models with progressive neurodegeneration and axon loss, the acute axon damage did not progress to discontinuity or loss of axons even after a period of chronic demyelination. Correlations of reversible axon pathology, demyelination, microglia/macrophage activation, and astrogliosis with regional axial and radial diffusivity measurements will facilitate the clinical application of diffusion tensor imaging in multiple sclerosis patients.

PIMD: 20534485

CXCR4 promotes differentiation of oligodendrocyte progenitors and remyelination.

Multiple sclerosis is a neurodegenerative disease characterized by episodes of autoimmune attack of oligodendrocytes leading to demyelination and progressive functional deficits. Because many patients exhibit functional recovery in between demyelinating episodes, understanding mechanisms responsible for repair of damaged myelin is critical for developing therapies that promote remyelination and prevent disease progression. The chemokine CXCL12 is a developmental molecule known to orchestrate the migration, proliferation, and differentiation of neuronal precursor cells within the developing CNS. Although studies suggest a role for CXCL12 in oligodendroglia ontogeny in vitro, no studies have investigated the role of CXCL12 in remyelination in vivo in the adult CNS. Using an experimental murine model of demyelination mediated by the copper chelator cuprizone, we evaluated the expression of CXCL12 and its receptor, CXCR4, within the demyelinating and remyelinating corpus callosum (CC). CXCL12 was significantly up-regulated within activated astrocytes and microglia in the CC during demyelination, as were numbers of CXCR4+NG2+ oligodendrocyte precursor cells (OPCs). Loss of CXCR4 signaling via either pharmacological blockade or in vivo RNA silencing led to decreased OPCs maturation and failure to remyelinate. These data indicate that CXCR4 activation, by promoting the differentiation of OPCs into oligodendrocytes, is critical for remyelination of the injured adult CNS.

PIMD: 20512905

Correlation of cognitive dysfunction and diffusion tensor MRI measures in patients with mild and moderate multiple sclerosis.

To compare the diffusion tensor imaging (DTI) measures of multiple sclerosis (MS) patients and healthy subjects in every brain voxel and to correlate them with Paced Auditory Serial Addition Test (PASAT) scores.Fractional anisotropy (FA), and mean, longitudinal, and transverse diffusivity are compared between control subjects and MS patients, which were subdivided as mildly and moderately impaired. In addition, PASAT scores are correlated for both MS groups with the diffusion measures. An optimized voxel based analysis (VBA) method, in terms of coregistration, atlas construction, and image smoothing, was thereby used.Diffusion differences between the control subjects and the patients with MS were found in the corpus callosum, inferior longitudinal fasciculus, cortico spinal tracts, forceps major, superior longitudinal fasciculus, and cingulum. In addition, we observed significant correlations of the FA and PASAT scores in the left inferior longitudinal fasciculus, the forceps minor, the capsula interna and externa, the genu of the corpus callosum, the left cingulum, the superior longitudinal fasciculus, and the corona radiata.Diffusion differences were observed between the mildly impaired MS patients and control subjects. In addition, different diffusion measures correlated with PASAT scores for cognitive decline in parietal, frontal, as well as temporal white matter (WM) regions.

PIMD: 20512899

Intercenter differences in diffusion tensor MRI acquisition.

To assess the effect on diffusion tensor (DT) magnetic resonance imaging (MRI) of acquiring data with different scanners.Forty-four healthy controls and 36 multiple sclerosis patients with low disability were studied using eight MR scanners with acquisition protocols that were as close to a standard protocol as possible. Between 7 and 13 subjects were studied in each center. Region-of-interest (ROI) and histogram-based analyses of fractional anisotropy (FA), axial (D(ax)), radial (D(rad)), and mean diffusivity (MD) were performed. The influence of variables such as the acquisition center and the control/patient group was determined with an analysis of variance (ANOVA) test.The patient/control group explained approximately 25% of data variability of FA and D(rad) from midsagittal corpus callosum (CC) ROIs. Global FA, MD, and D(rad) in the white matter differentiated patients from controls, but with lower discriminatory power than for the CC. In the gray matter, MD discriminated patients from controls (30% of variability explained by group vs. 17% by center).Significant variability of DT-MRI data can be attributed to the acquisition center, even when a standardized protocol is used. The use of appropriate segmentation methods and statistical models allows DT-derived metrics to differentiate patients from healthy controls.

PIMD: 20404306

Default-mode network dysfunction and cognitive impairment in progressive MS.

This study explores default-mode network (DMN) abnormalities in patients with secondary progressive (SP) and primary progressive (PP) multiple sclerosis (MS) and whether such abnormalities correlate with cognitive impairment and damage to selected white matter (WM) fiber bundles, quantified using diffusion tensor (DT) MRI tractography.Resting state (RS) functional MRI and DT MRI data were acquired from 33 patients with SPMS, 24 patients with PPMS, and 24 controls. Independent component analysis (ICA) was used to identify the DMN. SPM5 was used to assess within- and between-group activations.Between-group differences in DMN activity were found in the left medial prefrontal cortex (mPFC), left precentral gyrus (PcG), and anterior cingulate cortex (ACC). Compared to controls, patients with SPMS had reduced activity in the mPFC ($p = 0.01$) and PcG ($p = 0.02$), while patients with PPMS had reduced activity in the PcG ($p = 0.008$) and the ACC ($p = 0.002$). Compared to patients with PPMS, patients with SPMS had increased ACC activity ($p = 0.04$). Reduction of RS activity in the ACC was more pronounced in cognitively impaired vs cognitively preserved patients with MS ($p = 0.02$). In patients with MS, DMN abnormalities correlated with the PASAT and word list test scores (r values ranging from 0.35 to 0.45) and DT MRI changes in the corpus callosum and the cingulum (r values ranging from 0.82 to 0.87).These results suggest that a dysfunction of the anterior components of the default-mode network may be among the factors responsible for the accumulation of cognitive deficits in patients with progressive multiple sclerosis.

PIMD: 20347981

17beta-estradiol protects male mice from cuprizone-induced demyelination and oligodendrocyte loss.

In addition to regulating reproductive functions in the brain and periphery, estrogen has tropic and neuroprotective functions in the central nervous system (CNS). Estrogen administration has been demonstrated to provide protection in several animal models of CNS disorders, including stroke, brain injury, epilepsy, Parkinson's disease, Alzheimer's disease, age-related cognitive decline and multiple sclerosis. Here, we use a model of toxin-induced oligodendrocyte death which results in demyelination, reactive gliosis, recruitment of oligodendrocyte precursor cells and subsequent remyelination to study the potential benefit of 17beta-estradiol (E2) administration in male mice. The results indicate that E2 partially ameliorates loss of oligodendrocytes and demyelination in the corpus callosum. This protection is accompanied by a delay in microglia accumulation as well as reduced mRNA expression of the pro-inflammatory cytokine, tumor necrosis factor alpha (TNFalpha), and insulin-like growth factor-1 (IGF-1). E2 did not significantly alter the accumulation of astrocytes or oligodendrocyte precursor cells, or remyelination. These data obtained from a toxin-induced, T cell-independent model using male mice provide an expanded view of the beneficial effects of estrogen on oligodendrocyte and myelin preservation.

PIMD: 20345920

Structural and functional magnetic resonance imaging correlates of motor network dysfunction in primary progressive multiple sclerosis.

We combined functional magnetic resonance imaging (fMRI) and diffusion tensor tractography to investigate the functional and structural substrates of motor network dysfunction in patients with primary progressive multiple sclerosis (PPMS). In 15 right-handed PPMS patients and 15 age-matched healthy controls, we acquired diffusion tensor magnetic resonance imaging and fMRI during the performance of a simple motor task. Tractography was used to calculate diffusion tensor-derived measures of the corpus callosum, the corticospinal tract, the optic radiation, the fronto-occipital fasciculus, and the inferior longitudinal fasciculus. Analyses of fMRI activations and functional connectivity were performed using statistical parametric mapping (cluster threshold of $P = 0.001$, and extent cluster threshold of 10 voxels for comparison of activations; $P < 0.05$, family-wise error corrected for functional connectivity). As compared with controls, PPMS patients had more significant activations of the left postcentral gyrus, left secondary sensorimotor area, left parahippocampal gyrus, left cerebellum, right primary sensorimotor cortex (SMC), right basal ganglia, right insula, right cingulum, and cuneus bilaterally. As compared with PPMS patients, controls had increased functional connectivity between the left primary SMC and the ipsilateral inferior frontal gyrus. Conversely, PPMS patients showed increased functional connectivity between the left primary SMC and the right cuneus. Moderate correlations were found between functional activations and damage to the tracts studied (r-values between 0.82 and 0.84; $P < 0.001$). These results suggest that, as compared with healthy controls, PPMS patients show increased activations and abnormal functional connectivity measures in several areas of the sensorimotor network. Such changes are correlated with the structural damage to the white matter fiber bundles connecting these regions.

PIMD: 20336657

Structural integrity of callosal midbody influences intermanual transfer in a motor reaction-time task.

Training one hand on a motor task results in performance improvements in the other hand, also when stimuli are randomly presented (nonspecific transfer). Corpus callosum (CC) is the main structure involved in interhemispheric information transfer; CC pathology occurs in patients with multiple sclerosis (PwMS) and is related to altered performance of tasks requiring interhemispheric transfer of sensorimotor information. To investigate the role of CC in nonspecific transfer during a pure motor reaction-time task, we combined motor behavior with diffusion tensor imaging analysis in PwMS. Twenty-two PwMS and 10 controls, all right-handed, were asked to respond to random stimuli with appropriate finger opposition movements with the right (learning) and then the left (transfer) hand. PwMS were able to improve motor performance reducing response times with practice with a trend similar to controls and preserved the ability to transfer the acquired motor information from the learning to the transfer hand. A higher variability in the transfer process, indicated by a significantly larger standard deviation of mean nonspecific transfer, was found in the PwMS group with respect to the control group, suggesting the presence of subtle impairments in interhemispheric communication in some patients. Then, we correlated the amount of nonspecific transfer with mean fractional anisotropy (FA) values, indicative of microstructural damage, obtained in five CC subregions identified on PwMS's FA maps. A significant correlation was found only in the subregion including posterior midbody (Pearson's r = 0.74, P = 0.003), which thus seems to be essential for the interhemispheric transfer of information related to pure sensorimotor tasks.

PIMD: 20198382

Corpus callosum index and long-term disability in multiple sclerosis patients.

Prediction of long-term disability in patients with multiple sclerosis (MS) is essential. Magnetic resonance imaging (MRI) measurement of brain volume may be of predictive value but sophisticated MRI techniques are often inaccessible in clinical practice. The corpus callosum index (CCI) is a normalized measurement that reflects changes of brain volume. We investigated medical records and 533 MRI scans at diagnosis and during clinical follow-up of 169 MS patients (mean age 42 +/- 11 years, 86% relapsing-remitting MS, time since first relapse 11 +/- 9 years). CCI at diagnosis was 0.345 +/- 0.04 and correlated with duration of disease ($p = 0.002$; $r = -0.234$) and expanded disability status scale (EDSS) score at diagnosis ($r = -0.428$; $p < 0.001$). Linear regression analyses identified age, duration of disease, relapse rate and EDSS at diagnosis as independent predictors for disability after mean of 7.1 years (Nagelkerkes' R:0.56). Annual CCI decrease was 0.01 +/- 0.02 (annual tissue loss: 1.3%). In secondary progressive MS patients, CCI decrease was double compared to that in relapsing-remitting MS patients ($p = 0.04$). There was a trend of greater CCI decrease in untreated patients compared to those who received disease modifying drugs ($p = 0.2$). CCI is an easy to use MRI marker for estimating brain atrophy in patients with MS. Brain atrophy as measured with CCI was associated with disability progression but it was not an independent predictor of long-term disability.

PIMD: 20154684

CXCR2-positive neutrophils are essential for cuprizone-induced demyelination: relevance to multiple sclerosis.

Multiple sclerosis is an inflammatory demyelinating disorder of the CNS. Recent studies have suggested diverse mechanisms as underlying demyelination, including a subset of lesions induced by an interaction between metabolic insult to oligodendrocytes and inflammatory mediators. For mice of susceptible strains, cuprizone feeding results in oligodendrocyte cell loss and demyelination of the corpus callosum. Remyelination ensues and has been extensively studied. Cuprizone-induced demyelination remains incompletely characterized. We found that mice lacking the type 2 CXC chemokine receptor (CXCR2) were relatively resistant to cuprizone-induced demyelination and that circulating CXCR2-positive neutrophils were important for cuprizone-induced demyelination. Our findings support a two-hit process of cuprizone-induced demyelination, supporting the idea that multiple sclerosis pathogenesis features extensive oligodendrocyte cell loss. These data suggest that cuprizone-induced demyelination is useful for modeling certain aspects of multiple sclerosis pathogenesis.

PIMD: 20142309

MRI of the corpus callosum in multiple sclerosis: association with disability.

Inflammatory demyelination and axon damage in the corpus callosum are prominent features of multiple sclerosis (MS) and may partially account for impaired performance on complex tasks. The objective of this article was to characterize quantitative callosal MRI abnormalities and their association with disability. In 69 participants with MS and 29 healthy volunteers, lesional and extralesional callosal MRI indices were estimated via diffusion tensor tractography. expanded disability status scale (EDSS) and MS functional composite (MSFC) scores were recorded in 53 of the participants with MS. All tested callosal MRI indices were diffusely abnormal in MS. EDSS score was correlated only with age (r = 0.51). Scores on the overall MSFC and its paced serial auditory addition test (PASAT) and 9-hole peg test components were correlated with callosal fractional anisotropy (r = 0.27, 0.35, and 0.31, respectively) and perpendicular diffusivity (r = -0.29, -0.30, and -0.31) but not with overall callosal volume or callosal lesion volume; the PASAT score was more weakly correlated with callosal magnetization-transfer ratio (r = 0.21). Anterior callosal abnormalities were associated with impaired PASAT performance and posterior abnormalities with slow performance on the 9-hole peg test. In conclusion, abnormalities in the corpus callosum can be assessed with quantitative MRI and are associated with cognitive and complex upper-extremity dysfunction in MS.

PIMD: 20108225

Spatiotemporal distribution pattern of white matter lesion volumes and their association with regional grey matter volume reductions in relapsing-remitting multiple sclerosis.

The association of white matter (WM) lesions and grey matter (GM) atrophy is a feature in relapsing-remitting multiple sclerosis (RRMS). The spatiotemporal distribution pattern of WM lesions, their relations to regional GM changes and the underlying dynamics are unclear. Here we combined parametric and non-parametric voxel-based morphometry (VBM) to clarify these issues. MRI data from RRMS patients with progressive (PLV, n = 45) and non-progressive WM lesion volumes (NPLV, n = 44) followed up for 12 months were analysed. Cross-sectionally, the spatial WM lesion distribution was compared using lesion probability maps (LPMs). Longitudinally, WM lesions and GM volumes were studied using FSL-VBM and SPM5-VBM, respectively. WM lesions clustered around the lateral ventricles and in the centrum semiovale with a more widespread pattern in the PLV than in the NPLV group. The maximum local probabilities were similar in both groups and higher for T2 lesions (PLV: 27%, NPLV: 25%) than for T1 lesions (PLV: 15%, NPLV 14%). Significant WM lesion changes accompanied by cortical GM volume reductions occurred in the corpus callosum and optic radiations (P = 0.01 corrected), and more liberally tested (uncorrected P < 0.01) in the inferior fronto-occipital and longitudinal fasciculi, and corona radiata in the PLV group. Not any WM or GM changes were found in the NPLV group. In the PLV group, WM lesion distribution and development in fibres, was associated with regional GM volume loss. The different spatiotemporal distribution patterns of patients with progressive compared to patients with non-progressive WM lesions suggest differences in the dynamics of pathogenesis.

PIMD: 20099343

Relationships of brain white matter microstructure with clinical and MR measures in relapsing-remitting multiple sclerosis.

To assess the relationships of microstructural damage in the cerebral white matter (WM), as measured by diffusion tensor imaging (DTI), with clinical parameters and magnetic resonance imaging (MRI) measures of focal tissue damage in patients with multiple sclerosis (MS).Forty-five relapsing-remitting (RR) MS patients (12 male, 33 female; median age = 29 years, Expanded Disability Status Scale (EDSS) = 1.5, disease duration = 3 years) were studied. T2-lesion masks were created and voxelwise DTI analyses performed with Tract-Based Spatial Statistics (TBSS).T2-lesion volume (T2-LV) was significantly ($P < 0.05$, corrected) correlated with fractional anisotropy (FA) in both lesions and normal-appearing WM (NAWM). Relationships ($P = 0.08$, corrected) between increasing EDSS score and decreasing FA were found in the splenium of the corpus callosum (sCC) and along the pyramidal tract (PY). All FA associations were driven by changes in the perpendicular (to primary tract direction) diffusivity. No significant global and voxelwise FA changes were found over a 2-year follow-up.FA changes related to clinical disability in RR-MS patients with minor clinical disability are localized to specific WM tracts such as the sCC and PY and are driven by changes in perpendicular diffusivity both within lesions and NAWM. Longitudinal DTI measurements do not seem able to chart the early disease course in the WM of MS patients.

PIMD: 20093525

Functional and structural connectivity of the motor network in pediatric and adult-onset relapsing-remitting multiple sclerosis.

To elucidate the factors associated with the preservation of function in relapsing-remitting (RR) multiple sclerosis (MS) by investigating effective connectivity changes of the sensorimotor network in pediatric RR MS patients in comparison with adult patients with either clinically isolated syndromes (CIS) suggestive of MS or RR MS and in adult healthy control subjects by using functional magnetic resonance imaging (MR) imaging and a dynamic causal model approach and to assess the correlation between effective connectivity changes and structural damage to the corpus callosum and the corticospinal tracts (CSTs).The study was conducted with institutional review board approval. Written informed consent was obtained from each participant. Dual-echo, diffusion-tensor, and functional MR images were acquired from 17 pediatric RR MS patients, 16 adult patients with CIS, 14 adult RR MS patients, and 10 age-matched pediatric healthy control subjects during a simple motor task. Whole-brain, corpus callosum, and CST T2 lesion loads, as well as corpus callosum and CST diffusivity measures were determined. Functional MR imaging data were analyzed by using statistical parametric mapping.Coefficients of effective connectivity of the sensorimotor network were similar in control subjects and pediatric MS patients. In adult patients with CIS and even more evidently in those with RR MS, an increase of intra- and interhemispheric strengths of coefficients of effective connectivity was found (P = .05-.008). The increases in such coefficients were correlated with corpus callosum and CST damage, in terms of T2 lesion load and diffusion-tensor MR imaging quantities (r = -0.34 to 0.40).The preservation of brain adaptive properties might explain the favorable medium-term clinical outcome of pediatric MS patients. The progressive recruitment of cortical networks over time in patients with the adult RR forms of the disease might result in a loss of their plastic reservoir, thus possibly contributing to subsequent disease evolution.

PIMD: 20069121

DTI parameter optimisation for acquisition at 1.5T: SNR analysis and clinical application.

Magnetic Resonance (MR) diffusion tensor imaging (DTI) is able to quantify in vivo tissue microstructure properties and to detect disease related pathology of the central nervous system. Nevertheless, DTI is limited by low spatial resolution associated with its low signal-to-noise-ratio (SNR).The aim is to select a DTI sequence for brain clinical studies, optimizing SNR and resolution.We applied 6 methods for SNR computation in 26 DTI sequences with different parameters using 4 healthy volunteers (HV). We choosed two DTI sequences for their high SNR, they differed by voxel size and b-value. Subsequently, the two selected sequences were acquired from 30 multiple sclerosis (MS) patients with different disability and lesion load and 18 age matched HV. We observed high concordance between mean diffusivity (MD) and fractional anysotropy (FA), nonetheless the DTI sequence with smaller voxel size displayed a better correlation with disease progression, despite a slightly lower SNR. The reliability of corpus callosum (CC) fiber tracking with the chosen DTI sequences was also tested.The sensitivity of DTI-derived indices to MS-related tissue abnormalities indicates that the optimized sequence may be a powerful tool in studies aimed at monitoring the disease course and severity.

PIMD: 20061078

Brain MRI findings in long-standing and disabling multiple sclerosis in 84 patients.

To look for cerebral white matter MRI changes in patients with long-standing and disabling MS.We analyzed retrospectively brain MRIs (performed 10 or more years after symptom onset) of patients with MS diagnosis and expanded disability status scale of 6 or more. The following parameters were analyzed: total number of brain T2 hyperintensities; number of brainstem, cerebellar, corpus callosum, basal ganglia, and juxtacortical T2 hyperintensities; diffuse leukoencephalopathy score; total number of T1 hypointensities.Eighty-four patients were included. The mean time between symptom onset and MRI was 20.2 years. Eight percent had less than 9 cerebral T2 hyperintensities. Posterior fossa, juxtacortical, and corpus callosum T2 hyperintensities, and T1 hypointensities lacked in respectively 19%, 12%, 47%, and 8%. Overall, normal MRI was not seen, 6% had abnormal MRI but did not meet Barkhof's criteria, and the remaining 94% had MRI abnormalities fulfilling Barkhof's criteria. Moderate or severe diffuse leukoencephalopathy was seen in 69%. Extensive diffuse leukoencephalopathy predominant to nodular lesions was seen in 5%.Despite long-standing and disabling MS, typical MRI abnormalities lacked in a minority of patients, and 6% did not fulfil Barkhof's criteria. The majority showed moderate or severe diffuse leukoencephalopathy.

PIMD: 20019140

Clinically isolated syndrome suggestive of multiple sclerosis: voxelwise regional investigation of white and gray matter.

To quantify white matter (WM) and gray matter (GM) damage in patients who presented with clinically isolated syndrome (CIS), which is suggestive of multiple sclerosis (MS), by combining volume-based morphometry (VBM) and tract-based spatial statistics (TBSS).This prospective HIPAA-compliant study was approved by the institutional review board. Written informed consent was obtained from all participants. In this study, 34 consecutive patients (21 women, 13 men; mean age, 31.7 years +/- 7.7 [standard deviation]) who presented with CIS were recruited. The magnetic resonance (MR) examination included dual-echo fast spin-echo, three-dimensional T1, and diffusion-tensor imaging. Sixteen matched healthy volunteers served as control subjects. T2 lesion volumes were assessed with a semiautomatic technique. VBM and TBSS were used for the GM and WM analyses, respectively, to compare regional GM volumes and fractional anisotropy (FA) values in the two groups.TBSS analysis revealed a pattern of diffuse FA reductions in patients with CIS at the cluster level ($P < .05$). Regions of decreased FA involved most of the WM pathways, including the corticospinal tracts, corpus callosum, and superior and inferior longitudinal fasciculi. There were no significant differences between the two groups in terms of global GM, WM, or cerebrospinal fluid volume or in terms of regional GM volume.Diffuse WM damage not accompanied by any change in GM or WM volume is observed in patients with CIS. This suggests that WM involvement plays a relevant role in the early phases of MS. Subsequently detected GM damage may be secondary to WM alterations.

PIMD: 20016084

Transplanted neural precursors enhance host brain-derived myelin regeneration.

In multiple sclerosis lesions resident oligodendrocyte progenitor cells (OPCs) are present, but fail to remyelinate. In the current study we examined whether neural precursor cell (NPC) transplantation can facilitate host brain-derived remyelination. We used the chronic cuprizone-induced demyelination model in aged mice, in which slow remyelination follows cuprizone removal. NPCs were transplanted to the lateral ventricles (intracerebroventricular) of cuprizone-induced demyelinated brains. In this experimental setup, transplanted cells remained mostly in the periventricular area in an undifferentiated state. The extent of demyelination, remyelination, and proliferation of host brain regenerative cell population were examined at 1 week posttransplantation in the splenium of the corpus callosum, which was devoid of any transplanted cells. Transplantation of NPCs, but not of control, human embryonic kidney cells, significantly enhanced remyelination compared with sham-operated mice. Remyelination was performed exclusively by host brain OPCs. The proregenerative effect of transplanted NPCs was related to an increase in the proliferation of host brain OPCs. To examine the mechanism that underlies the proregenerative effect of NPCs in vitro, we used an NPC-OPC coculture system. These experiments indicated that NPCs induced the proliferation of OPCs and facilitated their differentiation into mature oligodendrocytes. The mitogenic effect of NPCs was mediated by platelet-derived growth factor-AA and fibroblast growth factor-2. In conclusion, NPC transplantation enhances host-derived myelin regeneration following chronic demyelination. This trophic effect may stimulate resident OPCs to overcome the remyelination failure in multiple sclerosis.

PIMD: 19963782

Atlas-based vs. individual-based deterministic tractography of corpus callosum in multiple sclerosis.

Diffusion tensor (DT) magnetic resonance imaging is able to quantify tissue microstructure properties and to detect pathological changes even in the normal appearing tissues. DT sequence parameters which provide optimal SNR and minimum acquisition time, and an individual-based tractography post-processing allowed corpus callosum tractography even in multiple sclerosis (MS) patients also with no need of a-priori atlas. In this preliminary study, we were able to obtain reliable individual-based tractography in 28/30 MS patients. DT-derived indices computed in tracks obtained with individual-based tractography were able to differentiate healthy volunteers from MS patients better than the same indices computed with the atlas method. This indicates that such an optimized sequence may be a reliable tool to be used in future MS studies.

PIMD: 19949029

Callosal lesion predicts future attacks after clinically isolated syndrome.

Current MRI criteria can help predict a second attack after a clinically isolated syndrome (CIS). Given the known association between corpus callosum lesions (CC) and multiple sclerosis (MS), such lesions on MRI could provide additional predictive information. This study assessed whether the presence of CC lesion on MRI could, next to the modified Barkhof criteria, further enhance prediction of conversion from CIS to MS.Follow-up study of 158 patients with CIS who underwent MRI after CIS was performed. MRI were scored for the Barkhof criteria and CC lesion. Patients were classified as having MS according to Poser criteria. Cox regression models were used for the time to conversion from CIS to MS.The Barkhof criteria and CC lesion were strongly associated with conversion to MS with hazard ratios (HR), respectively, of 2.6 (95% confidence interval [CI] 1.5-4.3) and 2.7 (95% CI 1.6-4.5). The HRs of CC lesion adjusted for the Barkhof criteria and the Barkhof criteria adjusted for CC lesion were similar (HRs 1.8, not significant). The combined prediction of the Barkhof criteria and CC lesion was 3.3 (95% CI 1.9-5.7). Patients not fulfilling the Barkhof criteria had a fourfold increased risk of MS (HR 3.8, 95% CI 1.5-9.3) when they had a lesion in the CC.Corpus callosum (CC) lesion and the Barkhof criteria both predicted conversion to multiple sclerosis (MS). When both variables were combined, the association was stronger. The assessment of CC lesion may be a useful additional tool for predicting conversion to MS in patients with clinically isolated syndrome.

PIMD: 19944769

Automated vs. conventional tractography in multiple sclerosis: variability and correlation with disability.

Diffusion-tensor-imaging fiber tractography enables interrogation of brain white matter tracts that subserve different functions. However, tract reconstruction can be labor and time intensive and can yield variable results that may reduce the power to link imaging abnormalities with disability. Automated segmentation of these tracts would help make tract-specific imaging clinically useful, but implementation of such segmentation is problematic in the presence of diseases that alter brain structure. In this work, we investigated an automated tract-probability-mapping scheme and applied it to multiple sclerosis, comparing the results to those derived from conventional tractography. We found that the automated method has consistently lower scan-rescan variability (typically 0.7-1.5% vs. up to 3% for conventional tractography) and avoids problems related to tractography failures within and around lesions. In the corpus callosum, optic radiation, and corticospinal tract, tract-specific MRI indices calculated by the two methods were moderately to strongly correlated, though systematic, tract-specific differences were present. In these tracts, the two methods also yielded similar correlation coefficients relating tract-specific MRI indices to clinical disability scores. In the optic tract, the automated method failed. With judicious application, therefore, the automated method may be useful for studies that investigate the relationship between imaging findings and clinical outcomes in disease.

PIMD: 19928690

[A case report of primary central nervous system lymphoma preceded by cerebral and cerebellar lesion diminishing spontaneously: consideration of two brain biopsy at the onset and after two years].

A 57-year-old man suffered a generalized seizure. Brain MRI showed a Gadolinium (Gd) enhanced lesion with massive edema in the left frontal lobe. He received in a brain biopsy a diagnosis of ganglioglioma, probable. After two weeks from the biopsy, brain MRI showed spontaneous remmision of the lesion. Eighteen months after his seizure, a follow-up brain MRI showed a new lesion in the left cerebellar peduncle. However, the lesion also improved spontaneously. After 2 years from the onset, a follow-up examination showed a new lesion in the corpus callosum. At that time even though high dose corticosteroid was given with the diagnosis of multiple sclerosis, the lesion enlarged progressively and uveitis occurred at the same time. He received in the second biopsy a diagnosis of diffuse large B cell lymphoma We report a case of primary central nervous system lymphoma preceded by cerebral and cerebellar lesion diminishing spontaneously, with consideration of two brain biopsy at the onset and after two years.

PIMD: 19919787

[Skew deviation. Strabismological diagnosis and treatment alternatives].

We undertook this study to analyze diagnostic and treatment alternatives in patients with skew deviation (SD).This is a prospective, observational and longitudinal study of patients with SD. The study took place in a third-level medical center during the period from September 2007 to May 2008. Strabismological exploration, multidisciplinary diagnosis and treatment alternatives were analyzed.Ten patients presenting SD were studied. Diagnoses were multiple sclerosis, arteriovenous malformation, epilepsy, hydrocephalus, ischemic encephalopathy, cortical atrophy, hypoplasia of corpus callosum and thalamic hemorrhage. Psychomotor retardation was present in 80%. Other diagnoses were Cogan apraxia, Parinaud syndrome, see-saw nystagmus, Foville syndrome, and hemiplegic alterations. Related strabismuses were exotropia (5), esotropia (3), hypertropia (2), and dissociated vertical deviation (1). Lesions of II, III and VII cranial nerves were found.Complete strabological study allows a better diagnosis of the lesion and consequently relapsing disease in order to achieve a better treatment according to each patient. Optical rehabilitation and botulinum applications are especially indicated.

PIMD: 19853662

In toxic demyelination oligodendroglial cell death occurs early and is FAS independent.

Oligodendroglial cell death is a frequent phenomenon of many neurological diseases, e.g. in demyelinating diseases such as multiple sclerosis (MS). The underlying mechanisms are largely unknown. Here, we demonstrate that in the toxic demyelination cuprizone model, oligodendroglial cell death and downregulation of myelin genes start days after initiation of the cuprizone diet and weeks before demyelination is obvious. In early - but not in later - stages, dying oligodendrocytes express activated caspase 3, suggesting a switch from classical apoptotic pathways to caspase 3-independent mechanisms during the course of the cuprizone diet. The expression level of FAS in the corpus callosum, a cell death receptor crucial for oligodendroglial cell death in experimental autoimmune encephalomyelitis (EAE), correlates with the expression of activated caspase 3 in oligodendrocytes. However, mice lacking FAS in oligodendrocytes are not protected against cuprizone-induced oligodendroglial cell death, showing that FAS is dispensable for oligodendroglial cell death in the cuprizone model.

PIMD: 19825276

Electrophysiological and clinical correlates of corpus callosum atrophy in patients with multiple sclerosis.

Multiple sclerosis (MS) is an idiopathic inflammatory demyelinating disorder of the central nervous system (CNS) characterized by demyelination and axonal degeneration. Corpus callosum (CC) is commonly involved during the disease process leading to atrophy (93%). Currently, there are no established markers of disease progression and the interplay of processes leading to brain atrophy in MS remains unknown. The primary aim of this study was to assess the frequency of CC atrophy in MS patients. Furthermore, the relationship between expanded disability status scale (EDSS) and transcranial magnetic stimulation (TMS) evoked motor potentials (MEP) were assessed to capture disease effects by independent parameters. Seventy-nine MS patients and 50 controls were included and their CC volumes were assessed. Out of 79 patients, 31 patients (39·2%) had CC atrophy. The distribution of EDSS scores among the group with CC atrophy [13 (32%) patients with EDSS 0-2; 11 (58%) patients with EDSS 2-4; 19 (24%) patients with EDSS ≥4] was not statistically significant ($p>0·05$). MEP latency was abnormal in 34 (43%) patients, 67 (85%) patients had abnormal MEP amplitude and CMCT was abnormal in 32 (41%) patients. The relation between EDSS and MEP was statistically significant among the patient population including the subgroup of patients with CC atrophy ($p<0.05$). Our results lacked to provide an association between disability and CC atrophy, but there was a correlation between CC atrophy and TMS evoked motor potentials. Early evolution of axonal degeneration and brain atrophy should be considered in terms of follow-up measures to provide long-term efficiency impacting disability, progression and brain atrophy.

PIMD: 19800949

Functional recovery of callosal axons following demyelination: a critical window.

Axonal dysfunction as a result of persistent demyelination has been increasingly appreciated as a cause of functional deficit in demyelinating diseases such as multiple sclerosis. Therefore, it is crucial to understand the ultimate causes of ongoing axonal dysfunction and find effective measures to prevent axon loss. Our findings related to functional deficit and functional recovery of axons from a demyelinating insult are important preliminary steps towards understanding this issue. Cuprizone diet for 3-6 wks triggered extensive corpus callosum (CC) demyelination, reduced axon conduction, and resulted in loss of axon structural integrity including nodes of Ranvier. Replacing cuprizone diet with normal diet led to regeneration of myelin, but did not fully reverse the conduction and structural deficits. A shorter 1.5 wk cuprizone diet also caused demyelination of the CC, with minimal loss of axon structure and nodal organization. Switching to normal diet led to remyelination and restored callosal axon conduction to normal levels. Our findings suggest the existence of a critical window of time for remyelination, beyond which demyelinated axons become damaged beyond the point of repair and permanent functional loss follows. Moreover, initiating remyelination early within the critical period, before prolonged demyelination-induced axon damage ensues, will improve functional axon recovery and inhibit disease progression.

PIMD: 19787715

Differentiating multiple sclerosis from other causes of demyelination using diffusion weighted imaging of the corpus callosum.

To compare diffusion weighted imaging metrics in gray and white matter brain regions of patients diagnosed with multiple sclerosis (MS) to those diagnosed with secondary demyelinating diseases such as neurosarcoid and acute disseminated encephalomyelitis (ADEM).Diffusion weighted scans were performed and apparent diffusion coefficients of 12 regions of interest were determined in 30 MS patients, 21 neurosarcoid patients, and 4 ADEM patients.Mean apparent diffusion coefficients were significantly higher in MS patients than in non-MS patients in 6 of 6 of the corpus callosal regions assessed but not in any of the non-callosal white or gray matter regions assessed.Elevated apparent diffusion coefficients within the corpus callosum on diffusion weighted imaging may potentially help differentiate between patients with MS and patients with other diseases affecting the central nervous system white matter.

PIMD: 19696139

Regional white matter atrophy--based classification of multiple sclerosis in cross-sectional and longitudinal data.

The different clinical subtypes of multiple sclerosis (MS) may reflect underlying differences in affected neuroanatomic regions. Our aim was to analyze the effectiveness of jointly using the inferior subolivary medulla oblongata volume (MOV) and the cross-sectional area of the corpus callosum in distinguishing patients with relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), and primary-progressive multiple sclerosis (PPMS).We analyzed a cross-sectional dataset of 64 patients (30 RRMS, 14 SPMS, 20 PPMS) and a separate longitudinal dataset of 25 patients (114 MR imaging examinations). Twelve patients in the longitudinal dataset had converted from RRMS to SPMS. For all images, the MOV and corpus callosum were delineated manually and the corpus callosum was parcellated into 5 segments. Patients from the cross-sectional dataset were classified as RRMS, SPMS, or PPMS by using a decision tree algorithm with the following input features: brain parenchymal fraction, age, disease duration, MOV, total corpus callosum area and areas of 5 segments of the corpus callosum. To test the robustness of the classification technique, we applied the results derived from the cross-sectional analysis to the longitudinal dataset.MOV and central corpus callosum segment area were the 2 features retained by the decision tree. Patients with MOV >0.94 cm(3) were classified as having RRMS. Patients with progressive MS were further subclassified as having SPMS if the central corpus callosum segment area was <55.12 mm(2), and as having PPMS otherwise. In the cross-sectional dataset, 51/64 (80%) patients were correctly classified. For the longitudinal dataset, 88/114 (77%) patient time points were correctly classified as RRMS or SPMS.Classification techniques revealed differences in affected neuroanatomic regions in subtypes of multiple sclerosis. The combination of central corpus callosum segment area and MOV provides good discrimination among patients with RRMS, SPMS, and PPMS.

PIMD: 19682809

Magnetic resonance imaging at first episode in pediatric multiple sclerosis retrospective evaluation according to KIDMUS and lesion dissemination in space criteria.

Several diagnostic imaging criteria are being described and examined in pediatric multiple sclerosis (MS). Compared to adults, children are more likely to experience acute or relapsing demyelinating episodes of various etiologies which show similar clinical and magnetic resonance imaging (MRI) findings.To investigate the fulfillment of MRI diagnostic criteria at initial episode in pediatric MS.We reviewed our series of children and adolescents with the final diagnosis of clinically definite MS and applied the McDonald dissemination in space (DIS) and KIDMUS criteria to their initial MRI scans.Thirty patients (17 girls, 13 boys), most with brainstem dysfunction and polysymptomatic presentation, were included in the study. Twenty-five (83.3%) patients fulfilled both McDonald and KIDMUS criteria. Patients who did not meet any McDonald DIS criteria did not meet KIDMUS criteria either. Only one patient met the McDonald criteria but not the KIDMUS criteria because of the absence of lesions perpendicular to corpus callosum.Our results show 5/30 (16.6%) of MS patients may not present the diagnostic MRI features initially. The variable sensitivity observed for the current MRI criteria in different series can be due to referral biases, differences between populations and length of follow-up, and the definition of MS patients by two attacks only.

PIMD: 19667217

Difference in disease burden and activity in pediatric patients on brain magnetic resonance imaging at time of multiple sclerosis onset vs adults.

To compare initial brain magnetic resonance imaging (MRI) characteristics of children and adults at multiple sclerosis (MS) onset.Retrospective analysis of features of first brain MRI available at MS onset in patients with pediatric-onset and adult-onset MS.A pediatric and an adult MS center.Patients with pediatric-onset <18 years) and adult-onset (> or =18 years) MS.We evaluated initial and second (when available) brain MRI scans obtained at the time of first MS symptoms for lesions that were T2-bright, ovoid and well defined, large (> or =1cm), or enhancing.We identified 41 patients with pediatric-onset MS and 35 patients with adult-onset MS. Children had a higher number of total T2- (median, 21 vs 6; P < .001) and large T2-bright areas (median, 4 vs 0; P < .001) than adults. Children more frequently had T2-bright foci in the posterior fossa (68.3% vs 31.4%; P = .001) and enhancing lesions (68.4% vs 21.2%; P < .001) than adults. On the second brain MRI, children had more new T2-bright (median, 2.5 vs 0; P < .001) and gadolinium-enhancing foci (P < .001) than adults. Except for corpus callosum involvement, race/ethnicity was not strongly associated with disease burden or lesion location on the first scan, although other associations cannot be excluded because of the width of the confidence intervals.While it is unknown whether the higher disease burden, posterior fossa involvement, and rate of new lesions in pediatric-onset MS are explained by age alone, these characteristics have been associated with worse disability progression in adults.

PIMD: 19650767

Cuprizone demyelination of the corpus callosum in mice correlates with altered social interaction and impaired bilateral sensorimotor coordination.

For studies of remyelination in demyelinating diseases, the cuprizone model of CC (corpus callosum) demyelination has experimental advantages that include overall size, proximity to neural stem cells of the subventricular zone, and correlation with a lesion predilection site in multiple sclerosis. In addition, cuprizone treatment can be ended to allow more direct analysis of remyelination than with viral or autoimmune models. However, CC demyelination lacks a useful functional correlate in rodents for longitudinal analysis throughout the course of demyelination and remyelination. In the present study, we tested two distinct behavioural measurements in mice fed 0.2% cuprizone. Running on a 'complex' wheel with varied rung intervals requires integration between cerebral hemispheres for rapid bilateral sensorimotor coordination. Maximum running velocity on the 'complex' wheel decreased during acute (6 week) and chronic (12 week) cuprizone demyelination. Running velocity on the complex wheel distinguished treated (for 6 weeks) from non-treated mice, even after a 6-week recovery period for spontaneous remyelination. A second behavioural assessment was a resident-intruder test of social interaction. The frequency of interactive behaviours increased among resident mice after acute or chronic demyelination. Differences in both sensorimotor coordination and social interaction correlated with demonstrated CC demyelination. The wheel assay is applicable for longitudinal studies. The resident-intruder assay provides a complementary assessment of a distinct modality at a specific time point. These behavioural measurements are sufficiently robust for small cohorts as a non-invasive assessment of demyelination to facilitate analysis of subsequent remyelination. These measurements may also identify CC involvement in other mouse models of central nervous system injuries and disorders.

PIMD: 19625027

Sexual dimorphism in the white matter of rodents.

Sexual dimorphism of astrocytes and neurons is well documented in many brain and spinal cord structures. Sexual dimorphism of oligodendrocytes (Olgs) and myelin has received less attention. We recently showed that density of Olgs in corpus callosum, fornix, and spinal cord of wild-type male rodents is more densely packed than in females; myelin proteins and myelin gene expression are likewise greater in males than in female rodents. However, glial cell proliferation and cell death were two times greater in female corpus callosum. Endogenous sex hormones, specifically lack of androgens, produce an Olg female phenotype in castrated male mouse. In vitro studies using Olgs culture also showed differences between males and females Olg survival and signaling pathways in response to sexual hormones. Sexual dimorphism of white matter tracts and glia in rodents indicates the necessity for controlling gender in the experimental studies of neurodegenerative disorders. Most importantly, our studies suggest that hormones may contribute to sexual dimorphism observed in certain human diseases including multiple sclerosis.

PIMD: 19504090

Lower fractional anisotropy at the anterior body of the normal-appearing corpus callosum in multiple sclerosis versus symptomatic carotid occlusion.

Not uncommonly, differentiating multiple sclerosis (MS) from ischemic cerebral vascular disease is difficult based on conventional magnetic resonance imaging (MRI). We aim to determine whether preferential occult injury in the normal-appearing corpus callosum (NACC) is more severe in patients with MS than symptomatic carotid occlusion by comparing fractional anisotropy (FA) from diffusion tensor imaging (DTI).Eighteen patients (eight men, ten women; mean age, 38.6 years) with MS and 32 patients (24 men, eight women; mean age, 64.0 years) with symptomatic unilateral internal carotid occlusion were included. DTI (1.5 T) were performed at corpus callosum which were normal-appearing on fluid-attenuated inversion recovery MRI. Mean FA was obtained from the genu, anterior body, posterior body, and splenium of NACC. Independent-sample t test statistical analysis was performed.The FA values in various regions of NACC were lower in the MS patients than symptomatic carotid occlusion patients, which was statistically different at the anterior body (0.67 +/- 0.12 vs 0.74 +/- 0.06, P = 0.009), but not at genu, posterior body, and splenium (0.63 +/- 0.09 vs 0.67 +/- 0.07, P = 0.13; 0.68 +/- 0.09 vs 0.73 +/- 0.05, P = 0.07; 0.72 +/- 0.09 vs 0.76 +/- 0.05, P = 0.13).MS patients have lower FA in the anterior body of NACC compared to patients with symptomatic carotid occlusion. It suggests that DTI has potential ability to differentiate these two conditions due to the more severe preferential occult injury at the anterior body of NACC in MS.

PIMD: 19489017

Comparison of MRI signatures in pattern I and II multiple sclerosis models.

The majority of individuals with multiple sclerosis (MS) exhibit T-cell- and macrophage-dominated lesions (patterns I and II; as opposed to III and IV). These lesions, in turn, may be distinguished on the basis of whether or not there are immunoglobulin and complement depositions at the sites of active myelin destruction; such depositions are found exclusively in pattern II lesions. The main aim of this study was to determine whether pattern I and pattern II MS lesions exhibit distinct MRI signatures. We have used a recently described focal MOG-induced EAE model of the rat brain, which recapitulates many of the hallmarks of pattern II MS; we compared this with our previous work in a delayed type hypersensitivity model of a pattern I type lesion in the rat brain. Demyelinating lesions with extensive inflammation were generated, in which the T2-weighted signal was increased. Magnetisation transfer ratio (MTR) maps revealed loss and subsequent incomplete recovery of the structure of the corpus callosum, together with changes in tissue water diffusion and an associated increase in ventricle size. Notably, the MTR changes preceeded histological demyelination and may report on the processes leading to demyelination, rather than demyelination per se. Immunohistochemically, these MRI-detectable signal changes correlated with both inflammatory cell infiltration and later loss of myelin. Breakdown of the blood-brain barrier and an increase in the regional cerebral blood volume were also evident in and around the lesion site at the early stage of the disease. Interestingly, however, the MRI signal changes in this pattern II type MS lesion were remarkably consistent with those previously observed in a pattern I lesion. These findings suggest that the observed signal changes reflect the convergent histopathology of the two models rather than the underlying mechanisms of the disease.

PIMD: 19453832

Comparison of diffusion tensor-based tractography and quantified brain atrophy for analyzing demyelination and axonal loss in MS.

We combined diffusion tensor imaging (DTI) measures of the corpus callosum (CC) and the superior longitudinal fascicle (SLF) with calculation of brain atrophy in 53 patients with relapsing-remitting multiple sclerosis (MS) and 15 healthy controls, to analyze their interrelation and their correlation with disease duration and clinical impairment. The lateral ventricle volume in MS patients was increased; the fractional anisotropy in the CC was decreased as was the fiber volume. Perpendicular (in the literature also referred to as radial) diffusivity (ped), which reflects the diffusion perpendicular to the long axis of the axons within the fiber bundle, was increased in the SLF and the posterior CC, but contrary to our predictions, parallel (also called axial) diffusivity (pad) that refers to the amount of diffusion in the direction of the axon was increased, too. Brain atrophy and DTI-derived parameters were highly intercorrelated and both correlated with disease duration. Discriminant analysis showed that DTI-derived atrophy measures are superior to brain atrophy measures in classifying patients and controls. In light of our results, animal studies focusing on demyelination and axonal loss are reinterpreted.

PIMD: 19444380

Occurrence of ankylosing spondylitis and multiple sclerosis-like syndrome in a HLA-B27 positive patient.

Occurrence of multiple sclerosis (MS) in patients with ankylosing spondylitis (AS) has been reported in isolated cases. We describe a white 33-year-old male with a definite familial HLAB27 positive AS and MS-like syndrome. The patient developed acute onset of gait difficulty, postural unsteadiness, dysarthria and right side weakness that resolved within 1 month; after 6 months he presented right-sided face sensory loss, disappeared after 2 weeks. Brain and cervical MRI was performed twice and showed disseminated lesions in space (multiple foci of increased signal intensity in the periventricular white matter, in the corpus callosum, in the hypothalamus, in the brainstem and in the cervical spinal cord) and in time (a new enhancing lesion >3 months after the onset of the clinical event). Visual evoked potentials were markedly altered. Cerebrospinal fluid examination was negative for intrathecal production of oligoclonal bands. Differential diagnosis was considered and other pathologies were excluded.

PIMD: 19435750

Occurrence of acute large and edematous callosal lesions in neuromyelitis optica.

The corpus callosum is commonly involved in multiple sclerosis (MS), but the characteristics of callosal lesions in neuromyelitis optica (NMO) are unknown.ObjectiveTo reveal the features of callosal lesions in NMO in comparison to MS.We retrospectively reviewed the medical records and the brain magnetic resonance imaging films of 56 patients with MS and 22 patients with NMO.In MS, 36 (64.3%) of 56 patients had callosal lesions, but only four patients had acute lesions. All such acute lesions were small, isolated and non-edematous, and the intensity was homotonic. Chronic lesions were observed in 34 patients with MS, and 32 (94%) of them presented small lesions located at the callosal lower margin ("hemi-oval pattern"). Meanwhile, four (18.2%) patients with NMO had callosal lesions, and three of them had acute lesions. Those acute lesions were multiple, large edematous ones with heterogeneous intensity ("marbled pattern"). In the chronic stage, the lesions shrank or disappeared.Acute large, edematous callosal lesions occasionally occur in NMO. Similar to longitudinally extensive transverse myelitis, such callosal lesions may reflect severe edematous inflammation in NMO, and may provide additional evidence that the pathogenesis in NMO is different from that in MS.

PIMD: 19419759

Corpus callosum function in verbal dichotic listening: inferences from a longitudinal follow-up of Relapsing-Remitting Multiple Sclerosis patients.

This study conducted a follow-up of 13 early-onset slightly disabled Relapsing-Remitting Multiple Sclerosis (RRMS) patients within an year, evaluating both CC area measurements in a midsagittal Magnetic Resonance (MR) image, and Dichotic Listening (DL) testing with stop consonant vowel (C-V) syllables. Patients showed a significant progressive loss of posterior CC areas (isthmus and splenium) related to increasing EDSS scores and an enhancing right ear advantage (REA) over time. A significant correlation between posterior CC areas and DL scores emerged in both evaluations, being negative for the right and positive for the left ear. The pattern of correlations suggests that the CC can serve an inhibitory and also excitatory influence on the contralateral hemisphere when studying the phonological processing of language. STATEMENT OF SIGNIFICANCE TO THE NEUROSCIENCE OF LANGUAGE: The scope of the manuscript is language lateralization. The task used in the experiment is a verbal dichotic listening task, tapping the most basic phonological aspects of language. Finally, the available research is scarce when focusing on the interhemispheric excitation or inhibition of the corpus callosum in linguistic functioning.

PIMD: 19396881

Selective reduction in microglia density and function in the white matter of colony-stimulating factor-1-deficient mice.

It is still debated whether microglia play a beneficial or harmful role in myelin disorders such as multiple sclerosis and leukodystrophies as well as in other pathological conditions of the central nervous system. The osteopetrotic (op/op) mouse has reduced numbers of cells of monocyte lineage as a result of an inactivating mutation in the colony stimulating factor-1 gene. To determine whether this mutant mouse might be used to study the role of microglia in myelin disorders, we quantified the number of microglia in the central nervous system of op/op mice and explored their ability to respond to brain injury created by a stab wound. Microglial density in the 2-month-old op/op mice was significantly decreased in the white matter tracts compared with the -ge matched wild-type controls (by 63.6% in the corpus callosum and 86.4% in the spinal dorsal column), whereas the decrease was less in the gray matter, cerebral cortex (24.0%). A similar decrease was seen at 7 months of age. Morphometric studies of spinal cord myelination showed that development of myelin was not affected in op/op mice. In response to a stab wound, the increase in the number of microglia/macrophages in op/op mice was significantly less pronounced than that in wild-type control. These findings demonstrate that this mutant is a valuable model in which to study roles of microglia/macrophages in the pathophysiology of myelin disorders.

PIMD: 19371354

Cerebellar cortical demyelination in the murine cuprizone model.

In multiple sclerosis, demyelination occurs beside the white-matter structures and in the cerebral and cerebellar cortex. We have previously shown that, in the cuprizone model, demyelination is present not only in the corpus callosum but also in the cerebral cortex. Here, we have performed a detailed analysis of the dynamics of de- and remyelination in the cerebellar cortex and white matter at nine timepoints in two cerebellar regions. To induce demyelination, C57BL/6 mice were fed with 0.2% cuprizone for 12 weeks followed by a recovery of 8 weeks. Both cortex and white-matter structures were significantly demyelinated after 12 weeks of cuprizone feeding. Remyelination occurred after withdrawal of cuprizone but was less prominent in the more caudal cerebellar region. Microglia infiltration was prominent in all analyzed cerebellar areas, preceding demyelination by approximately 2-4 weeks, and was delayed in the more caudal cerebellar region. Astrogliosis was also seen but did not reach the extent observed in the cerebrum. In summary, cuprizone feeding provides an excellent model for the investigation of de- and remyelination processes in the cerebellar cortex and white matter. Furthermore, demyelination, microglia and astrocyte changes were different in the cerebellum as compared with the cerebrum, indicating region-dependent pathomechanisms.

PIMD: 19369550

Systemic inflammatory response reactivates immune-mediated lesions in rat brain.

The potential association between microbial infection and reactivation of a multiple sclerosis (MS) lesion is an important issue that remains unresolved, primarily because of the absence of suitable animal models and imaging techniques. Here, we have evaluated this question in an empirical manner using immunohistochemistry and magnetic resonance imaging (MRI), before and after the induction of a systemic inflammatory response in two distinct models of MS. In a pattern-II-type focal myelin oligodendrocyte glycoprotein-experimental autoimmune encephalomyelitis model, systemic endotoxin injection caused an increase in regional cerebral blood volume (rCBV) around the lesion site after 6 h, together with a reduction in the magnetization transfer ratio of the lesioned corpus callosum. These changes were followed by an increase in the diffusion of tissue water within the lesion 24 h after endotoxin challenge and new leukocyte recruitment as revealed both immunohistochemically and by MRI tracking of ultrasmall superparamagnetic iron oxide-labeled macrophages. Importantly, we detected in vivo expression of E- and P-selectin in quiescent lesions by MRI-detectable glyconanoparticles conjugated to sialyl Lewis(X). This finding may explain, at least in part, the ability of quiescent MS lesions to rapidly reinitiate the cell recruitment processes. In a pattern-I-type delayed-type hypersensitivity response model, a similar effect of endotoxin challenge on rCBV was observed, together with delayed breakdown of the blood-brain barrier, showing that systemic infection can alter the pathogenesis of MS-like lesions regardless of lesion etiology. These findings will have important implications for the management and monitoring of individuals with MS.

PIMD: 19349355

Statin therapy inhibits remyelination in the central nervous system.

Remyelination of lesions in the central nervous system contributes to neural repair following clinical relapses in multiple sclerosis. Remyelination is initiated by recruitment and differentiation of oligodendrocyte progenitor cells (OPCs) into myelinating oligodendrocytes. Simvastatin, a blood-brain barrier-permeable statin in multiple sclerosis clinical trials, has been shown to impact the in vitro processes that have been implicated in remyelination. Animals were fed a cuprizone-supplemented diet for 6 weeks to induce localized demyelination in the corpus callosum; subsequent return to normal diet for 3 weeks stimulated remyelination. Simvastatin was injected intraperitoneally during the period of coincident demyelination and OPC maturation (weeks 4 to 6), throughout the entire period of OPC responses (weeks 4 to 9), or during the remyelination-only phase (weeks 7 to 9). Simvastatin treatment (weeks 4 to 6) caused a decrease in myelin load and both Olig2(strong) and Nkx2.2(strong) OPC numbers. Simvastatin treatment (weeks 4 to 9 and 7 to 9) caused a decrease in myelin load, which was correlated with a reduction in Nkx2.2(strong) OPCs and an increase in Olig2(strong) cells, suggesting that OPCs were maintained in an immature state (Olig2(strong)/Nkx2.2(weak)). NogoA+ oligodendrocyte numbers were decreased during all simvastatin treatment regimens. Our findings suggest that simvastatin inhibits central nervous system remyelination by blocking progenitor differentiation, indicating the need to monitor effects of systemic immunotherapies that can access the central nervous system on brain tissue-repair processes.

PIMD: 19281850

3 T MRI relaxometry detects T2 prolongation in the cerebral normal-appearing white matter in multiple sclerosis.

MRI at 3 T has increased sensitivity in detecting overt multiple sclerosis (MS) brain lesions; a growing body of data suggests clinically relevant damage occurs in the normal-appearing white matter (NAWM). We tested a novel pulse sequence to determine whether 3 T MRI spin-spin relaxometry detected damage in NAWM of MS patients (n=13) vs. age-matched normal controls [(NL) (n=11)]. Baseline characteristics of the MS group were: age (mean+/-SD) 42.5+/-5.4 (range 33-51 years), disease duration 9.0+/-6.4 (range 1-22 years), Expanded Disability Status Scale score 2.5+/-1.7 (range 1-6.5). Brain MRI measures, obtained at 3 T, included global and regional NAWM transverse relaxation rate [R2 (=1/T2)], derived from 3D fast spin-echo T2 prepared images, and global white matter volume fraction derived from SPGR images. The regional NAWM areas investigated were the frontal lobe, parietal lobe, and the genu and splenium of the corpus callosum. Mean NAWM R2 was lower (indicating T2 prolongation) in MS than NL in the whole brain ($p=0.00047$), frontal NAWM ($p=0.00015$), parietal NAWM ($p=0.0069$) and callosal genu ($p=0.0019$). Similarly, R2 histogram peak position was lower in NAWM in MS than NL in the whole brain ($p=0.019$). However, the normalized WM volume fractions were similar in both MS and NL ($p>0.1$). This pilot study suggests that a novel 3D fast spin-echo pulse sequence at 3 T, used to derive R2 relaxation maps, can detect tissue damage in the global and regional cerebral NAWM of MS patients that is missed by conventional lesion and atrophy measures. Such findings may represent demyelination, inflammation, glial proliferation and axonal loss.

PIMD: 19172642

A multiparametric evaluation of regional brain damage in patients with primary progressive multiple sclerosis.

The purpose of this study is to define the topographical distribution of gray matter (GM) and white matter (WM) damage in patients with primary progressive multiple sclerosis (PPMS), using a multiparametric MR-based approach. Using a 3 Tesla scanner, dual-echo, 3D fast-field echo (FFE), and diffusion tensor (DT) MRI scans were acquired from 18 PPMS patients and 17 matched healthy volunteers. An optimized voxel-based (VB) analysis was used to investigate the patterns of regional GM density changes and to quantify GM and WM diffusivity alterations of the entire brain. In PPMS patients, GM atrophy was found in the thalami and the right insula, while mean diffusivity (MD) changes involved several cortical-subcortical structures in all cerebral lobes and the cerebellum. An overlap between decreased WM fractional anisotropy (FA) and increased WM MD was found in the corpus callosum, the cingulate gyrus, the left short temporal fibers, the right short frontal fibers, the optic radiations, and the middle cerebellar peduncles. Selective MD increase, not associated with FA decrease, was found in the internal capsules, the corticospinal tracts, the superior longitudinal fasciculi, the fronto-occipital fasciculi, and the right cerebral peduncle. A discrepancy was found between regional WM diffusivity changes and focal lesions because several areas had DT MRI abnormalities but did not harbor T2-visible lesions. Our study allowed to detect tissue damage in brain areas associated with motor and cognitive functions, which are known to be impaired in PPMS patients. Combining regional measures derived from different MR modalities may be a valuable tool to improve our understanding of PPMS pathophysiology.

PIMD: 19084049

Demyelination of the hippocampus is prominent in the cuprizone model.

In multiple sclerosis demyelination not only affects the white matter, but also the grey matter of the brain. We have previously reported that in the murine cuprizone model for demyelination lesions occur in addition to the corpus callosum also in the neocortex and hippocampus. In the current study, we provide a detailed characterization of hippocampal demyelination in the cuprizone model. Male C57BL/6 mice were challenged with 0.2% cuprizone for 6 weeks. Defined structures within the hippocampus were investigated at week 0 (control), 3, 4, 4.5, 5, 5.5, and 6. Demyelination affected all hippocampal structures analyzed and was complete after 6 weeks of cuprizone treatment. Between the distinct hippocampal structures the temporal pattern of demyelination varied considerably. Furthermore, infiltration of activated microglia as well as astrogliosis was detected. In summary, cuprizone feeding provides a useful model for studying demyelination processes in the mouse hippocampus.

PIMD: 19067325

Corpus callosum damage and cognitive dysfunction in benign MS.

Corpus callosum (CC), the largest compact white matter fiber bundle of the human brain involved in interhemispheric transfer, is frequently damaged in the course of multiple sclerosis (MS). Cognitive impairment is one of the factors affecting quality of life of patients with benign MS (BMS). The aim of this study was to investigate the relationship between the cognitive profile of BMS patients and the extent of tissue damage in the CC. Brain conventional and DT MRI scans were acquired from 54 BMS patients and 21 healthy controls. Neuropsychological tests (NPT) exploring memory, attention, and frontal lobe cognitive domains were administered to the patients. DT tractography was used to calculate the mean diffusivity (MD) and fractional anisotropy (FA) of the CC normal appearing white matter (NAWM). An index of CC atrophy was also estimated. Nine (17%) BMS patients fulfilled criteria for cognitive impairment. Compared with controls, BMS had significantly different CC diffusivity and volumetry ($P < 0.001$). Compared with cognitively preserved patients, those with CI had significantly higher CC lesion volume (LV) ($P = 0.02$) and NAWM MD ($P = 0.02$). The scores obtained at PASAT were significantly correlated with CC T2 LV, and NAWM FA and MD (r values ranging from -0.31 to 0.66, P values ranging from 0.04 to <0.001). Cognitive impairment in BMS is associated with the extent of CC damage in terms of both focal lesions and diffuse fiber bundle injury. MRI assessment of topographical distribution of tissue damage may represent a rewarding strategy for understanding the subtle clinical deficits of patients with BMS.

PIMD: 19034902

Abnormal connectivity of the sensorimotor network in patients with MS: a multicenter fMRI study.

In this multicenter study, we used dynamic causal modeling to characterize the abnormalities of effective connectivity of the sensorimotor network in 61 patients with multiple sclerosis (MS) compared with 74 age-matched healthy subjects. We also investigated the correlation of such abnormalities with findings derived from structural MRI. In a subgroup of subjects, diffusion tensor (DT) MRI metrics of the corpus callosum and the left corticospinal tract (CST) were also assessed. MS patients showed increased effective connectivity relative to controls between: (a) the left primary SMC and the left dorsal premotor cortex (PMd), (b) the left PMd and the supplementary motor areas (SMA), (c) the left secondary sensorimotor cortex (SII) and the SMA, (d) the right SII and the SMA, (e) the left SII and the right SII, and (f) the right SMC and the SMA. MS patients had relatively reduced effective connectivity between the left SMC and the right cerebellum. No interaction was found between disease group and center. Coefficients of altered connectivity were weakly correlated with brain T2 LV, but moderately correlated with DT MRI-measured damage of the left CST. In conclusion, large multicenter fMRI studies of effective connectivity changes in diseased people are feasible and can facilitate studies with sample size large enough for robust outcomes. Increased effective connectivity in the patients for the simple motor task suggests local network modulation contributing to enhanced long-distance effective connectivity in MS patients. This extends and generalizes previous evidence that enhancement of effective connectivity may provide an important compensatory mechanism in MS.

PIMD: 19031445

17beta-estradiol and progesterone prevent cuprizone provoked demyelination of corpus callosum in male mice.

Sex hormones, for example, estrogen and progesterone, are thought to affect and delay progression of multiple sclerosis (MS) in pregnant women. Although both steroid hormones are neuroprotective in the brain and elevated during pregnancy, only estrogen was tested in clinical trials. To evaluate the role of 17beta-estradiol (E) and progesterone (P) in prevention demyelination, young adult male mice were fed with cuprizone for a defined time interval and simultaneously treated with steroids by repeated injections into the neck region. The status of myelination was analyzed by magnetic resonance imaging and conventional histological staining. The individual application of E and P resulted only in a moderate prevention of demyelination in the corpus callosum (CC). The combined treatment with both steroid hormones counteracted the process of demyelination. Expression of the mature (PLP and MBP) and premature (PDGF-alpha-R) oligodendrocyte markers were significantly increased after hormone application in the affected CC. In addition, both hormones stimulated astrogliosis and the expression of IGF-1. Microglial invasion in demyelinated CC was pronounced and additionally localized in the midline of CC after hormone treatment. These data show that sex steroids can protect the brain from demyelination and stimulate remyelination. It appears that only the administration of both hormones is fully effective. The beneficial steroid effect requires interactions with oligodendrocytes possibly by preventing their degeneration or recruitment from precursor cells which are stimulated to remyelinated fibers. The positive hormonal influence on myelination in the CNS may be a future therapeutically strategy for the treatment of MS.

PIMD: 19027076

Regional DTI differences in multiple sclerosis patients.

Diffusion tensor imaging (DTI) measures have shown to be sensitive to white matter (WM) damage in multiple sclerosis (MS), not only inside focal lesions but also in user-defined regions in the so-called normal-appearing white matter (NAWM). New analysis techniques for DTI measures are now available that allow for hypothesis-free localization of damage. We performed DTI measurements of 30 MS patients selected for low focal lesion loads, and of 31 age-matched healthy controls and analyzed these using tract-based spatial statistics (TBSS). Patients were found to have a lower fractional anisotropy (FA) compared to controls in a number of brain regions, including the fornices, the left corona radiata, the inferior longitudinal fasciculus in both hemispheres, both optic radiations, and parts of the corpus callosum. In the regions of reduced FA, an increase in radial diffusivity and a less pronounced increase of axial diffusivity were found. Neurocognitive assessment showed that patients had normal visuospatial memory performance, just-normal attention, and impaired processing speed; the latter was associated with abnormal FA in the corpus callosum, an area which was relatively devoid of lesions visible on proton density-weighted images in our patients. TBSS can be useful in future studies with other MS patient samples to provide an unbiased localization of damage and generate location-specific hypotheses.

PIMD: 19016742

SJL mice exposed to cuprizone intoxication reveal strain and gender pattern differences in demyelination.

The role of mouse strain and the influence of gender on demyelination were explored for the first time in SJL mice using the cuprizone intoxication model. We document here that SJL mice display a unique pattern of demyelination that did not follow the profile that is well-characterized in C57BL/6 mice. The SJL mice did not readily demyelinate at the midline within the corpus callosum but showed greater demyelination immediately lateral to midline. During continuous exposure to cuprizone, demyelination was not complete and appeared to plateau after week 7. Importantly, female mice were partially resistant to demyelination, whereas male mice were more severely demyelinated. Differences in the number of mature oligodendrocytes were consistent with the extent of demyelination; however, microglia, astrocyte and oligodendrocyte precursor cell populations did not differ between male and female mice. Thus, genetic factors and gender influence susceptibility to demyelinating disease in the cuprizone model, which may provide additional insights into the variability observed in human demyelinating diseases such as multiple sclerosis.

PIMD: 18987107

Fatigue in multiple sclerosis is associated with the disruption of frontal and parietal pathways.

Fatigue is one of the most frequent and disturbing symptoms in multiple sclerosis (MS), directly affecting the patient's quality of life. However, many questions remain unclear regarding the anatomic brain correlate of MS-related fatigue.To assess the relationship between fatigue and white matter lesion location and gray matter atrophy.In this study, 60 patients with MS were evaluated with the Modified Fatigue Impact Scale and magnetic resonance imaging. Location of white matter lesion was analyzed using a voxel-by-voxel lesion probability mapping approach and gray matter atrophy degree and location using an optimized voxel-based morphometry method.We found a correlation between lesion load and fatigue score (T2 lesion load: r=0.415, P=0.001; T1 lesion load r=0.328, P=0.011). Moreover, fatigue correlated with lesions in the right parietotemporal (periatrial area, juxtaventricular white matter deep in the parietal lobe and callosal forceps) and left frontal (middle-anterior corpus callosum, anterior cingulum and centrum semiovale of the superior and middle frontal gyri) white matter regions (P<0.001 in all cases). Finally, fatigue score significantly correlated with gray matter atrophy in frontal regions, specifically, the left superior frontal gyrus and bilateral middle frontal gyri (P<0.001 in all cases).Our results suggest that the symptom of fatigue is associated with a disruption of brain networks involved in cognitive/attentional processes.

PIMD: 18950873

Gene expression analysis of normal appearing brain tissue in an animal model for multiple sclerosis revealed grey matter alterations, but only minor white matter changes.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Recent studies suggest that, beside focal lesions, diffuse inflammatory and degenerative processes take place throughout the MS brain. Especially, molecular alterations in the so-called normal appearing white matter suggest the induction of neuroprotective mechanisms against oxidative stress preserving cellular homeostasis and function. In this study we investigated whether in an animal model for MS, namely in experimental autoimmune encephalomyelitis (EAE), similar changes occur. We isolated normal appearing white and grey matter from the corpus callosum and the above lying cerebral cortex from DA rats with rMOG-induced EAE and carried out a gene expression analysis. Examination of corpus callosum revealed only minor changes in EAE rats. In contrast, we identified a number of gene expression alterations in the cerebral cortex even though morphological and cellular alterations were not evident. One of the most striking observations was the downregulation of genes involved in mitochondrial function as well as a whole set of genes coding for different glutamate receptors. Our data imply that molecular alterations are present in neurons far distant to inflammatory demyelinating lesions. These alterations might reflect degenerative processes induced by lesion-mediated axonal injury in the spinal cord. Our results indicate that the MOG-induced EAE in DA rats is a valuable model to analyze neuronal alterations due to axonal impairment in an acute phase of a MS-like disease, and could be used for development of neuroprotective strategies.

PIMD: 18813697

Diffusion tensor MR imaging evaluation of the corpus callosum of patients with multiple sclerosis.

To evaluate the fractional anisotropy (FA) values of the normal-appearing white matter of the corpus callosum (CC) in patients with relapsing-remitting multiple sclerosis (MS).Fifty-seven patients with diagnosis of relapsing-remitting MS and 47 age- and gender-matched controls were studied. A conventional MR imaging protocol and a DTI sequence were performed. One neuroradiologist placed the regions of interest (ROIs) in the FA maps in five different portions of the normal-appearing CC (rostrum, genu, anterior and posterior portion of the body and splenium) in all cases. The statistical analysis was performed with the Mann-Whitney U test and $p<0.05$ was considered statistically significant.The FA values were lower in the MS patients compared with the controls ($p<0.05$) in the following CC regions: rostrum (0.720 vs 0.819), anterior body (0.698 vs 0.752), posterior body (0.711 vs 0.759) and splenium (0.720 vs 0.880).In this series, there was a robust decrease in the FA in all regions of the normal-appearing CC, being significant in the rostrum, body and splenium. This finding suggests that there is a subtle and diffuse abnormality in the CC, which could be probably related to myelin content loss, axonal damage and gliosis.

PIMD: 18784602

Recurrent alien hand syndrome in a multiple sclerosis case.

Alien hand syndrome is the strange feeling of one's hand behaving independently. This syndrome has rarely been reported in multiple sclerosis (MS) patients. Herein, we present a 34-year-old female MS patient who had recurrent symptoms of alien hand syndrome that were evaluated as MS attacks based on cranial magnetic resonance imaging that showed demyelinating lesions in the corpus callosum. Alien hand syndrome is classified according to the location of the lesion and the presenting symptoms. As such, our patient can best be classified as a callosal alien hand case.

PIMD: 18727673

Brain atrophy as a marker of cognitive impairment in mildly disabling relapsing-remitting multiple sclerosis.

We have studied the relationship between neuropsychological impairment and magnetic resonance imaging (MRI) measures in mildly disabling relapsing-remitting multiple sclerosis (RRMS).We compared measures of lesion burden and atrophy in 52 patients with Expanded Disability Status Scale <or= 3.0. Neuropsychological testing explored various cognitive domains: attention and processing speed (APS), verbal and visual memory (VerbM; VisM), visual/constructional processes (VC), executive functions and motor programming/coordination. Specific and global index scores were derived to classify patients as deteriorated or not deteriorated by comparing their performance with 51 matched normal control subjects. Brain MRI analysis included proton density (PD)-lesion volume and T1-hypointensity volume, measures of central atrophy, including the third ventricle width, and corpus callosum (CC).Patients with either APS, MCP or Verbal Learning impairments had a higher ventricular atrophy than unimpaired. The atrophy of the CC was only associated to VisM dysfunction. Patients with VisM deficits had higher lesion load on PD images. After controlling for age and education a higher third ventricle width was the best predictor for global and specific cognitive impairment.Our results suggest that cognitive impairment in RR patients with mild disease is better explained by atrophic changes than by total lesion load.

PIMD: 18632928

Corpus callosum and bimanual coordination in multiple sclerosis.

No abstract

PIMD: 18632784

A case of Fabry disease with central nervous system (CNS) demyelinating lesions: a double trouble?

We present the case of a 36-year-old woman affected with Fabry disease (FD), with neuroradiologic and laboratory tests suggestive of a coexistent inflammatory demyelinating disease. Since the age of 23, she presented recurrent neurologic deficits, such as right limb paresthesias, diplopia, and right leg weakness. Magnetic resonance imaging revealed multiple demyelinating lesions in periventricular areas, corpus callosum, and spinal cord. Cerebrospinal fluid analysis showed the presence of oligoclonal bands, while visual-evoked potentials were delayed with preserved morphology. FD is usually considered as a differential diagnosis of multiple sclerosis, but we think that the best explanation of all pathological features in this case is the coexistence of the two diseases.

PIMD: 18540378

[Case of suspected multiple sclerosis with transcallosal lesions involving the upper surface of the corpus callosum].

A 26-year-old woman noticed gradually progressive, right lower leg weakness over a 1.5-month period. Neurological examination revealed right hemiparesis with slightly increased deep tendon reflexes, Babinski's sign on the right side, loss of position sense in the right leg, and slight loss of superficial sensation in the right toes. MR FLAIR images showed a high intensity area measuring 5 x 2 x 3 cm in the left frontal lobe, extending to the outer surface of the body of the corpus callosum and the adjacent right cingulate gyrus. Gadolinium enhancement was seen along the cortex and the outer surface of the body of the corpus callosum. CSF findings showed no pleocytosis, a protein content of 32 mg/dl, a sugar level of 85 mg/dl, and an IgG index of 0.46. The biopsy specimen obtained from the superior frontal gyrus showed perivascular cuffing of T-lymphocytes and some B-lymphocytes, as well as multiple small foci of demyelination. Starting on the second day of admission, the patient was treated with methylprednisolone pulse therapy (1,000 mg/day for 3 days); she was then switched to oral prednisolone (20 mg/day). Thereafter, the patient had two clinical relapses: one was due to a lesion in the dorsal part of the medulla oblongata associated with a disturbance of deep sensation in both hands, and the other was due to a lesion involving the right internal capsule, the globus pallidus, and the caudate nucleus associated with left facial nerve palsy. Visual evoked potentials suggested a demyelinating lesion in the right optic nerve. We suspected a diagnosis of multiple sclerosis based on the presence of more than two clinical episodes of neurological deficits with identifiable lesions on MRI. Multiple sclerosis should be considered in the differential diagnosis of lesions located in the outer part of the corpus callosum and transcallosal bilateral hemispheres on MRI, even though inner callosal lesions are common in multiple sclerosis.

PIMD: 18458896

Early anisotropy changes in the corpus callosum of patients with optic neuritis.

Optic neuritis (ON) and any other early manifestation of multiple sclerosis (MS) are referred to as clinically isolated syndrome (CIS) as long as MS is suspected. In this prospective study we aimed to determine whether diffusion tensor imaging (DTI) could quantify structural changes in patients with early MS.A total of 24 patients and 15 control subjects were prospectively followed by clinical examinations and MRI. the main inclusion criterion was presentation with ON. Patients underwent serial MRI scans: MRI1 (baseline, n=24), MRI2 (mean 6.6 months, n=24), MRI3 (mean 13.0 months, n=14), MRI4 (mean 39.4 months, n=5). Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) maps were derived from DTI. Four regions of interest (ROIs) were defined in normal-appearing white matter (NAWM).In the temporal course FA decreased in the genu of the callosal body (GCC) from MRI1 to MRI4 (P=0.005) and in the splenium of the callosal body (SCC) (P=0.006). Patients already had lower FA values in the SCC (P<0.01) on MRI1 compared with the controls. Patients had lower FA values in the GCC (P<0.01) starting from MRI2. Patients with definite MS on follow-up (n=9) showed a correlation between FA in the SCC and time (r=-0.40, P=0.004), whereas patients without progression did not.Our findings suggest that the corpus callosum is an early site for development of anisotropy changes in MS patients with ON. There seems to be a primary FA decrease in all patients with ON that only deteriorates in the group developing definite MS.

PIMD: 18371992

Diffusion weighted callosal integrity reflects interhemispheric communication efficiency in multiple sclerosis.

We aimed to investigate the relation between damage in the corpus callosum and the performance on an interhemispheric communication task in patients with multiple sclerosis (MS). Relative callosal lesion load defined as the ratio between callosal area and the total lesion load in the total corpus callosum, and the diffusion tensor imaging (DTI) derived measures fractional anisotropy (FA) and transverse and longitudinal diffusivity were calculated in sixteen female MS patients and sixteen age and education matched female controls. The redundancy gain task was used to behaviorally evaluate interhemispheric communication efficiency. During this task, simple reaction times to uni- and bilateral presented stimuli are recorded. The advantage in reaction time for bilateral as compared to unilateral trials, the redundancy gain, was significantly larger for the MS-group. The DTI data showed significantly decreased FA and increased diffusivity parameters in the corpus callosum for the MS patients compared with the control group. Moreover, we found a significant correlation between the DTI-derived measures in the corpus callosum and the redundancy gain effect. Callosal damage in MS, as measured by DTI and defined as transverse diffusivity, is associated with alterations in a behavioral task that relies on interhemispheric transfer and communication.

PIMD: 18365493

[Brain damage assessment in patients with multiple sclerosis by means of MRI].

Brain magnetic resonance imaging (MRI) findings in 32 patients recently clinically diagnosed with multiple sclerosis (MS) by McDonald's criteria are presented. Demyelinization plaques were examined according to their number, size and location in brain tissue. Classification was done by Frederiksen's quantification. The study included 18 (56.3%) female and 1-4 (43.7%) male patients aged 17-44, mean 32 +/- 2.4 years. The predominant plaque location was periventricular (100%), involving lateral brain chambers, followed by subcortical, pontine, corpus callosum, cerebellar and other locations (medulla oblongata, spinal marrow). According to plaque number, patients were divided into six groups, from 2-6 plaques (group 1), to 26 lesions (divided into four subgroups). Patients with at least one plaque 15 mm in diameter were allocated to a separate group. The largest was the group with 7-15 plaques (37%). According to plaque size, patients were divided into three groups: plaque of up to 6 mm in diameter, 6-15 mm in diameter, and at least one plaque 15 mm in diameter. Patients with plaque size 6-15 mm were found to predominate (64%). There was a surprisingly high incidence of severe brain damage, i. e. higher degrees by Frederiksen's quantification. The third and fourth quantification degrees were most common, with a significant number of plaques not exceeding 15 mm in diameter; however, there also were been patients with plaques of 15 mm in diameter, which is quite surprising at this early stage of the disease. This pilot study indicated that research should be extended to patients newly clinically diagnosed with MS, comparing their clinical symptoms and Frederiksen's quantification.

PIMD: 18354026

Callosal contributions to simultaneous bimanual finger movements.

Corpus callosum (CC) is involved in the performance of bimanual motor tasks. We asked whether its functional role could be investigated by combining a motor behavioral study on bimanual movements in multiple sclerosis (MS) patients with a quantitative magnetic resonance diffusion tensor imaging (DTI) analysis of CC, which is shown to be damaged in this disease. MS patients and normal subjects were asked to perform sequences of bimanual finger opposition movements at different metronome rates; then we explored the structural integrity of CC by means of DTI. Significant differences in motor performance, mainly referred to timing accuracy, were observed between MS patients and control subjects. Bimanual motor coordination was impaired in MS patients as shown by the larger values of the interhand interval observed at all the tested metronome rates with respect to controls. Furthermore, DTI revealed a significant reduction of fractional anisotropy (FA), indicative of microstructural tissue damage, in the CC of MS patients. By correlating the mean FA values with the different motor behavior parameters, we found that the degree of damage in the anterior callosal portions mainly influences the bimanual coordination and, in particular, the movement phase preceding the finger touch. Finally, the described approach, which correlates quantitative measures of tissue damage obtained by advanced magnetic resonance imaging tools with appropriate behavioral measurements, may help the exploration of different aspects of motor performance impairment attributable to the disease.

PIMD: 18349131

Cortical demyelination is prominent in the murine cuprizone model and is strain-dependent.

The cuprizone model of toxic demyelination in the central nervous system is commonly used to investigate the pathobiology of remyelination in the corpus callosum. However, in human demyelinating diseases such as multiple sclerosis, recent evidence indicates a considerable amount of cortical demyelination in addition to white matter damage. Therefore, we have investigated cortical demyelination in the murine cuprizone model. To induce demyelination, C57BL/6 mice were challenged with 0.2% cuprizone feeding for 6 weeks followed by a recovery phase of 6 weeks with a cuprizone-free diet. In addition to the expected demyelination in the corpus callosum, the cortex of C57BL/6 mice was completely demyelinated after 6 weeks of cuprizone feeding. After withdrawal of cuprizone the cortex showed complete remyelination similar to that in the corpus callosum. When C57BL/6 mice were fed cuprizone for a prolonged period of 12 weeks, cortical remyelination was significantly delayed. Because interstrain differences have been described, we also investigated the effects of cuprizone on cortical demyelination in BALB/cJ mice. In these mice, cortical demyelination was only partial. Moreover, cortical microglia accumulation was markedly increased in BALB/cJ mice, whereas microglia were absent in the cortex of C57BL/6 mice. In summary, our results show that cuprizone feeding is an excellent model in which to study cortical demyelination and remyelination, including contributing genetic factors represented by strain differences.

PIMD: 18325301

Treatment of Susac's Syndrome.

Susac's syndrome (SS) consists of the triad of encephalopathy, branch retinal artery occlusions (BRAO), and hearing loss. It usually affects women aged 20 to 40, but men are also affected, and the age range extends from 9 to 72 years. It tends to be unrecognized, even in major academic centers. The complete triad may not be present at the onset, which makes diagnosis more difficult. However, since this disorder is treatable, early diagnosis is important. The encephalopathy is usually associated with headaches, multifocal neurologic manifestations, and psychiatric features (particularly paranoia). MRI shows a white matter disturbance that is frequently confused with multiple sclerosis and acute disseminated encephalomyelitis. During the encephalopathy, the corpus callosum is always affected and shows central involvement--small to large "snowballs" and linear defects, "spokes." As the acute changes (microinfarcts) resolve, central callosal "holes" develop, a pathognomonic finding. The deep gray matter (70%) and leptomeninges (33%) also may be involved. Dilated fundus examination will reveal branch retinal artery occlusions. Fluorescein angiography may disclose pathognomonic staining of the arterioles proximal to the occlusions and of nonoccluded arterioles. The cochlear hearing loss, sometimes associated with vertigo, is usually bilateral, and deafness becomes a major disabling problem. Brain biopsies, anatomic observations, and responses to immunosuppressive therapy suggest that SS represents an autoimmune endotheliopathy in the microvasculature of the brain, retina, and cochlea. Treatment requires immunosuppression. High-dose corticosteroid therapy is the mainstay, but additional therapies such as intravenous immunoglobulin, mycophenolate mofetil, and cyclophosphamide are often necessary. Rituximab is the newest therapy to consider. Treatment should be prompt, aggressive, and sustained to avoid the dreaded residuals of dementia, deafness, and blindness.

PIMD: 18208899

Anterior periventricular linear lesions in optic-spinal multiple sclerosis: a combined neuroimaging and neuropathological study.

There are two distinct subtypes of multiple sclerosis (MS) in Asians, optic-spinal (OSMS) and conventional (CMS). In OSMS, severe spinal cord lesions are characteristic while brain lesions are scant. We sought to clarify atypical brain lesions in OSMS by neuroimaging and pathological studies. For brain MRI, 124 consecutive Japanese patients with clinically definite MS based on Poser criteria were enrolled, 57 with OSMS and 67 with CMS. Ten autopsied cases (seven OSMS and three CMS) were studied pathologically. Although the frequency of brain lesions fulfilling Barkhof criteria was significantly higher in CMS than in OSMS, periventricular linear lesions along with the anterior portion of the corpus callosum and the lateral ventricles were significantly more common in OSMS than in CMS. Pathologically, periventricular lesions in CMS extended deeply into the white matter, while those in OSMS were confined to periventricular areas. T cell infiltration in lesions was prominent in CMS but not in OSMS. Although severe axonal loss and cavity formation were commonly seen in periventricular and spinal cord lesions in OSMS, lymphocytic infiltrates and vessel wall thickening were observed only in the latter. Thus, we suggested that anterior periventricular linear lesions without ovoid ones are characteristic of OSMS.

PIMD: 18201701

Neuroaxonal ion dyshomeostasis of the normal-appearing corpus callosum in experimental autoimmune encephalomyelitis.

Atrophy of the corpus callosum (CC) is a well-documented observation in clinically definite multiple sclerosis (MS) patients. One recent hypothesis for the neurodegeneration that occurs in MS is that ion dyshomeostasis leads to neuroaxonal damage. To examine whether ion dyshomeostasis occurs in the CC during MS onset, experimental autoimmune encephalomyelitis (EAE) was utilized as an animal MS model to induce autoimmunity-mediated responses. To date, in vivo investigations of neuronal ion homeostasis has not been feasible using traditional neuroscience techniques. Therefore, the current study employed an emerging MRI method, called Mn2+-enhanced MRI (MEMRI). Mn2+ dynamics is closely associated with important neuronal activity events, and is also considered to be a Ca2+ surrogate. Furthermore, when injected intracranially, Mn2+ can be used as a multisynaptic tracer. These features enable MEMRI to detect neuronal ion homeostasis within a multisynaptic circuit that is connected to the injection site. Mn2+ was injected into the visual cortex to trace the CC, and T1-weighted imaging was utilized to observe temporal changes in Mn2+-induced signals in the traced pathways. The results showed that neuroaxonal functional changes associated with ion dyshomeostasis occurred in the CC during an acute EAE attack. In addition, the pathway appeared normal, although EAE-induced immune-cell infiltration was visible around the CC. The findings suggest that ion dyshomeostasis is a major neuronal aberration underlying the deterioration of normal-appearing brain tissues in MS, supporting its involvement in neuroaxonal functioning in MS.

PIMD: 18155611

The topographical distribution of tissue injury in benign MS: a 3T multiparametric MRI study.

We compared the global and regional distribution of white matter (WM) and gray matter (GM) damage and T2-visible lesion between patients with benign (B) and relapsing remitting (RR) multiple sclerosis (MS). BMS and RRMS patients did not differ in terms of global volumes and diffusion tensor (DT) MRI metrics of the WM and GM. Compared to controls, BMS and RRMS patients had bilateral thalamic loss. Compared to controls, BMS and RRMS patients had lower WM fractional anisotropy (FA) in the corpus callosum (CC) and in several regions of temporal and occipital lobes. BMS also had a decreased WM FA in the parietal lobes. RRMS patients had also lower WM FA in several regions of the frontal lobes. Compared to BMS, RRMS patients had decreased WM FA in the frontal lobes, while the opposite comparison showed lower WM FA in the CC, the temporal lobes and the cuneus in BMS. Contrasted to controls, both MS groups showed several regions of increased MD in WM and GM, but no difference was found between MS sub-groups. T2-visible lesions were mainly located in the posterior regions of the brain in BMS patients, while they involved also regions in the frontal lobes, in RRMS patients. BMS and RRMS patients differ in terms of the topographical distribution of WM damage rather than in the overall extent of brain structural changes. The less prominent involvement of the frontal lobe WM and of the NAWM in general in BMS might be associated to their favorable clinical status.

PIMD: 18096162

Epileptic seizures and hippocampal damage after cuprizone-induced demyelination in C57BL/6 mice.

Epileptic seizures are known to occur in different animal models of demyelination and have also been described in demyelinating diseases of the central nervous system (CNS) such as multiple sclerosis. How myelin deficiency might cause seizures is unknown, but may involve axonal pathology and resultant alterations in neuronal excitability. The cause of seizures occurring in rodent demyelination models is unknown. In the present study, we used EEG/video monitoring to record seizures occurring during chronic demyelination of C57BL/6 mice fed for 12 weeks with 0.2% cuprizone. Furthermore, in the search for a morphological correlate of the seizures, the hippocampal formation was examined histologically. Epileptiform spikes resembling interictal spikes known from chronic epilepsy were recorded in all cuprizone-treated mice, but not in controls. Most cuprizone-treated animals exhibited generalized tonic-clonic seizures upon stress-inducing stimuli. In addition to the known demyelination of the corpus callosum, massive demyelination was found in the hippocampal formation. This was associated with neuronal alterations, including a loss of neurons in the hilus of the dentate gyrus. In view of the role of the dentate gyrus in epileptogenesis, demyelination leading to axonal pathology and thus neuronal damage as observed in the hilus may be causally involved in the paroxysmal alterations observed after prolonged treatment with cuprizone. The present data suggest a potential role of the hippocampal formation for seizures occurring as a consequence of neuronal damage secondary to CNS demyelination.

PIMD: 18094848

Corpus callosum index: a practical method for long-term follow-up in multiple sclerosis.

Rather than acute inflammation, long-standing multiple sclerosis (MS) course is hallmarked by relentless axonal loss and brain atrophy, both with subtle clinical expression and scarcely visible on conventional MRI studies. Brain atrophy imaging has sophisticated methodological requirements, not always practical and accessible to most centers. Corpus callosum (CC) is a major inter-hemispheric white matter bundle, grossly affected by long term MS and easily assessed by MRI. To determine whether a practical imaging method can reliably follow presumed axonal loss in patients with progressive MS, we designed a 5-year prospective open label study, enrolling 128 consecutive patients (75 relapsing-remitting (RR) and 53 secondary-progressive (SP)), on regular immunomodulatory therapy compared to control group, formed by 23 patients with MRI considered normal. On a conventional best mid-sagittal T1W, CC index (CCI) was obtained by measuring anterior, medium and posterior segments of CC, normalized to its greatest anteroposterior diameter using an orthogonal semi-automated linear system. CCI was measured at baseline and at least once yearly. Results were plotted intra-individually; baseline values were used as reference. At baseline, CCI was able to distinguish SP patients from RR and controls, and on follow-up, despite some overlap, demonstrated a progressive reduction from baseline on both RR and SP groups compared to controls. From the third year on, difference between SP and RR patients reached statistical significance, which did not correlated with disability measured by EDSS. So, a corpus callosum index proved practical and feasible to longitudinally demonstrate morphometric callosal changes with potential to be used as a tool for long-term follow-up, mostly in SP patients.

PIMD: 18002404

Longitudinal, regional and deformation-specific corpus callosum shape analysis for multiple sclerosis.

The corpus callosum (CC) is an anatomical structure which connects the two brain hemispheres. Neurological diseases can cause atrophy of the CC resulting in a change in its size and shape. The measurement and analysis of this change is one of the goals of clinical research. We perform statistical analysis of the shape of the CC extracted from MR brain scans of a group of multiple sclerosis patients undergoing a longitudinal (serial) study. In contrast to the classical boundary-based, global shape variability measures, e.g. principal component analysis (PCA) of CC boundary vertices, we perform a deformation-specific PCA for analyzing the global and regional shape of the CC. This deformation-specific PCA is based on a medial-based shape representation. The adopted shape representation describes shape variability in terms of intuitive deformations (e.g. bending, stretching and thickness). We present qualitative and quantitative results for 412 MR images of the CC. We show that our method is successful in identifying and quantifying the effect of each type of deformation on the shape variability of the CC. In addition to analyzing the spatial shape variability in the CC, we explore shape changes as the disease progresses. Our method allows the exploration of the shape variability quantitatively (e.g. the amount of variance explained by a particular principal mode of shape variation) as well as in a qualitative visual manner (e.g. by visualizing, say, the 2nd principal mode of shape variation due to bending at the 4th sub-region of the CC) which is useful for developing an intuitive understanding of the effects of MS on the CC shape.

PIMD: 17984680

Platelet-derived growth factor promotes repair of chronically demyelinated white matter.

In multiple sclerosis, remyelination becomes limited after repeated or prolonged episodes of demyelination. To test the effect of platelet-derived growth factor-A (PDGF-A) in recovery from chronic demyelination we induced corpus callosum demyelination using cuprizone treatment in hPDGF-A transgenic (tg) mice with the human PDGF-A gene under control of an astrocyte-specific promoter. After chronic demyelination and removal of cuprizone from the diet, remyelination and oligodendrocyte density improved significantly in hPDGF-A tg mice compared with wild-type mice. In hPDGF-A tg mice, oligodendrocyte progenitor density and proliferation values were increased in the corpus callosum during acute demyelination but not during chronic demyelination or the subsequent recovery period, compared with hPDGF-A tg mice without cuprizone or to treatment-matched wild-type mice. Proliferation within the subventricular zone and subcallosal zone was elevated throughout cuprizone treatment but was not different between hPDGF-A tg and wild-type mice. Importantly, hPDGF-A tg mice had reduced apoptosis in the corpus callosum during the recovery period after chronic demyelination. Therefore, PDGF-A may support oligodendrocyte generation and survival to promote remyelination of chronic lesions. Furthermore, preventing oligodendrocyte apoptosis may be important not only during active demyelination but also for supporting the generation of new oligodendrocytes to remyelinate chronic lesions.

PIMD: 17968901

MRI identification of the rostral-caudal pattern of pathology within the corpus callosum in the cuprizone mouse model.

To characterize and compare histological and MRI-based changes within the corpus callosum (CC) in the cuprizone mouse model of multiple sclerosis (MS).A total of 12 C57/BL6 mice were fed cuprizone from eight weeks of age for four weeks. One cohort of six cuprizone and two control mice were scanned with a T2-weighted (T2W) sequence. The other cohort of six cuprizone and four control mice were scanned using a dual-echo sequence for T2-mapping and a diffusion-weighted sequence with two orthogonal diffusion encoding directions to calculate water diffusivities parallel and perpendicular to the CC fiber (apparent diffusion coefficients [ADC](parallel) and ADC(perpendicular)). After the mice were killed, the rostral-caudal pattern of CC demyelination and other pathologies were examined using Luxol Fast Blue, neurofilament staining, and immunohistochemistry for microglia and were correlated with MRI.In contrast to control mice, T2W imaging (T2WI) hyperintensity, reduced ADC(parallel), and elevated ADC(perpendicular) were detected in the CC of cuprizone-fed mice, particularly in the caudal segment. The T2 value was increased in the entire CC. Marked demyelination, as well as axonal injury, microglia accumulation, and cellular infiltration were found in the caudal section of the cuprizone mouse CC. The rostral-caudal pattern of abnormalities within the CC in MRI measurements correlated well with histopathological findings.Noninvasive MRI using quantitative T2 and ADC mapping accurately characterized the rostral-caudal pattern of CC demyelination and other pathologies in cuprizone challenged mice, and thus could provide an effective way to assess the structural response to experimental therapeutics being designed for the treatment of MS.

PIMD: 17961136

Sequential myelin protein expression during remyelination reveals fast and efficient repair after central nervous system demyelination.

To understand the mechanisms of remyelination and the reasons for regeneration failure is one of the major challenges in multiple sclerosis research. This requires a good knowledge and reliable analysis of experimental models. This work was undertaken to characterize the pattern of myelin protein expression during experimental remyelination. Acute demyelination of the corpus callosum was induced by feeding of 0.3% cuprizone for 6 weeks, followed by a 10-week remyelination period. We used a combination of Luxol fast blue (LFB) myelin staining, electron microscopy (EM) and immunohistochemistry for the myelin proteins 2',3'-cyclic nucleotide 3' phosphodiesterase (CNPase), myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG). Early remyelination was detected by the re-expression of CNPase, MBP and PLP as early as 4 days. MOG, as a marker for late differentiation of oligodendrocytes, was not detectable until 2 weeks of remyelination. EM data correlated well with the LFB myelin staining and myelin protein expression, with 50% of the axons being rapidly remyelinated within 2 weeks. While particularly MBP but also PLP and CNPase are re-expressed very early before significant remyelination is observed by EM, the late marker MOG shows a lag behind the remyelination detected by EM. The presented data indicate that immunohistochemistry for various myelin proteins expressed early and late during myelin formation is a suitable and reliable method to follow remyelination in the cuprizone model. Furthermore, investigation of early remyelination confirms that the intrinsic repair programme is very fast and switched on within days.

PIMD: 17885738

Transient focal lesion in the splenium of the corpus callosum: MR imaging with an attempt to clinical-physiopathological explanation and review of the literature.

This article discusses the possible pathophysiological conditions responsible for magnetic resonance imaging (MRI) finding of transient focal lesions in the splenium of the corpus callosum on the basis of our experience and a review of the literature.In six patients undergoing computed tomography (CT) and MRI examinations, focal nonhemorrhagic lesions of the splenium of the corpus callosum were incidentally discovered. Patients had been referred for suspected encephalitis (n=2), dural sinus thrombosis (n=1) and multiple sclerosis (n=3). MRI examinations were repeated after 4, 8 and 12 weeks and in two cases also after 6 and 9 months. MRI and medical records were retrospectively reviewed with respect to patients' clinical history, medication and laboratory findings to define lesion aetiology.In all patients, the lesions were isolated, reversible and with no contrast enhancement. In four patients, the lesion disappeared after complete remission of the underlying disease, whereas in two patients, they persisted for 6 and 9 months, respectively.To our knowledge and according to previous reports, the fact that these lesions are detected in a relatively large number of conditions with heterogeneous etiopathogenetic factors leads to the hypothesis that a common underlying pathophysiological mechanism that, considering signal characteristic, reversibility and white matter location, could be represented by vasogenic oedema.

PIMD: 17673493

Use of combined conventional and quantitative MRI to quantify pathology related to cognitive impairment in multiple sclerosis.

Cognitive impairment is one of the frequent and early findings in multiple sclerosis (MS).To determine the relation between cognitive abnormalities and the extent of macroscopic and microscopic tissue damage in the corpus callosum (CC), revealed by conventional magnetic resonance imaging (MRI), magnetisation transfer imaging (MTI) and diffusion tensor imaging (DTI).Conventional dual-echo, DTI and MTI of the brain were obtained from 36 patients with relapsing remitting (RR) MS, and 13 age and gender matched normal controls. Voxels from CC were identified using a tractography based algorithm. Mean apparent diffusion coefficient (ADC(av)) and MT ratio were measured for the CC as defined by tractography. Corpus callosum area (CCA) was measured using edge detection on the mid-sagittal slice on high resolution MRI images. The Expanded Disability Status Scale (EDSS) and Paced Auditory Serial Addition Test (PASAT) were scored.Nine patients (25%) were found to be cognitively impaired. The CCA was not significantly different in the whole cohort of patients from controls (608.2 (428.6-713.0) mm(2) vs 674.2 (585.8-754.4) mm(2), p = 0.1), but was smaller in cognitively impaired than unimpaired group (417 (290-634) mm(2) vs 652 (511-718) mm(2), p = 0.04). The mean MT ratio of CC in patients was lower than in controls (0.41 (0.39-0.042) vs 0.43 (0.42-0.43), p<0.001). The ADC(av) in the CC in patients was higher than in controls (0.94 (0.89-0.99) vs 0.87 (0.85-0.89), p<0.001). PASAT was correlated with mean MT ratio (r = 0.47, p = 0.0046), ADC(av) (r = -0.53, p = 0.0012), CCA (r = 0.42, p = 0.01) and total T(2) lesion load (r = -0.4, p = 0.017), but not with T(2) lesion load within the CC (r = -0.24, p = 0.16), disease duration (r = -0.2, p = 0.24) or EDSS (r = -0.27, p = 0.12).ADC(av), MTR and atrophy measures in the CC may offer a sensitive method detecting subtle macroscopic and microscopic changes associated with cognitive impairment in MS.

PIMD: 17617614

The human endogenous retrovirus envelope glycoprotein, syncytin-1, regulates neuroinflammation and its receptor expression in multiple sclerosis: a role for endoplasmic reticulum chaperones in astrocytes.

Retroviral envelopes are pathogenic glycoproteins which cause neuroinflammation, neurodegeneration, and endoplasmic reticulum stress responses. The human endogenous retrovirus (HERV-W) envelope protein, Syncytin-1, is highly expressed in CNS glia of individuals with multiple sclerosis (MS). In this study, we investigated the mechanisms by which Syncytin-1 mediated neuroimmune activation and oligodendrocytes damage. In brain tissue from individuals with MS, ASCT1, a receptor for Syncytin-1 and a neutral amino acid transporter, was selectively suppressed in astrocytes ($p < 0.05$). Syncytin-1 induced the expression of the endoplasmic reticulum stress sensor, old astrocyte specifically induced substance (OASIS), in cultured astrocytes, similar to findings in MS brains. Overexpression of OASIS in astrocytes increased inducible NO synthase expression but concurrently down-regulated ASCT1 ($p < 0.01$). Treatment of astrocytes with a NO donor enhanced expression of early growth response 1, with an ensuing reduction in ASCT1 expression ($p < 0.05$). Small-interfering RNA molecules targeting Syncytin-1 selectively down-regulated its expression, preventing the suppression of ASCT1 and the release of oligodendrocyte cytotoxins by astrocytes. A Syncytin-1-transgenic mouse expressing Syncytin-1 under the glial fibrillary acidic protein promoter demonstrated neuroinflammation, ASCT1 suppression, and diminished levels of myelin proteins in the corpus callosum, consistent with observations in CNS tissues from MS patients together with neurobehavioral abnormalities compared with wild-type littermates ($p < 0.05$). Thus, Syncytin-1 initiated an OASIS-mediated suppression of ASCT1 in astrocytes through the induction of inducible NO synthase with ensuing oligodendrocyte injury. These studies provide new insights into the role of HERV-mediated neuroinflammation and its contribution to an autoimmune disease.

PIMD: 17613597

Magnetization transfer ratio measurement in multiple sclerosis normal-appearing brain tissue: limited differences with controls but relationships with clinical and MR measures of disease.

We investigated the magnetization transfer ratio (MTR) of normal-appearing white (NAWM) and grey matter (NAGM) in a relatively large group of multiple sclerosis (MS) patients, and the relations of MTR changes with clinical disability. MTR was measured in 66 MS patients (12 PP, 35 RR, 19 SP) and 23 healthy controls, using a whole-brain 3D-FLASH technique corrected post-hoc for B1-induced variation. Histogram parameters of conservatively selected NAWM and cortical NAGM were analysed using Bonferroni-corrected ANOVA with age as covariate. Additionally, manually outlined regions of interest were analysed using a multilevel method. Lesions had low MTR (mean 22.7+/-6.9%), but NAWM exhibited limited changes: MTR histogram peak position was 32.8+/-1.0% in controls and 32.4+/-0.9% in MS patients, with a significant decrease compared to controls only in SPMS patients (31.9+/-1.1%, p=0.045). Cortical NAGM histograms did not differ significantly between patients and controls. In SPMS, regional mean MTR was significantly decreased in corpus callosum and hippocampus. MTR histogram parameters of NAGM and NAWM were correlated with EDSS and MSFC scores, with lesion volume and with normalized brain volume. We conclude that disease-induced MTR changes were small in MS NAWM and NAGM, but did correlate with clinical decline, lesion volume and overall cerebral atrophy.

PIMD: 17522347

Relapsing neuromyelitis optica and relapsing-remitting multiple sclerosis: differentiation at diffusion-tensor MR imaging of corpus callosum.

To prospectively assess sensitivity and specificity of diffusion indexes of the corpus callosum (CC) for differentiating relapsing neuromyelitis optica (RNMO) from relapsing-remitting multiple sclerosis (RRMS), by using final clinical diagnosis as the reference standard.Participants provided informed consent; the study was approved by the institutional review board. Forty-six consecutive patients with RRMS (18 men, 28 women; mean age, 37.7 years; range, 18-58 years) and 26 consecutive patients with RNMO (two men, 24 women; mean age, 38.6 years; range, 19-59 years) underwent diffusion-tensor magnetic resonance imaging. Mean diffusivity (MD) and fractional anisotropy (FA) of the region of interest (ROI) of the CC in the midsagittal plane were measured and used as discriminative indexes. Bayesian classification with leave-one-out cross-validation was used to determine diagnostic accuracy. Differences in diffusion indexes of ROIs among groups were evaluated by using the Kruskal-Wallis test, followed by the Mann-Whitney U test for multiple comparisons and Bonferroni correction.Mean MD (8.48 x 10(-4) mm(2)/sec) and FA (0.729) of the ROI in patients with RNMO were significantly (P<.001) different from those (MD=10.64 x 10(-4) mm(2)/sec, FA=0.599) in patients with RRMS. Sensitivity and specificity for differentiation were 92.3% (24 of 26 patients with RNMO) and 93.5% (43 of 46 patients with RRMS) for FA and 88.5% (23 of 26 patients with RNMO) and 89.1% (41 of 46 patients with RRMS) for MD, respectively.Measurement of diffusion indexes of the CC may be useful for distinguishing patients with RNMO from those with RRMS.

PIMD: 17476496

Susac syndrome in a young child.

Susac syndrome is a microangiopathy of unknown origin affecting the brain, retina and inner ear. This rare entity is often misdiagnosed as a demyelinating condition such as multiple sclerosis or acute disseminated encephalomyelitis. A high index of suspicion must be present as the majority of patients do not have the complete clinical triad at the time of onset of symptoms. The radiologist plays an important role when the disease is suspected and helps orient the investigations. The syndrome has characteristic imaging features on MRI that include multifocal white matter and occasional grey matter lesions, the corpus callosum being always involved. The predominant central callosal lesions, especially with rapid cystic transformation (central callosal holes) can be considered pathognomonic of this condition in the appropriate clinical setting. This disease is extremely rare in children. We report a case of Susac syndrome in a 9-year-old girl to increase the awareness among paediatric radiologists of this entity, which is usually not considered as a differential diagnosis of multifocal white matter involvement in this age group.

PIMD: 17416836

Correlation of diffusion tensor and dynamic perfusion MR imaging metrics in normal-appearing corpus callosum: support for primary hypoperfusion in multiple sclerosis.

Hypoperfusion of the normal-appearing white matter in multiple sclerosis (MS) may be related to ischemia or secondary to hypometabolism from wallerian degeneration (WD). This study evaluated whether correlating perfusion and diffusion tensor imaging (DTI) metrics in normal-appearing corpus callosum could provide support for an ischemic mechanism for hypoperfusion.Fourteen patients with relapsing-remitting MS (RRMS) and 17 control subjects underwent perfusion MR imaging and DTI. Absolute measures of cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT) were calculated. Mean diffusivity (MD) and fractional anisotropy (FA) maps were computed from DTI data. After visual coregistration of perfusion and DTI images, regions of interest were placed in the genu, central body, and splenium of normal-appearing corpus callosum. Pearson product-moment correlation coefficients were calculated using mean DTI and perfusion measures in each region.In the RRMS group, CBF and CBV were significantly correlated with MD in the splenium ($r = 0.83$ and $r = 0.63$, respectively; both $P < .001$) and in the central body ($r = 0.86$ and $r = 0.65$, respectively; both $P < .001$), but not in the genu ($r = 0.23$ and 0.25, respectively; both P is nonsignificant). No significant correlations were found between MTT and DTI measures or between FA and any perfusion measure in the RRMS group. No significant correlations between diffusion and perfusion metrics were found in control subjects.In the normal-appearing corpus callosum of patients with RRMS, decreasing perfusion is correlated with decreasing MD. These findings are more consistent with what would be expected in primary ischemia than in secondary hypoperfusion from WD.

PIMD: 17398118

Discordant white matter N-acetylasparate and diffusion MRI measures suggest that chronic metabolic dysfunction contributes to axonal pathology in multiple sclerosis.

Diffusion MRI and magnetic resonance spectroscopic measurements of selectively neuronally localised N-acetylaspartate (NAA) both have been used widely to assess white matter integrity and axonal loss. We have tested directly the relationship between changes in diffusion MRI parameters and NAA concentrations in the corpus callosum (CC) in an in vivo study of patients with MS. Fifteen MS patients (median EDSS 2.5, range 1-4) were studied with T(1) anatomical, T(2)-weighted, and diffusion-sensitised MRI and PRESS single-voxel MRS. A recently described method, tract-based spatial statistics (TBSS) [Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E. et al., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487-1505] also was used to perform exploratory voxelwise whole-brain analysis of white matter diffusion fractional anisotropy (FA). We found a strong correlation between callosal size and both mean FA ($r=0.68$, $p<0.005$) (related specifically to changes in the radial tensor component) and mean inter-hemispheric motor tract connectivity probability ($r=0.74$, $p<0.001$). TBSS confirmed that the diffusion anisotropies of white matter voxels specifically within the callosum were correlated with the callosal size. Individual patient global T(2) lesion volumes were correlated with both the probability of callosal connectivity ($r=-0.69$, $p<0.005$) and fractional anisotropy across the callosum ($r=-0.76$, $p<0.001$). However, absolute concentrations of NAA from the voxel showed no correlation with callosal cross-sectional area, mean connectivity or fractional anisotropy within the callosal pathway. We conclude that diffusion MRI shows changes consistent with sensitivity to axonal loss, but that relative NAA changes are not necessarily related directly to this. Axonal metabolic function, independent of structural integrity, may be a major determinant of NAA measures in MS.

PIMD: 17331742

In vivo fiber tracking in the rat brain on a clinical 3T MRI system using a high strength insert gradient coil.

In vivo neuroimaging methods permit longitudinal quantitative examination of the dynamic course of neurodegenerative conditions in humans and animal models and enable assessment of therapeutic efforts in mitigating disease effects on brain systems. The study of conditions affecting white matter, such as multiple sclerosis, demyelinating conditions, and drug and alcohol dependence, can be accomplished with diffusion tensor imaging (DTI), a technique uniquely capable of probing the microstructural integrity of white matter fibers in the living brain. We used a 3T clinical MR scanner equipped with an insert gradient coil that yields an order of magnitude increase in performance over the whole-body hardware to acquire in vivo DTI images of rat brain. The resolution allowed for fiber tracking evaluation of fractional anisotropy (FA) and apparent diffusion coefficients in the genu and splenium of the corpus callosum. A comparison of short (46 min) and long (92 min) acquisition time DTI protocols indicated low but adequate signal-to-noise ratio (SNR=6.2) of the shorter protocol to conduct quantitative fiber tracking enhanced by multiple acquisitions. As observed in human studies, FA in the rat splenium was higher than in the genu. Advantages of this technology include the use of similar user interface, pulse sequences, and field strength for preclinical animal and clinical human research, enhancing translational capabilities. An additional benefit of scanning at lower field strength, such as 3 T, is the reduction of artifacts due to main field inhomogeneity relative to higher field animal systems.

PIMD: 17294610

Onset and underpinnings of white matter atrophy at the very early stage of multiple sclerosis--a two-year longitudinal MRI/MRSI study of corpus callosum.

Atrophy of corpus callosum (CC), a white matter structure linking the two hemispheres, is commonly observed in multiple sclerosis (MS). However, the occurrence and processes leading to this alteration are not yet determined.To better characterize the onset and progression of CC atrophy from the early stage of MS, we performed a two-year follow-up magnetic resonance imaging/magnetic resonance spectroscopic imaging (MRI/MRSI) exploration of CC in 24 patients with clinically isolated syndrome. These patients were explored using the same protocol at month (M)6, M12 and M24. MRI/MRSI techniques were applied to measure CC volume, and relative concentrations of N-acetylaspartate (NAA), creatine/phosphocreatine (Cr) and choline-containing compounds (Cho). A group of matched controls was also explored.Atrophy of CC, not present at baseline, was observed at M12 and progressed over the second year (M24). At baseline, a decrease in relative NAA level was observed in the anterior and posterior body of CC, with normalization during the follow-up period. In the anterior body, an increase in relative Cho level was observed, with normalization at M6. Normal relative Cr levels were observed at all time points in all sub-regions. The rate of CC atrophy was correlated with the change in the Expanded Disability Status Scale (EDSS) during the follow-up period.These results suggest that CC atrophy appears over a period of one year after the first acute inflammatory episode, and that this atrophy is accompanied, especially in the anterior body of CC, by a normalization of the relative Cho levels, marker of acute inflammation, and NAA levels, marker of neuronal dysfunction and/or loss.

PIMD: 17191231

Serial in vivo MR tracking of magnetically labeled neural spheres transplanted in chronic EAE mice.

Neural stem cell (NSC) transplantation has been shown to attenuate the severity of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS). Central to the future success of NSC transplantation in MS is the ability of transplanted cells to migrate from the site of transplantation to relevant foci of disease. Using magnetically labeled mouse neurospheres and human embryonic stem cell (hESC)-derived neurospheres, we applied serial magnetic resonance imaging (MRI) to assess the biodynamics of transplanted cell migration in a chronic mouse EAE model. Magnetic labeling did not affect the in vitro and in vivo characteristics of cells as multipotential precursors. Cell migration occurred along white matter (WM) tracts (especially the corpus callosum (CC), fimbria, and internal capsule), predominantly early in the acute phase of disease, and in an asymmetric manner. The distance of cell migration correlated well with clinical severity of disease and the number of microglia in the WM tracts, supporting the notion that inflammatory signals promote transplanted cell migration. This study shows for the first time that hESC-derived neural precursors also respond to tissue signals in an MS model, similarly to rodent cells. The results are directly relevant for designing and optimizing cell therapies for MS, and achieving a better understanding of in vivo cell dynamics and cell-tissue interactions.

PIMD: 17119006

Progression of non-age-related callosal brain atrophy in multiple sclerosis: a 9-year longitudinal MRI study representing four decades of disease development.

In multiple sclerosis (MS), multiple periventricular lesions are commonly the first findings on MRI. However, most of these MS lesions are clinically silent. The brain atrophy rate has shown better correlation to physical disability, but it is not clear how atrophy develops over decades. Corpus callosum forms the roof of the third and lateral ventricles. The corpus callosum area (CCA) in a midsagittal image is age independent in a normal adult population up to the seventh decade; therefore it can be used as a marker for non-age-related, pathological brain atrophy.To investigate whether and how CCA decreases in size over time in patients with MS.In a clinical observational study, 37 patients with MS with a wide range of disease duration at baseline (1-33 years) were followed. Three different MS courses were represented. The mean of individual MRI follow-up was 9 years. Multiple sclerosis severity score (MSSS) was also applied to evaluate disability at baseline and after 9 years of follow-up.A significant decrease in CCA over 9 years ($p<0.001$) and a persisting association between CCA and the disability status were found. The atrophy rate was similar ever four decades of MS for all MS courses. The mean annual CCA decrease was 9.25 mm2 (1.8%). Surprisingly, atrophy rate did not correlate with sex, disease duration, age at MS onset or MS course.Serial evaluations of CCA might be a robust method in monitoring a non-age-related decrease in CCA, reflecting progression of irreversible destructive changes in MS.

PIMD: 17114854

Ataxia and deafness in a young male: an unusual aetiology.

We report here a case of 18 year old male with tremors of hands, deafness, tendency to fall while walking, drowsiness and double vision of total duration 1(1/2) years. He had internuclear ophthalmoplegia, broken saccades, hypertonia and hyperreflexia of all four limbs, intention tremors, signs of gait and limb ataxia. Pupillary reactions and fundus examination were normal and signs of meningeal irritation or sensory neurological deficit were absent. MRI head and cervical spine with gadolinium enhancement revealed demyelination as evident from multiple oblong foci isointense on T1-weighted images and hyperintense on T2-weighted and fluid attenuated inversion recovery sequences in corpus callosum, sub-cortical white matter, right thalamus, pons and periaqueductal region of midbrain. Ill-defined linear hyperintense signals were observed in cervical spinal cord. No skeletal abnormality was noted in the skull or cervical spine. Oligoclonal bands were present in the cerebrospinal fluid. Brainstem auditory evoked potentials were abnormal, although visual evoked potentials were in normal range. A diagnosis of primary progressive multiple sclerosis (PPMS) was made fulfilling the revised criteria as laid down. In view of its presentation, it is a unique case of PPMS from India.

PIMD: 17086902

Identifying reliable change in tactile temporal thresholds in multiple sclerosis: test-retest reliability.

Tactile temporal thresholds are typically significantly higher (ie, prolonged) in multiple sclerosis (MS) patients when compared to controls and increase significantly during relapses, probably reflecting integrity of conduction across a portion of the corpus callosum. As part of an ongoing validation study of tactile temporal thresholds, the test-retest reliability of these thresholds was examined in patients with MS.Tactile temporal thresholds were measured in 61 MS patients during two separate test sessions within three weeks. Test-retest reliability and the standard error of measurement were calculated. The threshold of change in tactile temporal thresholds in MS patients that would correspond to real change beyond measurement error with 95% certainty was also calculated.The test-retest reliability of this measure of tactile temporal thresholds was 0.93. The threshold indicating change beyond chance or measurement error with 95% certainty was 19 ms.This measure of tactile temporal thresholds has excellent test-retest reliability and a change of greater than 19 ms is highly likely to represent real change. This measure is promising as a precise, reliable outcome measure in MS.

PIMD: 17080438

Effect of corpus callosum damage on ipsilateral motor activation in patients with multiple sclerosis: a functional and anatomical study.

Functional MRI (fMRI) studies have shown increased activation of ipsilateral motor areas during hand movement in patients with multiple sclerosis (MS). We hypothesized that these changes could be due to disruption of transcallosal inhibitory pathways. We studied 18 patients with relapsing-remitting MS. Conventional T1- and T2-weighted images were acquired and lesion load (LL) measured. Diffusion tensor imaging (DTI) was performed to estimate fractional anisotropy (FA) and mean diffusivity (MD) in the body of the corpus callosum (CC). fMRI was obtained during a right-hand motor task. Patients were studied to evaluate transcallosal inhibition (TCI, latency and duration) and central conduction time (CCT). Eighteen normal subjects were studied with the same techniques. Patients showed increased MD ($P < 0.0005$) and reduced FA ($P < 0.0005$) in the body of the CC. Mean latency and duration of TCI were altered in 12 patients and absent in the others. Between-group analysis showed greater activation in patients in bilateral premotor, primary motor (M1), and middle cingulate cortices and in the ipsilateral supplementary motor area, insula, and thalamus. A multivariate analysis between activation patterns, structural MRI, and neurophysiological findings demonstrated positive correlations between T1-LL, MD in the body of CC, and activation of the ipsilateral motor cortex (iM1) in patients. Duration of TCI was negatively correlated with activation in the iM1. Our data suggest that functional changes in iM1 in patients with MS during a motor task partially represents a consequence of loss of transcallosal inhibitory fibers.

PIMD: 17024655

Identification of fibers at risk for degeneration by diffusion tractography in patients at high risk for MS after a clinically isolated syndrome.

Focal inflammatory/demyelinating lesions are thought to be the source of Wallerian degeneration or other injury to local, transiting fiber tracts in the brain or spinal cord in multiple sclerosis (MS). A methodology is established to isolate connections between focal demyelinating lesions and intersecting fibers to permit explicit analyses of the pathology of secondary fiber injury distant from the focal lesion.A strategy is described and feasibility demonstrated in three patients with a clinically isolated syndrome and positive MRI (at high risk for MS). The strategy utilizes streamtube diffusion tractography to identify neuronal fibers that intersect a focal lesion and pass through a region of interest, in this case the corpus callosum, where distal (to focal lesion) interrogation can be accomplished.A sizeable fraction of the normal appearing white matter (NAWM) in the early stages of disease can be defined in the corpus callosum, which is distinctive in that this tissue connects to distant demyelinating lesions.The new class of tissue called fibers-at-risk for degeneration (FAR) can be identified and interrogated by a variety of quantitative MRI methodologies to better understand neuronal degeneration in MS.

PIMD: 17011585

Ipsilateral silent period: a marker of callosal conduction abnormality in early relapsing-remitting multiple sclerosis?

The corpus callosum (CC) is commonly affected in multiple sclerosis (MS). The ipsilateral silent period (iSP) is a putative electrophysiological marker of callosal demyelination. The purpose of this study was to re-assess, under recently established optimised protocol conditions [Jung P., Ziemann U. Differences of the ipsilateral silent period in small hand muscles. Muscle Nerve in press.], its diagnostic sensitivity in MS, about which conflicting results were reported in previous studies.ISP measurements (onset, duration, and depth) were obtained in the abductor pollicis brevis (APB) muscle of either hand in 49 patients with early relapsing-remitting MS (RRMS) (mean EDSS, 1.3). Standard central motor conduction times to the APB (CMCT(APB)) and tibial anterior muscles (CMCT(TA)), and magnetic resonance images (MRI) were also obtained.ISP measurements showed a similar diagnostic sensitivity (28.6%) as CMCT(APB) (24.5%), while diagnostic sensitivities of CMCT(TA) (69.4%) and MRI of the CC (78.6%) were much higher. Prolongation of iSP duration was the most sensitive single iSP measure. ISP prolongation occurred more frequently when CMCT(APB) to the same hand was also prolonged (40.0% vs. 8.4%, $p<0.0001$). The correlation between iSP duration and CMCT(APB) was significant (Pearson's $r=0.24$, $p<0.02$), suggesting that iSP duration can be contaminated by demyelination of the contralateral corticospinal tract. ISP duration did not correlate with MRI abnormalities of the CC.ISP measures are neither a sensitive nor a specific marker of callosal conduction abnormality in early RRMS.

PIMD: 16996280

Pattern of hemodynamic impairment in multiple sclerosis: dynamic susceptibility contrast perfusion MR imaging at 3.0 T.

This study aimed to determine regional pattern of tissue perfusion in the normal-appearing white matter (NAWM) of patients with primary-progressive (PP), relapsing-remitting (RR) multiple sclerosis (MS) and healthy controls, and to investigate the association between perfusion abnormalities and clinical disability. Using dynamic susceptibility contrast (DSC) perfusion MRI at 3 T, we studied 22 patients with clinically definite MS, 11 with PP-MS and 11 with RR-MS and 11 age- and gender-matched healthy volunteers. The MRI protocol included axial dual-echo, dynamic susceptibility contrast enhanced (DSC) T2*-weighted and post-contrast T1-weighted images. Absolute cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) were measured in the periventricular, frontal, occipital NAWM and in the splenium of the corpus callosum. Compared to controls, CBF and CBV were significantly lower in all NAWM regions in both PP-MS patients (p values from <0.0001 to 0.001) and RR-MS (p values from <0.0001 to 0.020). Compared to RR-MS, PP-MS patients showed significantly lower CBF in the periventricular NAWM (p=0.002) and lower CBV in the periventricular and frontal NAWM (p values: 0.0029 and 0.022). EDSS was significantly correlated with the periventricular CBF (r=-0.48, p=0.0016) and with the periventricular and frontal CBV (r=-0.42, p=0.015; r=-0.35, p=0.038, respectively). This study suggests that the hemodynamic abnormalities of NAWM have clinical relevance in patients with MS. DSC perfusion MRI might provide a relevant objective measure of disease activity and treatment efficacy.

PIMD: 16944115

Loss of interhemispheric inhibition in patients with multiple sclerosis is related to corpus callosum atrophy.

Axonal injury and loss in the corpus callosum (CC) is characteristic of the pathology of multiple sclerosis (MS). Functional magnetic resonance imaging (fMRI) potentially allows neurophysiological consequences of this interhemispheric axonal loss to be defined quantitatively. Here we have used 3T fMRI to study the activation in the contralateral primary sensorimotor cortex and deactivation (mediated by transcallosal tracts) in the homologous ipsilateral region in 14 patients with MS and in 14 matched healthy controls during a simple hand-tapping task. Both healthy controls and MS patients showed similar activation in the motor cortex contralateral to the hand moved, but the patients showed a significantly smaller relative deactivation in the ipsilateral motor cortex (P = 0.002). The difference was accounted for by the sub-group of MS patients who previously had impairment of motor function of the hand tested (MS-phd). The CC of the whole patient group was significantly thinner than for the controls (P = 0.001). Atrophy of the CC was correlated with loss of deactivation for the whole patient group (r = -0.50, P = 0.035), but particularly for MS-phd (r = -0.914, P = 0.004). Interhemispheric physiological inhibition thus is impaired in patients with MS, potentially contributing to impairment of motor control. This work suggests one way in which FMRI monitoring of the transcallosal interactions in motor cortex could become a tool for evaluation of therapies that may enhance function in reversibly impaired pathways.

PIMD: 16857191

Effects of commissural de- and remyelination on motor skill behaviour in the cuprizone mouse model of multiple sclerosis.

Feeding of copper chelator cuprizone induces reversible demyelination, predominantly of the corpus callosum in C57/Bl6 mice. With the availability of knockout and transgenic mice, this animal model of multiple sclerosis has increasingly attracted scientists to study the roles of various factors involved in de- and remyelination. However, central motor deficits have not been reported in this model so far. In the present study, we introduce a novel murine motor test, the motor skill sequence (MOSS). This test is designed to detect latent deficits in motor performance. In a first step, we habituated mice to training wheels composed of regularly spaced crossbars till maximal wheel-running performance was achieved. Subsequently, the animals were exposed to wheels with irregularly spaced crossbars demanding high-level motor coordination. This two-step approach minimized a contribution of cardiopulmonary and musculoskeletal training to any improvement of motor performance on the complex wheels. We applied the MOSS test under acute cuprizone-induced demyelination as well as in remyelinated mice after cuprizone withdrawal. Demyelinated animals on a cuprizone diet already showed reduced running performance on the training wheels as compared to control animals. This was even more pronounced when these mice were subsequently exposed to the complex wheels. In contrast, remyelinated animals after cuprizone withdrawal did not exhibit any functional impairment on the training wheels. Latent motor skill deficits were however revealed on the complex wheels, although clearly ameliorated as compared to acutely demyelinated mice. Our results show that latent motor deficits of cuprizone-induced demyelination and after remyelination can be quantified by MOSS. This motor test thus expands the usability of the cuprizone model to a functional level and might also be applicable to other animal models of human CNS diseases associated with subtle motor deficits of central origin.

PIMD: 16756061

Tumor-like manifestation, uncommon form of multiple sclerosis: report of a patient.

Multiple Sclerosis (MS) is a demyelinating disease of the central nervous system, characterised by focal neurological dysfunction with relapsing and remitting course. Acute widespread or tumor-like manifestation is one of the rare clinical variants and has poor prognosis. Here, the authors report a 36-year-old man who presented with left hemifacial and left hemibody anesthesia for one month. His symptoms gradually progressed MRI brain showed multiple large hypersignal intensity lesions in both right and left frontoparietal lobes, surrounding with brain edema. Brain biopsy showed perivenous infiltration of mature lymphocyte with demyelination. He was dramatically improved with high dose steroid. However, he later developed transverse myelitis syndrome. The second MRI showed new foci in both sides of splenium of corpus callosum and T9-10 spinal cord. The findings were compatible with an unusual form of multiple sclerosis that is rarely seen.

PIMD: 16687534

Diffusion tensor imaging in the assessment of normal-appearing brain tissue damage in relapsing neuromyelitis optica.

Normal-appearing brain tissue (NABT) damage was established in multiple sclerosis by histology, MR spectroscopy, magnetization transfer imaging and diffusion tensor imaging (DTI). However, whether this phenomenon can be detected in relapsing neuromyelitis optica (RNMO) remains unclear. The aim of this study was to use DTI to investigate the presence of NABT damage in RNMO patients and its possible mechanism.Conventional MR imaging and DTI scans were performed in 16 patients with RNMO without visible lesions on brain MR imaging and in 16 sex- and age-matched healthy control subjects. Histogram analysis of mean diffusivity (MD) and fractional anisotropy (FA) was performed in the entire brain tissue (BT), white matter (WM), and gray matter (GM). Region of interest (ROI) analysis of MD and FA was also performed in WM regions connected with the spinal white matter tracts or optic nerve (including medulla oblongata, cerebral peduncle, internal capsule, and optic radiation), in corpus callosum without direct connection with them, and in some GM regions.From histogram analysis, we found the RNMO group had a higher average MD of the BT, WM, and GM, a lower average MD peak height and a higher average MD peak location of the GM, and a higher average FA peak height of the WM than did the control group. From ROI analysis, compared with control subjects, RNMO patients had a higher average MD and a lower average FA in ROIs of WM connected with the spinal white matter tracts or optic nerve and a normal average MD and FA in corpus callosum without direct connection with them. In addition, a high average MD was found in parietal GM in these patients.Our findings confirm the presence of abnormal diffusion in brain tissue in patients with RNMO and suggest that secondary degeneration caused by lesions in the spinal cord and optic nerve might be an important mechanism for this abnormality.

PIMD: 16677958

Insights into brain microstructure from the T2 distribution.

T2 weighting is particularly sensitive, but notoriously unspecific, to a wide range of brain pathologies. However, careful measurement and analysis of the T2 decay curve from brain tissue promise to provide much improved pathological specificity. In vivo T2 measurement requires accurate 180 pulses and appropriate manipulation of stimulated echoes; the most common approach is to acquire multiple echoes from a single slice. The T2 distribution, a plot of component amplitude as a function of T2, can be estimated using an algorithm capable of fitting a multi-exponential T2 decay with no a priori assumptions about the number of exponential components. T2 distributions from normal brain show peaks from myelin water, intra/extracellular water and cerebral spinal fluid; they can be used to provide estimates of total water content (total area under the T2 distribution) and myelin water fraction (MWF, fractional area under the myelin water peak), a measure believed to be related to myelin content. Experiments on bovine brain suggest that magnetization exchange between water pools plays a minor role in the T2 distribution. Different white matter structures have different MWFs. In normal white matter (NWM), MWF is not correlated with the magnetization transfer ratio (MTR) or the diffusion tensor fractional anisotropy (FA); hence it provides unique information about brain microstructure. Normal-appearing white matter (NAWM) in multiple sclerosis (MS) brain possesses a higher water content and lower MWF than controls, consistent with histopathological findings. Multiple sclerosis lesions demonstrate great heterogeneity in MWF, presumably due to varying myelin contents of these focal regions of pathology. Subjects with schizophrenia were found to have significantly reduced MWF in the minor forceps and genu of the corpus callosum when compared to controls, suggesting that reduced frontal lobe myelination plays a role in schizophrenia. In normal controls, frontal lobe myelination was positively correlated with both age and education; this result was not observed in subjects with schizophrenia. A strong correlation between MWF and the optical density from the luxol fast blue histological stain for myelin was observed in formalin-fixed brain, supporting the use of the MWF as an in vivo myelin marker.

PIMD: 16651886

Endogenous cell repair of chronic demyelination.

In multiple sclerosis lesions, remyelination typically fails with repeated or chronic demyelinating episodes and results in neurologic disability. Acute demyelination models in rodents typically exhibit robust spontaneous remyelination that prevents appropriate evaluation of strategies for improving conditions of insufficient remyelination. In the current study, we used a mouse model of chronic demyelination induced by continuous ingestion of 0.2% cuprizone for 12 weeks. This chronic process depleted the oligodendrocyte progenitor population and impaired oligodendrocyte regeneration. Remyelination remained limited after removal of cuprizone from the diet. Fibroblast growth factor 2 (FGF2) expression was persistently increased in the corpus callosum of chronically demyelinated mice as compared with nonlesioned mice. We used FGF2 mice to determine whether removal of endogenous FGF2 promoted remyelination of chronically demyelinated areas. Wild-type and FGF2 mice exhibited similar demyelination during chronic cuprizone treatment. Importantly, in contrast to wild-type mice, the FGF2 mice spontaneously remyelinated completely during the recovery period after chronic demyelination. Increased remyelination in FGF2 mice correlated with enhanced oligodendroglial regeneration. FGF2 genotype did not alter the density of oligodendrocyte progenitor cells or proliferating cells after chronic demyelination. These findings indicate that attenuating FGF2 created a sufficiently permissive lesion environment for endogenous cells to effectively remyelinate viable axons even after chronic demyelination.

PIMD: 16626812

Age increases axon loss associated with primary demyelination in cuprizone-induced demyelination in C57BL/6 mice.

Axon loss is recognised as a significant contributor to the progression of the disability associated with multiple sclerosis. Although evidence of axon damage is found in areas of chronic demyelination it is more frequently seen in association with acute demyelination. This study compares the incidence of axon degeneration associated with the areas undergoing demyelination in young adult (8-10 weeks) and aged (6-7 months) C57BL/6 mice in cuprizone intoxication; a widely used model of demyelination. The incidence of axon transection, as indicated by the presence of SMI 32 positive axonal spheroids, and evidence of axon loss in the medial corpus callosum, were significantly greater in aged mice, as was the magnitude of the macrophage and astrocyte response to demyelination. Aged C57BL/6 mice are thus more prone to axon degeneration in association with demyelination than young adult mice. A retrospective study indicated that the incidence of axon degeneration was much higher in C57BL/6 mice than in the Swiss albino mice used in the early cuprizone intoxication studies which were fed much higher doses of cuprizone. These results indicate both a genetic and age susceptibility to demyelination-associated axon transection.

PIMD: 16459729

Core hypothermia in multiple sclerosis: case report with magnetic resonance imaging localization of a thalamic lesion.

Hypothermia is a rare condition in multiple sclerosis (MS). We report on a patient with a long-standing secondary progressive MS and six episodes of recurring hypothermia down to 29.9 degrees C with associated hypotension, bradycardia, coagulopathy and electrolyte dysequilibrium. Magnetic resonance imaging (MRI) demonstrated severe involvement of the corpus callosum with an associated lesion in the right posterior thalamus. These findings may link hypothermia in MS with callosal and associated thalamic pathology to Shapiro's syndrome, where agenesis of the corpus callosum and associated abnormalities are related to episodic spontaneous hypothermia. In MS, hypothermic episodes may be triggered by preceding infections, as shown in the present case.

PIMD: 16452667

Proliferation and death of oligodendrocytes and myelin proteins are differentially regulated in male and female rodents.

Sexual dimorphism of neurons and astrocytes has been demonstrated in different centers of the brain, but sexual dimorphism of oligodendrocytes and myelin has not been examined. We show, using immunocytochemistry and in situ hybridization, that the density of oligodendrocytes in corpus callosum, fornix, and spinal cord is 20-40% greater in males compared with females. These differences are present in young and aged rodents and are independent of strain and species. Proteolipid protein and carbonic anhydrase-II transcripts, measured by real-time PCR, are approximately two to three times greater in males. Myelin basic protein and 2', 3'-cyclic nucleotide 3'-phosphodiesterase, measured by Western blots, are 20-160% greater in males compared with females. Surprisingly, both generation of new glia and apoptosis of glia, including oligodendrocytes, are approximately two times greater in female corpus callosum. These results indicate that the lifespan of oligodendrocytes is shorter in females than in males. Castration of males produces a female phenotype characterized by fewer oligodendrocytes and increased generation of new glia. These findings indicate that exogenous androgens differentially affect the lifespan of male and female oligodendrocytes, and they can override the endogenous production of neurosteroids. The data imply that turnover of myelin is greater in females than in males. Mu-calpain, a protease upregulated in degeneration of myelin, is dramatically increased at both transcriptional and translational levels in females compared with males. These morphological, molecular, and biochemical data show surprisingly large differences in turnover of oligodendrocytes and myelin between sexes. We discuss the potential significance of these differences to multiple sclerosis, a sexually dimorphic disease, whose progression is altered by exogenous hormones.

PIMD: 16417174

The correlation of changes of the optic nerve diameter in the acute retrobulbar neuritis with the brain changes in multiple sclerosis.

The aim of this paper is to compare diameter of healthy and affected optic nerve determined by ultrasound with brain lesions in acute retrobulbar neuritis in patients with multiple sclerosis. In this prospective study 20 patients with multiple sclerosis and acute retrobulbar neuritis were examined. Optic nerve diameter was measured by ultrasound. Brain lesions were detected by magnetic resonance. Correlation between demyelinating lesions of the brain in multiple sclerosis and optic nerve diameter was tested by Kruskal-Wallis test. Significant difference in diameter between healthy and affected optic nerve in acute retrobulbar neuritis was found. Demyelinating brain changes examined by magnetic resonance revealed periventricular lesions, subcortical lesions and lesions in corpus callosum. There is statistically significant correlation between optic nerve diameter and number of brain lesions in multiple sclerosis, $p < 0.05$. Diameter of optic nerve in retrobulbar neuritis measured by ultrasound correlates with brain lesions detected by magnetic resonance in multiple sclerosis.

PIMD: 16400831

The role of MRI in the diagnosis of multiple sclerosis.

There is no single test that is diagnostic of MS, including MRI. The lesions detected with MRI are pathologically nonspecific. The principles of MS diagnosis are based on showing dissemination of white matter lesions in space and time. MRI is the most sensitive method for revealing asymptomatic dissemination of lesions in space and time. The pattern and evolution of MRI lesions, in the appropriate clinical setting, has made MRI abnormalities invaluable criteria for the early diagnosis of MS. The first important role for MRI in the diagnosis of MS allows for an early diagnosis of MS for CIS patients using the IP diagnostic criteria, including MRI for dissemination in space (DIS) and time (DIT). The sensitivity of diagnosing MS within the first year after a single attack is 94%, with a specificity of 83%. The MRI evidence required to support the diagnosis varies, depending on the strength of the clinical findings. Allowing a new MRI lesion to substitute for a clinical attack doubles the number of CIS patients who can be diagnosed as having MS within 1 year of symptom onset. Increasing the sensitivity of the test with more lenient criteria, as recommended by the AAN subcommittee, can result in decreased specificity. The second important role for MRI in the diagnostic work-up of suspected MS patients is to rule out alternative diagnoses obvious on MRI, such as spinal stenosis and most brain tumors. Characteristic lesions that favor MS include Dawson Fingers, ovoid lesions, corpus callosum lesions, and asymptomatic spinal cord lesions. However, other white matter diseases can have similar appearances on MRI. Persistent gadolinium enhancement greater than three months, lesions with mass effect, and meningeal enhancement suggest other disorders. A standardized MRI protocol for brain and spinal cord is crucial for comparing across studies or between centers. T2W MRI cannot distinguish between acute and chronic lesions. Gadolinium provides useful information about new lesion activity and is helpful in ruling out alternative diagnoses such as neoplasm, vascular malformations, and leptomeningeal disease. A single gadolinium-enhanced MRI can potentially provide evidence for dissemination in space and time. Spinal cord imaging is equally valuable to rule out spinal stenosis or tumor, and for detecting asymptomatic lesions when brain imaging is nondiagnostic in patients suspected of having MS. Precise criteria may be too suggestive that MS can be diagnosed by MRI and a negative MRI at the time of CIS does not rule out MS. MRI evidence plays a supportive role in what is ultimately a clinical diagnosis of MS, in the appropriate clinical situation, and always at the exclusion of alternative diagnoses.

PIMD: 16374777

Upregulation of the stress-associated gene p8 in mouse models of demyelination and in multiple sclerosis tissues.

Cuprizone-induced demyelination is a mouse model of multiple sclerosis (MS) as cuprizone-fed mice exhibit neuroinflammation and demyelination in the brain. Upon removal of cuprizone from the diet, inflammation is resolved and reparative remyelination occurs. In an Affymetrix GeneChip analysis, the stress-associated gene p8 was strongly upregulated (>10x) during cuprizone-induced demyelination but not remyelination. We verified this upregulation (>15x) of p8 in the CNS during demyelination by real-time polymerase chain reaction (PCR). This upregulation is brain-specific, as p8 is not elevated in the liver, lung, kidney, spleen, and heart of cuprizone-treated mice. We also localized the cellular source of p8 during cuprizone treatment, and further found elevated expression during embryogenesis but not in normal adult brain. Compared with wild-type controls, the death of oligodendrocytes in p8-/- mice is delayed, as is microglial recruitment to areas of demyelination. The corpus callosum of p8-/- mice demyelinates at a slower rate than wild-type mice, suggesting that p8 exacerbates CNS inflammation and demyelination. Enhanced expression of p8 is also observed in the spinal cords of mice with acute experimental autoimmune encephalomyelitis (EAE) induced by PLP139-151 peptide (10x). Increased expression is detected during disease onset and expression wanes during the remission phase. Finally, p8 is found upregulated (8x) in post-mortem tissue from MS patients and is higher in the plaque tissue compared with adjacent normal-appearing white and gray matter. Thus, p8 is an excellent candidate as a novel biomarker of demyelination.

PIMD: 16372011

NMDA receptors are expressed in oligodendrocytes and activated in ischaemia.

Glutamate-mediated damage to oligodendrocytes contributes to mental or physical impairment in periventricular leukomalacia (pre- or perinatal white matter injury leading to cerebral palsy), spinal cord injury, multiple sclerosis and stroke. Unlike neurons, white matter oligodendrocytes reportedly lack NMDA (N-methyl-d-aspartate) receptors. It is believed that glutamate damages oligodendrocytes, especially their precursor cells, by acting on calcium-permeable AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)/kainate receptors alone or by reversing cystine-glutamate exchange and depriving cells of antioxidant protection. Here we show that precursor, immature and mature oligodendrocytes in the white matter of the cerebellum and corpus callosum exhibit NMDA-evoked currents, mediated by receptors that are blocked only weakly by Mg2+ and that may contain NR1, NR2C and NR3 NMDA receptor subunits. NMDA receptors are present in the myelinating processes of oligodendrocytes, where the small intracellular space could lead to a large rise in intracellular ion concentration in response to NMDA receptor activation. Simulating ischaemia led to development of an inward current in oligodendrocytes, which was partly mediated by NMDA receptors. These results point to NMDA receptors of unusual subunit composition as a potential therapeutic target for preventing white matter damage in a variety of diseases.

PIMD: 16284771

Acquired lesions of the corpus callosum: MR imaging.

In this pictorial review, we illustrate acquired diseases or conditions of the corpus callosum that may be found by magnetic resonance (MR) imaging of the brain, including infarction, bleeding, diffuse axonal injury, multiple sclerosis, acute disseminated encephalomyelitis, Marchiafava-Bignami disease, glioblastoma, gliomatosis cerebri, lymphoma, metastasis, germinoma, infections, metabolic diseases, transient splenial lesion, dilated Virchow-Robin spaces, wallerian degeneration after hemispheric damage and focal splenial gliosis. MR imaging is useful for the detection and differential diagnosis of corpus callosal lesions. Due to the anatomical shape and location of the corpus callosum, both coronal and sagittal fluid-attenuated inversion recovery images are most useful for visualizing lesions of this structure.

PIMD: 16281908

p75NTR independent oligodendrocyte death in cuprizone-induced demyelination in C57BL/6 mice.

Feeding C57Bl/6 J mice the copper chelator cuprizone leads to selective apoptosis of mature oligodendrocytes and concomitant demyelination predominantly in the corpus callosum. The process of oligodendrocyte apoptosis in this animal model for multiple sclerosis (MS) involves early microglial activation, but no infiltration of T-lymphocytes. Therefore, this model could mimic early stages of oligodendrocyte degeneration Affected oligodendrocytes express the common neurotrophin receptor, p75(NTR), a 'stress-receptor' which under certain circumstances can induce apoptosis. Only affected oligodendrocytes in MS lesions and MS animal models express this receptor. In order to study the significance of p75(NTR) in the fate of oligodendrocytes, we have exposed wild-type as well as p75(NTR)-knockout mice to a 0.2% (w/w) cuprizone diet and performed a comparative immunohistochemical analysis of the corpus callosum at various time points. Surprisingly, our results show that the absence of p75(NTR) did not alter cuprizone-induced oligodendrocyte death (and subsequent de- or remyelination). Apparently, intracellular apoptosis pathways in adult oligodendrocytes do not require p75(NTR) activated signal transduction in the absence of T-lymphocytes and T-lymphocyte derived cytokines.

PIMD: 16155155

The ependymal "Dot-Dash" sign: an MR imaging finding of early multiple sclerosis.

Corpus callosum lesions are of specific interest in the evaluation of suspected multiple sclerosis in brain MR imaging. Using thin-section sagittal fluid-attenuated inversion recovery images, researchers have shown that the finding of "subcallosal striations" correlates significantly with the diagnosis of multiple sclerosis. Using the same MR imaging technique, we describe a finding of ependymal irregularity that we call the "Dot-Dash" sign, which we believe to be associated with early multiple sclerosis.Sagittal 2-mm fast fluid-attenuated inversion recovery images were obtained in 70 patients. Thirty-five patients had multiple sclerosis according to the Poser criteria, and 35 were age-matched controls. The images were reviewed in a blinded fashion by an experienced neuroradiologist for the presence or absence of the Dot-Dash sign.The correlation between the Dot-Dash sign and definite clinical multiple sclerosis is highly significant (P < .001), with a sensitivity of 91.4% and a specificity of 65.7%. In the age group of < or =50 years, the sensitivity was 95.7% and the specificity, 71.9%.The Dot-Dash sign of ependymal irregularity on thin-section sagittal fluid-attenuated inversion recovery images is an early marker for multiple sclerosis, which is particularly useful in the younger patient. This finding appears to be more sensitive for early lesion detection than any other multiple sclerosis imaging finding yet described in the literature.

PIMD: 16109428

'Importance sampling' in MS: use of diffusion tensor tractography to quantify pathology related to specific impairment.

Specific neurological impairments in multiple sclerosis (MS) are dependent on the pathology in clinically eloquent areas of the central nervous system. We aimed to use diffusion tensor fiber tracking to identify the pyramidal tracts and corpus callosum in MS patients, measure the apparent diffusivity within the tracts, and evaluate whether this would correlate with relevant disability scores. Dual-echo and diffusion tensor magnetic resonance imaging (DT-MRI) brain scans were obtained from 29 patients with relapsing remitting MS, and 13 age and gender matched normal controls. Voxels from pyramidal tracts and corpus callosum were automatically identified using a tractography based algorithm. Mean apparent diffusion coefficient (ADC(av)) was measured for these tracts. Scores of Expanded Disability Status Scale (EDSS) and Paced Auditory Serial Addition Test (PASAT) were obtained. The median EDSS score was 2.5 (inter-quartile range 2-3.25). The ADC(av) in the pyramidal tracts (p=0.02) and corpus callosum (p=0.0004) in patients was significantly higher than in controls. Pyramidal tracts ADC(av) was correlated with pyramidal FSS (r=0.5, p=0.008). Corpus callosum ADC(av) was correlated with PASAT (r=-0.58, p=0.001). Global T2 lesion volume did not correlate with the EDSS, but correlated with ADC(av) of the pyramidal tracts (r=0.6, p=0.0007) and corpus callosum (r=0.8, p<0.0001). T2 lesion volume within the pyramidal tracts and corpus callosum correlated with ADC(av) in the pyramidal tracts (r=0.6, p=0.0009) and corpus callosum (r=0.65, p=0.0002) respectively, but not with pyramidal FSS or PASAT score. DT-MRI quantifies pathology in specific white matter tracts and may increase the specificity of MRI in monitoring progression of motor and cognitive deficits in MS.

PIMD: 16086436

Multicontrast MRI of remyelination in the central nervous system.

Although magnetic resonance imaging (MRI) represents the most sensitive tool for the detection of white matter abnormalities in patients with multiple sclerosis (MS), the heterogeneity of MS placques severely hampers the elucidation of specific pathophysiological processes. In order to identify putative MRI markers for de- and remyelination, we employed the cuprizone mouse model which leads to a selective and reversible demyelination of the corpus callosum with little or no axonal damage. Apart from histopathology, animals were studied with high-resolution three-dimensional MRI in vivo using multiple contrasts. While individual MRI findings significantly correlated with electron microscopy, the differentiation of regions with normal, demyelinated or remyelinated white matter by one contrast alone was less specific than by histology or electron microscopy. However, an accurate MRI prediction of the in vivo myelin status was achieved by a discriminant function analysis using a combination of T1, T2 and magnetization transfer contrast. With a correct assignment of 95% of all animals examined, the procedure will allow for the survey of new therapeutic approaches aiming at improved remyelination.

PIMD: 15989940

Disconnection agraphia in a case of multiple sclerosis: the isolation of letter movement plans from language.

We report the case of a left-handed man (MCR), who presented with a peripheral agraphia as an early sign of multiple sclerosis. His left-handed writing was neologistic, whilst oral spelling, typing and spelling with the right hand were intact. Structural MRI scanning revealed a lesion of the body of the corpus callosum. Dichotic listening tests indicated that MCR displayed left hemisphere dominance for language. It is proposed that MCR represents a case of a disconnection syndrome in which right hemisphere systems that provide the basis for movement templates during left-handed writing are isolated from left hemisphere language systems. Analysis of left-handed writing indicated that peripheral movement control was highly structured with both individual letter frequency and sequential dependencies between letters represented within these motor control units. This case represents an opportunity to explore the mechanisms of movement control for writing and to examine the characteristics of isolated letter templates.

PIMD: 15906348

Diffusion tensor fractional anisotropy of the normal-appearing seven segments of the corpus callosum in healthy adults and relapsing-remitting multiple sclerosis patients.

To investigate the utility of whole-brain diffusion tensor imaging (DTI) in elucidating the pathogenesis of multiple sclerosis (MS) using the normal-appearing white matter (NAWM) of the corpus callosum (CC) as a marker of occult disease activity.A high signal-to-noise ratio (SNR) and optimized entire brain DTI data were acquired in 26 clinically-definite relapsing and remitting multiple sclerosis (RRMS) patients and 32 age-matched healthy adult controls. The fractional anisotropy (FA) values of seven functionally distinct regions in the normal-appearing CC were compared between patients and controls.This study indicates that 1) there was a gender-independent FA heterogeneity of the functionally specialized CC segments in normal volunteers; 2) FA in the MS group was significantly decreased in the anterior (P=0.0039) and posterior (P=0.0018) midbody subdivisions of the CC, possibly due to a reduction of small-caliber axons; and 3) the FA of the genu of the CC was relatively intact in the MS patients compared to the healthy age-matched controls (P=0.644), while the splenium showed an insignificant trend of reduced FA values (P=0.248). The decrease in FA in any of the CC subdivisions did not correlate with disease duration (DD) or the expanded disability status scale (EDSS) score.The preliminary results are consistent with published histopathology and clinical studies on MS, but not with some published DTI reports. This study provides insights into the pathogenesis of MS, and the role played by compromised axonal integrity in this disease.

PIMD: 15891418

Update on Susac's syndrome.

PURPOSE OF VIEW: We review recent developments in the clinical course and imaging modalities for Susac's syndrome, a clinical triad consisting of encephalopathy, branch retinal artery occlusions and sensorineural hearing loss.Susac's syndrome has variable clinical presentations; recently described presentations include epileptic seizures and transient inverted vision. Advances in neuroradiology suggest that magnetic resonance imaging demonstrates distinctive patterns in the white and grey matter and in the leptomeninges. Reports have verified that Susac's syndrome is under-diagnosed because of its multisystem involvement and confusion with other imitating disorders (such as multiple sclerosis), and because of the fact that neuroradiologists are not acquainted with this syndrome.The precise aetiology of Susac's syndrome is still unknown and many areas have not yet been explored. Magnetic resonance imaging is the neuroimaging study of choice. Findings include multiple small hyperintense foci on T2-weighted images and contrast enhancement in white and grey matter of both supratentorial and infratentorial structures, corpus callosum and, occasionally, leptomeninges. Callosal lesions typically involve the central fibres and are probably pathognomonic for Susac's syndrome. When assessing patients with unexplained encephalopathy involving white and grey matter, leptomeninges and corpus callosum, the findings of sensorinueral hearing loss or visual disturbances may yield important clues regarding the possibility of Susac's syndrome.

PIMD: 15884397

Experimental demyelination caused by primary oligodendrocyte dystrophy. Regional distribution of the lesions in the nervous system of mice [corrected].

Heterogeneity of multiple sclerosis lesions has been recently indicated: In addition to T-cell-mediated or T-cell plus antibody-mediated autoimmune mechanisms (patterns I-II) two other patterns (III-IV) were described. Patterns Ill-IV are characterized by primary oligodendrocyte dystrophy, reminiscent of virus- or toxin-induced demyelination rather than autoimmunity. It was described more than 30 years ago that dietary application of a copper-chelating agent called cuprizone results in primary oligodendrocyte degeneration which is followed by demyelination. The aim of the present study was to examine the regional distribution of cuprizone induced oligodendrocyte dystrophy and demyelination in the nervous system of mice. MATERIAL A METHODS: Demyelination was induced in male weanling Swiss-Webster mice by feeding them on a diet containing 0.6% (W/W) cuprizone bis(cyclohexanone)-oxalyldihydrazone (G. F. Smith Chemical, Columbus OH) for 8 weeks. Animals were sacrificed after 3, 7, 14, 27, 35, 56 days of cuprizone administration. Samples were taken from corpus callosum, anterior commissure, optic nerve, cervical spinal cord and sciatic nerve. Samples were examined by immunohistochemistry, in situ hybridization for myelin proteins and myelin protein mRNA-s, respectively. Conventional neuropathological stainings and electron microscopy was also performed.Oligodendrocyte degeneration and demyelination followed a particular standard pattern in the central nervous system. Profound myelin loss developed in the superior cerebellar peduncle, anterior commissure and corpus callosum, whereas the optic nerves, velum medullare anterior and spinal cord showed little or no demyelination. Sciatic nerves were unaffected. No infiltration by lymphocytes or blood-brain barrier damage was observed during cuprizone treatment.Cuprizone induced oligodendrocyte damage and demyelination follows a particular standard pattern in the central nervous system of mice. Cuprizone induced demyelination might be considered as a model for human demyelinating disorders with primary oligodendrocyte dystrophy and apoptosis.

PIMD: 15862213

Demyelination increases radial diffusivity in corpus callosum of mouse brain.

Myelin damage, as seen in multiple sclerosis (MS) and other demyelinating diseases, impairs axonal conduction and can also be associated with axonal degeneration. Accurate assessments of these conditions may be highly beneficial in evaluating and selecting therapeutic strategies for patient management. Recently, an analytical approach examining diffusion tensor imaging (DTI) derived parameters has been proposed to assess the extent of axonal damage, demyelination, or both. The current study uses the well-characterized cuprizone model of experimental demyelination and remyelination of corpus callosum in mouse brain to evaluate the ability of DTI parameters to detect the progression of myelin degeneration and regeneration. Our results demonstrate that the extent of increased radial diffusivity reflects the severity of demyelination in corpus callosum of mouse brain affected by cuprizone treatment. Subsequently, radial diffusivity decreases with the progression of remyelination. Furthermore, radial diffusivity changes were specific to the time course of changes in myelin integrity as distinct from axonal injury, which was detected by betaAPP immunostaining and shown to be most extensive prior to demyelination. Radial diffusivity offers a specific assessment of demyelination and remyelination, as distinct from acute axonal damage.

PIMD: 15754791

[Cognitive impairment in multiple sclerosis patients].

In addition to neurological symptoms, multiple sclerosis is characterized by cognitive function impairment. Disturbances of memory, recall, information processing, visual-spacial perception, attention, and executive function, in less extent of speech, are present in about 60% of patients. They are similar to disorders in other subcortical dementias. Once they appear, they rarely recede. Conventional, and especially nonconventional magnetic resonance imaging evaluates more precisely the tissue substrate--diffuse neuroaxonal lesion of the entire brain parenchyma--than clinical findings, already in the early stage of the disease. Alterations in the brain imaging are manifested by T2 hyperintensive and T1 hypointensive lesions, decreased neuronal marker N-acetyl-aspartate in magnetic spectroscopy, decreased magnetization transfer ratio, and increased diffusivity with reduced anisotropy in diffusion-weighted imaging. Total volume of brain lesion, corpus callosum diameter, and relation of measures of brain chambers and the rest of the brain, are best indices of cognitive dysfunction in multiple sclerosis. Their diagnosis in the very beginning of the disease allows early application of therapeutic procedures. Symptomatic treatment of these disorders is not efficient, and immunomodulation, particularly the use of biologic versions of interferon-beta, shows disputable effects. Cognitive dysfunctions affect relationships and working ability of patients.

PIMD: 15709132

Regional brain atrophy evolves differently in patients with multiple sclerosis according to clinical phenotype.

Progressive brain atrophy is a well-known feature of multiple sclerosis (MS). We characterized the spatial evolution of atrophy in different MS phenotypes.Dual-echo and T1-weighted MR images were obtained in 70 patients with MS and 10 healthy control subjects at entry and after 15 months. Within-group changes in regional atrophy were assessed by applying Structural Image Evaluation Using Normalization of Atrophy software and statistical parametric mapping analysis. Reported differences are for P <.001.During follow-up, patients with relapsing-remitting MS (RRMS) differences significant atrophy around the ventricular system; pericerebellar spaces; cerebellar tentorium; putamen; corpus callosum; cingulate sulcus; hippocampus; parieto-occipital fissure; lateral fissure; and frontal, parietal, temporal, and occipital cortex. Patients with secondary progressive MS developed significant atrophy of the cingulate sulcus; pulvinar; caudate nucleus; anterior orbital gyrus; mammillary body; fourth ventricle; and regions of frontal, parietal, temporal, and occipital cortex. Patients with primary progressive MS developed significant atrophy of the bilateral central sulcus; caudate nucleus; prepontine and quadrigeminal cisterns; lateral ventricle; and regions of frontal, parietal, temporal, and occipital cortex. In all phenotypes, the development of atrophy in some regions was significantly correlated with the accumulation of T2- and T1-visible lesions and clinical disability (r = -0.57 to -0.86).In MS, brain atrophy develops involving different structures in the different phenotypes. While ventricular enlargement is predominant in RRMS, cortical atrophy seems to be more important in the progressive forms. Measures of regional brain atrophy were significantly correlated with disability, suggesting that this approach is promising for bridging the gap between clinical and MR imaging findings in MS.

PIMD: 15678001

[Lesion mechanism dependent, differential changes in neurofilaments and microtubules: a pathological and experimental study].

The consequences of axonal or demyelinating injuries on the axonal cytoskeleton have rarely been described.We have compared the density of fibers labeled by anti-neurofilaments (NF) and -beta tubulin (TUB) to the density of total fibers in nine patients with axonal neuropathies of undetermined etiology (AUE), six with necrotizing angeitis with neuropathy (NAN), seven with chronic inflammatory demyelinating neuropathy (CIDP) and in five controls, as well as in six patients with chronic multiple sclerosis (MS). We also studied demyelinated rat corpus callosum after lysophosphatidyl (LPC) microinjection.In AUE and NAN NF positive fibers decreased together with total fiber density, whereas TUB increased. In demyelinating lesions TUB was not altered (CIDP) or strongly decreased (MS, LPC); NF were strongly reduced in MS (where axon loss was prominent) and in LPC lesions (despite the lack of fiber degeneration) and for fiber densities<3900/mm2 in CIDP.The initial mechanism of a disease, either axonal degeneration or demyelination, could result into a specific pattern of axonal cytoskeleton alterations.

PIMD: 15661713

Local tissue damage assessed with statistical mapping analysis of brain magnetization transfer ratio: relationship with functional status of patients in the earliest stage of multiple sclerosis.

In the early stage of Multiple Sclerosis (MS), conventional MR imaging parameters such as T2 lesion load fail to explain the clinical status of patients. In the present work, we aimed to determine the ability of magnification transfer imaging to better reflect the relationship between local tissue damage and functional status of MS patients.We performed a comparative statistical mapping analysis on brain tissue magnetization transfer ratio (MTR) data measured in 18 patients with clinically isolated syndrome suggestive of MS (CISSMS) and 18 matched control subjects.In the patients with CISSMS, a pattern of significant low MTR values was observed in the white matter, corpus callosum, bilateral occipitofrontal fascicles, right fornix, right parietal white matter, external capsule, right superior longitudinal fasciculus (SLF), right inferior longitudinal fasciculus, optica radiata, parietal white matter, right cingulum, gray matter, bilateral thalamus, bilateral caudate, right insula, and left Brodmann area (BA) 8. No correlation was found between local MTR decrease and Expanded Disability Status Scale score. Significant correlations between MTR and MS Functional Composite scores (Spearman rank test, P <.05) were observed in the left BA40, right SLF, right frontal white matter, splenium, and anterior corpus callosum. Local MTR values correlated with Paced Auditory Serial Addition Test scores in the left BA40, right BA4, right SLF, and splenium.Statistical mapping analysis of brain MTR data provides valuable information on the relationship between the location of brain tissue damage and its functional impact in patients with MS, even in the earliest stage of the disease.

PIMD: 15607101

Susac syndrome: serial diffusion-weighted MR imaging.

Susac syndrome (SS) is a clinical triad of hearing loss, retinal artery occlusion and encephalopathy. The typical MR imaging findings of multiple focal lesions in the corpus callosum and subcortical white matter can be easily misdiagnosed as multiple sclerosis. On diffusion-weighted (DW) MR imaging, new lesions were hyperintense, with reduced apparent diffusion coefficient (ADC). These lesions later became less prominent or hypointense on subsequent DW MR imaging. Serial DW imaging and ADC maps may be useful in differentiating SS from demyelinating diseases.

PIMD: 15596619

Congenital adrenal hyperplasia and multiple sclerosis: is there an increased risk of multiple sclerosis in individuals with congenital adrenal hyperplasia?

Congenital adrenal hyperplasia (CAH) is an inherited recessive disorder of adrenal steroidogenesis, generally caused by a total or partial deficiency in 21-hydroxylase, due to a deletion of or mutations in the CYP21 gene (the gene that codes for 21-hydroxylase). Impaired cortisol biosynthesis results in corticotropin hypersecretion, which leads to overproduction of intermediate metabolites and androgens.To describe for the first time, to our knowledge, a patient with CAH and multiple sclerosis (MS).Case report.A 22-year-old woman, diagnosed at birth as having a salt-losing 21-hydroxylase deficiency, had sudden visual loss in the right eye and pyramidal, sensory, and cerebellar signs. Repeated brain magnetic resonance images showed focal white matter lesions in periventricular areas, the corpus callosum, the cerebellum, and the brainstem. A cerebrospinal fluid examination revealed several oligoclonal bands. Thereafter, she had 2 relapses, characterized by ataxia and diplopia, and recovered after corticosteroid treatment.The reported case fulfills the diagnostic criteria for CAH and MS.Some clues suggest that the association between CAH and MS could be nonincidental: a possible MS susceptibility locus is on chromosome 6p21, on which the CYP21 gene is located; the CYP21 gene and the CYP21P pseudogene alternate in tandem with the C4 genes (the genes that code for the homonym complement protein) (C4AQ0 is particularly frequent in patients with relapsing-remitting MS); and, in previous studies, brain magnetic resonance imaging showed T2-hyperintense focal areas in the white matter of CAH patients. Our observation should alert neurologists to the presence of signs and symptoms suggestive of late-onset CAH in MS patients and, in turn, endocrinologists to the appearance of neurological signs and symptoms in CAH patients.

PIMD: 15584497

Alexia without agraphia in multiple sclerosis: case report with magnetic resonance imaging localization.

The syndrome of alexia without agraphia occurs rarely in multiple sclerosis (MS). We report a patient with right homonymous hemianopsia and alexia without agraphia as his initial manifestations of relapsing-remitting MS. Magnetic resonance imaging (MRI) demonstrated a hyperintense lesion in the left occipital subcortical white matter (WM) and an enhancing lesion in the splenium of the corpus callosum. The clinical presentation and MRI findings were consistent with disconnection of the functional right occipital visual cortex from structures responsible for language comprehension in the left hemisphere. The diagnosis of MS was confirmed by subsequent development of additional periventricular WM lesions.

PIMD: 15497071

Experimental autoimmune encephalomyelitis (EAE): lesion visualization on a 3 Tesla clinical whole-body system after intraperitoneal contrast injection.

To investigate the intravital visibility of CNS lesions in rats with experimental autoimmune encephalomyelitis (EAE), the animal correlate of multiple sclerosis, using a 3-Tesla (T) whole-body MR system.Three healthy Dark Agouti (DA) rats and 16 DA rats with clinical signs of EAE were examined on a 3T whole body-system using a normal wrist coil. In total, 25 examinations were preformed using T2- and T1-weigthed images in transverse and sagittal orientation with a slice thickness of 2 mm or 1 mm (voxel size up to 0.2 x 0.2 x 1 mm). Sedation was achieved by intraperitoneal injection of ketamine and xylazine. In addition, T1-weighted images were obtained after the instillation of 1.0 ml of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) (0.5 mmol/ml) into the peritoneal cavity.T2- and T1-weighted images of the brain and spinal cord with high spatial and contrast resolution could be obtained in all animals. The anatomical details of the olfactory bulb glomeruli, cerebellum foliae, ventricles and corpus callosum were clearly visible. The EAE lesions presented as hyperintense areas in T2-weighted images and could be demonstrated in all clinically affected animals by MRI and histologically verified. In total, the 16 affected rats had 28 cerebral and 2 spinal cord lesions (range 1 to 4, median 2). Contrast enhancement was noted in 12 animals and ranked as severe in ten and moderate in two cases. No adverse effects were noted due to sedation or intraperitoneal contrast injection.The intravital demonstration of cerebral and spinal cord EAE lesions in rats is possible on a 3T whole-body MR scanner using a normal wrist coil. Intraperitoneal injection of ketamine/xylazine and contrast agent is an easy, safe and effective procedure in rats.

PIMD: 15387980

[Value of magnetization transfer imaging in judging microchanges lesions in normal-appearing white matter of multiple sclerosis].

To explore the value of magnetization transfer imaging (MTI) in judging microscopic lesions in normal-appearing white matter of multiple sclerosis (MS).Forty-one patients with brain MS, 17 males and 24 females, aged 13 approximately 65, and 21 healthy people, 8 males and 13 females, aged 18 approximately 57, used as controls underwent magnetic resonance imaging (MRI) using 3D-spoiled grass (3D-SPGR) series, to scan the whole brain with saturated pulses on and off respectively. The signal values were measured directly in the pictures of these 2 series. The formula MTR = (M(0)-MS)/M(0) x 100% was used, where M0 represents the signal value of region of interest with the saturated pulses off, and Ms represents signal value of region of interest with the saturated pulses on, to calculate the MTR value. With reference to T(2)WI imaging, the MTR values of 17 regions of interest (ROI) in the normal-appearing brain white matter, including the white matter of pons, bilateral cerebellar peduncles, knees of internal capsules, splenium and genu of corpus callosum, and the white matter by the anterior horn and posterior horn of lateral ventricle, body of lateral ventricle, and deep in the frontal and parietal lobes, were measured. The average MTR value of the 17 ROI was used to represent the MTR value of the whole normal-appearing brain and used to make comparison with that of the healthy samples statistically.Compared with those of the healthy samples, the average MTR values of each ROI of the MS patients were lower at different degrees. The difference in the MTR values of the white matter of splenium of corpus callosum, and by lateral ventricle and deep in parietal lobe were especially bigger. The MTR value of the whole brain white matter in the healthy persons ranged from 22.76% to 25.42%, with an average value of 23.97%, both significantly higher than those of the MS patients (19.45% to 24.15%, and 22.44% respectively, both $P < 0.05$).MTI can be used to detect the microchange of normal appearing white matter in MS. MTR is a sensitive indicator to reflect the damage of structure of tissues.

PIMD: 15327035

Multiple sclerosis pathology in the normal and abnormal appearing white matter of the corpus callosum by diffusion tensor imaging.

Lesions in the corpus callosum in multiple sclerosis (MS) include those that are hyperintense on T2-weighted images, which can be either focal (isolated) or connected, but there is evidence that the corpus callosum, similar to other white matter regions, contains normal appearing white matter (NAWM) which is abnormal based on quantitative MR methodologies. In this pilot study, diffusion tensor based measures were determined in corpus callosum from 10 patients with MS and 12 age and gender matched controls. T2-hyperintense lesions were carefully segmented out from normal appearing corpus callosum to minimize contamination of the NAWM fraction with these lesions. The orientationally averaged diffusion coefficient was increased and the fractional anisotropy reduced in the NAWM fraction of the MS patients. These results confirm prior studies which suggest that pathology in the NAWM occurs independent of focal MS lesions, and are not likely the result of sample contamination through or across slices. This injury to the NAWM may be the result of focal, microscopic T2-invisible lesions and/or secondary degeneration related to distant lesions whose related fibres cross the corpus callosum.

PIMD: 15326616

Expression of the low-affinity neurotrophin receptor, p75(NTR), is upregulated by oligodendroglial progenitors adjacent to the subventricular zone in response to demyelination.

Precursor cells have the capacity to repopulate the demyelinated brain, but the molecular mechanisms that facilitate their recruitment are largely unknown. The low-affinity neurotrophin receptor, p75(NTR), may be one of these regulators; however, its expression profile by oligodendroglia within the multiple sclerosis (MS) brain remains uncertain. We therefore assessed the expression profile of this receptor within 8 MS and 4 control brains. We found no evidence of expression of p75(NTR) by mature oligodendrocytes. Instead, we demonstrated the presence of p75(NTR) on a subgroup of NG2-positive oligodendroglial progenitors in a periventricular plaque in one MS sample. Notably, p75(NTR)-expressing cells were also detected within the subventricular zone (SVZ) of this brain, adjacent to the periventricular plaque. In animals with experimental demyelination we observed similar patterns of p75(NTR) expression, initially confined to precursor cells within the SVZ, followed at later stages in the disease course by its expression amongst a subset of oligodendroglial progenitors within the corpus callosum. These data suggest that a population of precursor cells within the SVZ can be induced to express p75(NTR) and to subsequently assume an oligodendroglial progenitor phenotype in response to demyelination in the adjacent white matter.

PIMD: 15314115

Mechanisms of normal appearing corpus callosum injury related to pericallosal T1 lesions in multiple sclerosis using directional diffusion tensor and 1H MRS imaging.

To investigate the extent of tissue damage in a region of normal appearing corpus callosum (NACC) for different forms of multiple sclerosis (MS) using diffusion tensor and proton magnetic resonance (MR) spectroscopic imaging.A total of 47 patients with MS and 15 controls were included. Regions of interest from the NACC were manually segmented using high resolution anatomical images. Diffusion tensor eigenvalues and metabolite ratio of N-acetyl-aspartate (NAA) to creatine/phosphocreatine (Cr) were calculated in the NACC region.Increased apparent diffusion coefficients (ADCs) and decreased anisotropy were observed in the NACC for patients with MS relative to the control subjects. These resulted from increased diffusion tensor eigenvalues perpendicular to the maximum diffusion direction. The NAA:Cr ratio was decreased in the NACC for patients with MS relative to the control subjects. Significant correlations between pericallosal T1 lesion load and MR modalities in the NACC were observed for patients with relapsing remitting/secondary progressive MS (RR/SPMS), but not for patients with primary progressive MS (PPMS).This study provides further insight into changes in the ADC and diffusion anisotropy based on the diffusion tensor eigenvalues for patients with MS. The changes in the diffusion tensor eigenvalues and NAA:Cr ratio in the NACC for patients with RR/SPMS suggest axonal injury and/or dysfunction induced by wallerian degeneration. The lack of correlation between these variables in the NACC and focal MS lesions for patients with PPMS further supports intrinsic differences related to tissue injury between these subtypes of MS.

PIMD: 15289266

MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood.

The prognostic factors for relapse of the initial MRI findings after a first episode of acute CNS inflammatory demyelination are unclear in children. In this study we aimed to identify initial MRI factors that are predictive of a second attack and disability after a first episode of acute CNS inflammatory demyelination in childhood. A cohort of 116 children who had a first episode of acute CNS inflammatory demyelination between 1990 and 2002 was studied using survival analysis methods. The initial MRI data were reviewed in a systematic, standardized, double-blind manner. The average follow-up was 4.9 +/- 3 years. Multivariate analysis showed that the rate of second attack was higher in patients with corpus callosum long axis perpendicular lesions (34 out of 116 patients, 30%) on the initial MRI [hazard ratio (HR) 2.89; 95% confidence interval (CI) 1.65-5.06] and/or with the sole presence of well-defined lesions (46 out of 116 patients, 40%) (HR 1.71; 95% CI 1.29-2.27). Both criteria were more specific predictors (100%) of relapse, demonstrating conversion to multiple sclerosis, than the three Barkhof criteria (63%), but were less sensitive (21% compared with 52%). None of the MRI criteria was predictive of severe disability. Using initial MRI and survival analysis methods, we identified two specific predictors of relapse and conversion to multiple sclerosis after a first episode of acute CNS inflammatory demyelination in childhood. Their low sensitivity, however, shows that this prediction remains difficult.

PIMD: 15262739

Corpus callosum axonal injury in multiple sclerosis measured by proton magnetic resonance spectroscopic imaging.

Axonal damage has been observed in normal-appearing white matter (NAWM) for patients with multiple sclerosis (MS).To investigate changes in brain metabolite ratios in a region of normal-appearing corpus callosum (CC) for patients with MS and to test its relationship to changes in other regions of NAWM.Data were collected from 24 patients with MS and 15 control subjects. Two-dimensional proton magnetic resonance spectroscopic imaging was performed centered at the CC. Regions of interest from normal-appearing CC were manually segmented using anatomical images. The NAWM outside the CC region was segmented based on the signal intensity in T1- and T2-weighted images.The N-acetylaspartate-creatine-phosphocreatine ratio was lower in both regions for patients with secondary progressive MS compared with the controls; the N-acetylaspartate-creatine-phosphocreatine was lower only in the normal-appearing CC region for patients with relapsing-remitting MS (P<.001) compared with the controls. The ratio of choline-containing compound compared with the creatine-phosphocreatine ratio was also lower in the region of normal-appearing CC for patients with relapsing-remitting MS (P =.003) compared with the controls. There was a correlation between the N-acetylaspartate-creatine-phosphocreatine ratio in the normal-appearing CC and T1 lesions (r = -0.53, P =.01) for all patients.The CC was a more sensitive location for depicting axonal injury than other regions of NAWM. A correlation between the reduction of the N-acetylaspartate-creatine-phosphocreatine ratio in the normal-appearing CC and the T1 lesions may suggest that transection of axons in lesions may cause distant axonal damage and/or dysfunction that are expressed and more sensitively detectable in the CC.

PIMD: 15257531

[Applications of verbal dichotic listening in neurological and neuropsychiatric clinical practice].

To review the most recent data regarding clinical applications of the dichotic listening technique in neurology and neuropsychiatry.The technique is described, in addition to the two main cognitive abilities we can measure with it. First, language lateralization, following Kimura's model as an anatomical explanation of the right ear advantage effect. Second, the attentional function, including Kinsbourne's model and the forced attention paradigm from Hugdahl as a valuable working tool to evaluate selective attention and executive functions. In subsequent sections, a review is offered respecting both types of cognitive processes for schizophrenia, depression, dyslexia and Multiple Sclerosis, along with data from our laboratory regarding the last illness.The dichotic listening is a useful technique to evaluate the integrity of the temporal and frontal lobes, as well as the interhemispheric communication across the corpus callosum. Application to the clinical practice pretends to incorporate it to the diagnostic, to the description of the pathologies profiles and also to the prediction of illness course, resulting promising in some cases although with reasonable limits while looking for additional research.

PIMD: 15221802

Preferential occult injury of corpus callosum in multiple sclerosis measured by diffusion tensor imaging.

To investigate the feasibility of diffusion tensor imaging (DTI) assessment of microscopic fiber tract injury in the corpus callosum (CC) and other normal-appearing white matter (NAWM) in patients with early multiple sclerosis (MS).DTI was performed in 12 healthy volunteers and 15 patients who have relatively short disease duration (mean = 2.7 years). Both fractional anisotropy (FA) and mean diffusivity (MD) were obtained in different regions of normal-appearing CC (NACC) and NAWM in frontal and occipital regions.The data showed significantly lower FA ($P < 0.001$) and higher MD ($P < 0.04$) for NACC regions, but not for frontal and occipital NAWM regions, in patients than in those in healthy volunteers after Bonferroni adjustment. The increase of MD in the entire NACC regions was correlated with the total cerebral lesion volume ($r = 0.75$, $P = 0.001$) in patients.The water diffusion changes indicate that in the early phase of disease there is a preferential occult injury of CC, which is likely due to the Wallerian degeneration from distant lesions.

PIMD: 15198458

Foreign accent syndrome in a patient with multiple sclerosis.

Foreign accent syndrome is a speech disorder which leads listeners to perceive the patient as having a foreign accent. It has been recognized previously after stroke, brain injury or unknown causes.A 52-year-old woman with clinically definite relapsing remitting multiple sclerosis (MS) presented with episodes of what was perceived as a Dutch accent along with other neurologic symptoms that would resolve simultaneously. She was assessed by a speech therapist both during an episode and after complete recovery. Speech and MRI changes (showing deep white matter lesions in the corpus callosum, left pariental lobe and left frontal lobe) were consistent with previous reports of foreign accent syndrome.This patient's episodes of foreign accent are thought to be due to her MS.

PIMD: 15086129

Seizure as the manifestation of relapse of multiple sclerosis in a military pilot.

A case of a seizure in an active pilot with multiple sclerosis is presented. A 40-yr-old Canadian Forces pilot experienced a secondary generalized tonic-clonic seizure while taxiing a CC-130 (Hercules) transport after landing. His multiple sclerosis had been in remission since 1997 and he had been returned to restricted flying duties. He was assessed and treated, with no further seizures or adverse sequelae. An MRI showed a new demyelinating lesion in the anterior corpus callosum. His seizure was the only clinical manifestation of his MS relapse. The prevalence of seizures in MS patients, possible causal mechanisms, and the disposition of pilots with MS are discussed.

PIMD: 15015007

Water content and myelin water fraction in multiple sclerosis. A T2 relaxation study.

Measurements of the T2 decay curve provide estimates of total water content and myelin water fraction in white matter in-vivo, which may help in understanding the pathological progression of multiple sclerosis (MS).Thirty-three MS patients (24 relapsing remitting, 8 secondary progressive, 1 primary progressive) and 18 controls underwent MR examinations. T2 relaxation data were acquired using a 32-echo measurement. All controls and 18 of the 33 MS patients were scanned in the transverse plane through the genu and splenium of the corpus callosum. Five white matter and 6 grey matter structures were outlined in each of these subjects. The remaining 15 MS patients were scanned in other transverse planes. A total of 189 lesions were outlined in the MS patients. Water content and myelin water fraction were calculated for all regions of interest and all lesions.The normal appearing white matter (NAWM) water content was, on average, 2.2% greater than that from controls, with significant differences occurring in the posterior internal capsules, genu and splenium of the corpus callosum, minor forceps and major forceps ($p<0.0006$). On average, MS lesions had 6.3% higher water content than contralateral NAWM ($p<0.0001$). Myelin water fraction was 16% lower in NAWM than for controls, with significant differences in the major and minor forceps, internal capsules, and splenium ($p<0.05$). The myelin water fraction of MS lesions averaged 52 % that of NAWM.NAWM in MS has a higher water content and lower myelin water fraction than control white matter. The cause of the myelin water fraction decrease in NAWM could potentially be due to either diffuse edema, inflammation, demyelination or any combination of these features. We present a simple model which suggests that myelin loss is the dominant feature of NAWM pathology.

PIMD: 14745069

Clinical and MRI outcome after autologous hematopoietic stem cell transplantation in MS.

The authors report the outcome of 14 patients with severe multiple sclerosis treated with autologous hematopoietic stem cell transplantation (AHSCT) after a median follow-up period of 3 years. The 3-year actuarial probability of progression-free survival was 85.7% and that of disease activity-free survival was 46.4%. On MRI, no T1-enhanced lesions were detected after AHSCT. The mean change in T2 lesion volume from baseline to the third year was -20.2% and that of the corpus callosum area was -12.7%; 50% of this reduction was seen during the first year.

PIMD: 14664467

MRI/MRS of corpus callosum in patients with clinically isolated syndrome suggestive of multiple sclerosis.

Atrophy of corpus callosum (CC) related to axonal loss has previously been observed in patients at the early stage of clinically definite multiple sclerosis (CDMS). Atrophy increases with the progression of the disease. Nevertheless, no data concerning the onset of atrophy of CC are currently available. The purpose of this study is to determine if damage in callosal tissue was present at the earliest stage of MS, in a subgroup of patients presenting with a clinically isolated syndrome suggestive of MS (CISSMS), fulfilling the dissemination in space criteria according to McDonald. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) techniques were applied to measure CC volume, magnetization transfer ratio (MTR), mean diffusivity (MD), N-acetyl aspartate/choline-containing compounds (NAA/Cho) ratio, N-acetyl aspartate/total creatine (NAA/Cr) ratio and Cho/Cr ratio inside the CC of 46 CISSMS patients and 24 sex- and age-matched controls. No atrophy of CC was observed in the CISSMS group. CC of patients was characterized by decreased MTR and increased MD. No change in the NAA/Cr ratio was observed while the NAA/Cho ratio decreased and Cho/Cr ratio increased in the splenium and the central anterior part of CC. These abnormalities were present in patients with, but also without, macroscopic lesions inside the CC. Our results indicate that diffuse structural and metabolic changes, which may be interpreted as representing predominantly myelin pathology, occur in the CC at the earliest stage of MS before any atrophy is detected.

PIMD: 14629906

Multiple sclerosis vs acute disseminated encephalomyelitis in childhood.

The initial presenting clinical and laboratory findings of either acute disseminated encephalomyelitis or the first attack of multiple sclerosis in the pediatric population were compared and contrasted. A retrospective review of the medical records was conducted of all children younger than 17 years who presented with either the diagnosis of acute disseminated encephalomyelitis or multiple sclerosis between 1987 and 2001. Seventeen cases of clinically definite multiple sclerosis (seven female, mean age 12.4 +/- 4.5 years) and seven cases of acute disseminated encephalomyelitis (three female; mean age 8.7 +/- 3.8 years) were reviewed. Systemic and nonfocal neurologic symptoms were more commonly evident in acute disseminated encephalomyelitis than in multiple sclerosis: fever (43% vs 6%), headache (57% vs 24%), fatigue (71% vs 29%), vomiting (57% vs 0%), and encephalopathy (71% vs 6%). In multiple sclerosis patients, T(2)-weighted white matter magnetic resonance imaging lesions were more commonly located in the corpus callosum (64% vs 17%) and the periventricular area (91% vs 50%) compared with those in patients with acute disseminated encephalomyelitis. These results suggest that acute disseminated encephalomyelitis and multiple sclerosis can be differentiated to some degree according to clinical and radiologic data at initial presentation, which is important because the long-term prognosis for childhood multiple sclerosis appears to be less favorable.

PIMD: 14604264

The relation between brain MRI lesions and depressive symptoms in multiple sclerosis.

The authors investigated the relationship between depression and involvement of specific brain areas in multiple sclerosis (MS) patients. 20 MS patients (10 depressed and 10 non-depressed) were evaluated. The emotional state was assessed by several neuropsychological tests, and all of the patients underwent 1.5 Tesla magnetic resonance (MRI) including T1 and T2 weighted images. MRI data were analyzed by measuring the regional area of lesions (in mm2) in the frontal, temporal and corpus callosum locations, side and the number of lesions. The correlation of MRI findings between depressed and non-depressed groups of patients has shown that a statistically significant difference was achieved between regional frontal lesions area ($p = 0.02$), aa well as significant difference between regional temporal area of lesions ($p = 0.13$). In the depressed group of patients a greater lesions area was achieved in the right when compared with the left frontal lobe. No differences were obtained for the temporal lobe. The highest number of lesions were observed in the right frontal lobe in the depressed group of patients. Our findings have shown that depressive symptoms are associated with the area and location of brain lesions. (Tab. 1, Fig. 2, Ref. 8.)

PIMD: 14508778

Directional diffusion in relapsing-remitting multiple sclerosis: a possible in vivo signature of Wallerian degeneration.

To examine the role of directional dependence of the apparent diffusion coefficients in the evaluation of normal-appearing brain regions of patients with relapsing-remitting multiple sclerosis.The role of diffusion tensor eigenvalues was investigated in the normal-appearing brain regions for 18 patients with relapsing-remitting multiple sclerosis and 15 age-matched normal controls.The isotropic apparent diffusion was increased in all regions. However, reduced anisotropy was significant only in regions with high anisotropy, including the corpus callosum and the internal capsule, and was due to increased diffusion tensor eigenvalues corresponding to diffusion transverse to the fibers without significant increase along the fibers. This characteristic pattern of changes in diffusion tensor eigenvalues has been observed previously in cases of Wallerian degeneration. Low-anisotropy regions corresponded to gray matter and gray/white interface regions. Since fiber tract orientations are not determined for regions of low anisotropy, this characteristic pattern of diffusion change is not detectable in these regions.Examination of diffusion tensor eigenvectors may provide insight into the changes observed in diffusion and a signature of Wallerian degeneration in the normal-appearing white matter of relapsing-remitting multiple sclerosis patients.

PIMD: 12815694

Diffusely elevated cerebral choline and creatine in relapsing-remitting multiple sclerosis.

It is well known that multiple sclerosis (MS) pathogenesis continues even during periods of clinical silence. To quantify the metabolic characteristics of this activity we compared the absolute levels of N-acetylaspartate (NAA), creatine (Cr), and choline (Cho) in the normal-appearing white matter (NAWM) between relapsing-remitting (RR) MS patients and controls. Metabolite concentrations were obtained with 3D proton MR spectroscopy at 1.5 T in a 480 cm(3) volume-of-interest (VOI), centered on the corpus callosum of 11 MS patients and 9 matched controls. Gray/white-matter/cerebral-spinal-fluid (CSF) volumes were obtained from MRI segmentation. Patients' average VOI tissue volume (V(T)), 410.8 +/- 24.0 cm(3), and metabolite levels, NAA = 6.33 +/- 0.70, Cr = 4.67 +/- 0.52, Cho = 1.40 +/- 0.17 mM, were different from the controls by -8%, -9%, +22% and +32%. The Cho level was the only single metric differentiating patients from controls at 100% specificity and >90% sensitivity. Diffusely elevated Cho and Cr probably reflect widespread microscopic inflammation, gliosis, or de- and remyelination in the NAWM. Both metabolites are potential prognostic indicators of current disease activity, preceding NAA decline and atrophy.

PIMD: 12810788

MRI lesion volume heterogeneity in primary progressive MS in relation with axonal damage and brain atrophy.

To investigate whether axonal damage in primary progressive (PP) multiple sclerosis (MS), as measured by proton magnetic resonance spectroscopy (HMRS) imaging and brain atrophy, is a function of T2 weighted brain lesion volume.34 PP MS patients were divided into two categories: low (<3 cm(3), n = 18) or high (>or=3 cm(3), n = 16) T2 lesion load (LL). An Index of Brain Atrophy (IBA) was calculated and HMRS metabolite ratios were derived from a central brain area centred at the corpus callosum.Patient groups did not differ with regard to clinical characteristics and showed lower mean IBA and mean N-acetylaspartate:creatinine (NAA:Cr) ratios compared to healthy controls.PP patients with low and high brain T2LL have detectable brain atrophy and NAA:Cr reduction compared to healthy controls. In PP MS, T2 lesions alone are insufficient to explain the presence of brain atrophy and decrease in NAA:Cr.

PIMD: 12638018

A study of the mechanisms of normal-appearing white matter damage in multiple sclerosis using diffusion tensor imaging--evidence of Wallerian degeneration.

Diffusion tensor imaging (DTI) investigates brain tissue microstructure in vivo. In multiple sclerosis (MS) Wallerian degeneration of axons traversing focal lesions is a potential mechanism of damage in normal-appearing white matter. In vivo evidence for this hypothesis is limited. The present study investigated the relationship between DTI-derived indices in the normal-appearing corpus callosum (CC) and the lesion loads (LLs) in connected cerebral regions. DTI was performed in 39 MS patients and in 21 age-matched controls. Fractional anisotropy (FA) and mean diffusivity (MD) were estimated in the genu, body and splenium of CC. Patients showed lower FA and higher MD in the CC than controls and both correlated with the total LL ($r = -0.56$ and $r = 0.54$, $p < 0.0001$). The LL of individual cerebral lobes correlated with both FA and MD in the corresponding callosal regions, with the body showing the strongest correlations with frontal and parietal LL ($p < 0.0001$). The strong correlations between DTI indices in the CC and the extent of lesions in connected brain regions support the hypothesis that Wallerian degeneration of axons transected by remote, but connected focal lesions, is an important pathogenic mechanism of damage in MS.

PIMD: 12635518

Incidental stereotactic diagnosis of cerebral insults.

Among the patients (6854 patients 1990-1999) who underwent computer-assisted stereotactic biopsy most were referred with the presumptive diagnosis of a brain mass lesion. Forty-three cases (0.63%) were found in which the final histopathological diagnosis excluded a neoplastic, infectious or inflammatory lesion but disclosed a cerebral insult. Histologically these could be subdivided into ischemic insults in 38 cases (88%) and hemorrhagic insults in five cases (12%). On the basis of clinical and radiological findings in this group, 35 patients (81%) were sent to our department because of suspected neoplasmatic lesions, two patients (5%) because of multiple sclerosis, two patients (5%) because of inflammatory disease and one patient (2%) because of a suspected infectious parasitic disease. All patients underwent initial CT examinations which showed hypodense lesions of the brain in 38 patients (88%) and hyperdense lesions in five cases (12%). Constant enhancement on CT scans of the mass lesion was found in 12 patients (28%) only. Fourteen lesions (33%) were located in the right hemisphere, five lesions (12%) in the left hemisphere, nine lesions (21%) in the basal ganglia, four lesions (9%) in the midbrain, two lesions (4.5%) in the corpus callosum and one lesion (2%) in a thalamus. Multiple lesions were present in eight cases (19%). The most common initial neurological symptoms upon clinical presentation were hemiparesis (18 patients, 42%), epilepsy (eight patients, 18%), a change in mental status (six patients, 14%). There was no mortality and no operative morbidity associated with the stereotactic biopsy in this group of patients. The most common neurological disorder, cerebrovascular insult, rarely poses diagnostic problems. If there are doubts a serial stereotactic biopsy can safely clarify the situation.

PIMD: 12501577

[Brain atrophy and cognitive disorder in multiple sclerosis].

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system causing severe disability via the progressive damage of white matter. Beyond physical signs cognitive dysfunction might be present as well. The aim of this study was to investigate the frequency and characteristics of brain atrophy and cognitive alterations. Significant cortical and subcortical atrophy was found on brain MRI of 30 MS patients included in this study comparing to healthy controls. Abnormal findings were detected in more than 60% of patients using a cognitive test battery. Generally, verbal abstraction, visuospatial orientation, attention, short-term memory was impaired and the psychomotor speed was decreased, even in the early stage of the disease. Depression-related complaints were found in 57% of this population. The Kurtzke scale, the atrophy of corpus callosum and widening of 3rd ventricle and Sylvian fissures were related to impaired cognitive performances. The authors would like to call attention to the early cognitive deficit and the need of treatment in MS.

PIMD: 12467867

3-D echo planar (1)HMRS imaging in MS: metabolite comparison from supratentorial vs. central brain.

To determine if metabolite ratios as measured by 3-dimensional echo planar spectroscopy imaging (3D-EPSI) from central brain regions of interest (ROI) centered at the corpus callosum reflect imaging metrics of large volumes of supratentorial brain (STB) from patients with multiple sclerosis.48 MS patients with relapsing-remitting, secondary progressive, and primary progressive disease underwent a 3D-EPSI sequence covering large volumes of STB. Metabolite ratios were first estimated from all voxels within a STB mask using a linear regression of N-acetylaspartate (NAA) over Creatine (Cr), NAA over choline (Cho) and Cho over Cr. Secondly, spectroscopic voxels from a central brain (CB) ROI centered at the corpus callosum were selected within the STB. Ratios were compared using Bland-Altman regression analysis and Spearman's correlation coefficients between STB versus central brain. Ratios from studied ROIs were correlated with the EDSS and compared to normal controls.Very strong correlations ranging from 0.884 and 0.938 ($p < 0.0001$) were found for all metabolite ratios between STB versus central brain. NAA/Cr ratios were similarly and negatively correlated with the EDSS across all ROIs, trends ranging from -0.257 to -0.314 ($p < 0.1$). NAA/Cr from all MS patients was similarly decreased compared to controls across all ROIs ($p < 0.01$).Metabolite ratios from a central brain ROI were statistically equivalent and highly correlated with ratios from the STB. The study of NAA/Cr using (1)HMRS from a central brain ROI centered at the corpus callosum seems to be representative of brainwide axonal changes in patients with MS.

PIMD: 12382153

Choline is increased in pre-lesional normal appearing white matter in multiple sclerosis.

Our aim was to determine if the resonance intensity of choline-containing compounds (Cho) measured using proton magnetic resonance spectroscopy (MRS) was increased in pre-lesional normal appearing white matter (NAWM) in patients with multiple sclerosis (MS) relative to NAWM that remained stable in subsequent scans.The Cho peak in MR spectra is associated with membrane phospholipids and increases in acute MS plaques, possibly even before the appearance of MRI-visible MS lesions.Three combined proton MRI and MRS imaging examinations of the corpus callosum and adjacent periventricular white matter were performed on 12 MS patients at intervals of 6 months. Proton density (PD) images were visually matched across 3 time points and the lesion volume in each voxel of the volume of interest was determined. The voxels were subdivided into four groups based on the presence or absence of lesion at baseline and change or no change in lesion volume on the subsequent scan.We found a significantly higher baseline Cho/Creatine (Cr) ratio in NAWM voxels that displayed MRI visible lesions 6 months later than NAWM voxels that remained unchanged (1.57 +/- 0.30 and 1.37 +/- 0.33, respectively, $p < 0.001$). The 12-month interval data revealed similar pre-lesional elevated Cho/Cr, (1.51 +/- 0.29 versus 1.39 +/- 0.32, $p = 0.009$). Voxels that contained lesion at baseline and increased in lesion volume at 6 months also showed a significantly higher Cho/Cr ratio than those whose lesion volume did not change (1.60 +/- 0.32 and 1.49 +/- 0.36, respectively, $p = 0.043$).The results of this study are consistent with focal pre-lesional myelin membrane pathology in the NAWM at least 12 months before lesions become visible on conventional MRI. This could reflect altered myelin chemistry or the presence of inflammation as seen in experimental allergic encephalomyelitis.

PIMD: 12242553

T1 relaxation time mapping of white matter tracts in multiple sclerosis defined by diffusion tensor imaging.

T(1) relaxation time (T(1)) is a quantitative magnetic resonance measure that enables a global evaluation of white matter disease in multiple sclerosis (MS). We aimed to investigate whether mapping of T(1) values in critical white matter tracts, defined by diffusion tensor (DT) imaging, could provide a stronger surrogate marker of disability. 25 patients with relapsing-remitting MS and 14 healthy controls were imaged with a dual-echo T(2)-weighted sequence. Whole brain T(1) maps were acquired using a multi-slice inversion recovery sequence and DT images generated from a spin-echo, echo-planar diffusion weighted sequence. Trajectories were defined to follow the course of white matter fibre tracts in the pyramidal pathways and corpus callosum. T(1) values were sampled along these trajectories. Total white matter T(1) was sampled by defining white matter masks on axial slices of the T(1) maps. Median T(1) in the pyramidal tracts, corpus callosum and total white matter of MS patients was significantly longer than in controls ($p < 0.0001$). Median pyramidal tract T(1) correlated significantly with the pyramidal Kurtzke Functional Systems Score ($r = 0.64$, $p = 0.0007$) and the Expanded Disability Status Scale ($r = 0.55$, $p = 0.005$). By contrast, no correlation with disability was observed for corpus callosum T(1) or total white matter T(1). Our findings show that quantifying pathology within the pyramidal tracts, by utilizing T(1), provides a strong correlate of disability compared with the overall white matter burden of disease. Pyramidal tract T(1) may also provide an objective, sensitive measure for monitoring the progression of motor deficits and disability.

PIMD: 12166504

Baseline MRI characteristics of patients at high risk for multiple sclerosis: results from the CHAMPS trial. Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study.

The baseline MRI studies from the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) trial, a randomized, longitudinal, double-blind trial of 383 patients with a first acute clinical demyelinating event and evidence of prior subclinical demyelination on magnetic resonance imaging (MRI) of the brain, provides a large MRI database for patients likely in the earliest stages of multiple sclerosis (MS). High-resolution baseline MRIs revealed a median of 13 T2 lesions (maximum = 103 lesions) and 2.05 cm3 of T2 lesion volume (maximum 35.04 cm3), with 30% of patients having one or more enhancing lesions despite receiving a standardized high-dose course of intravenous corticosteroids. Periventricular, discrete, and juxtacortical T2 lesions were present in 99%, 92% and 67% of the patients, respectively. Large (> 6 mm), T1-hypointense, infratentorial, and corpus callosum lesions were present in 69%, 50%, 55% and 58%, respectively. Clinical presentation groups showed differences in T2 lesion volume, and enhancing lesion number and volume. At baseline, 97%, 81% and 72% of the patients met 'Paty', 'Fazekas', and 'Barkhof' research criteria for MS, respectively, with the percentages similar according to clinical presentation group. These results support and extend those of smaller and/or retrospective series, which have shown substantial subclinical injury, based on brain MRI, at the earliest identifiable stages of disease.

PIMD: 12140672

Intra-voxel and inter-voxel coherence in patients with multiple sclerosis assessed using diffusion tensor MRI.

Previous diffusion tensor magnetic resonance imaging (DT-MRI) studies reported mean diffusivity () and fractional anisotropy (FA) changes in lesions and normal-appearing white matter (NAWM) of patients with multiple sclerosis (MS), but neglected the additional information which can be obtained by the analysis of the inter-voxel coherence (C). The present study is based on a large sample of patients with MS and it is aimed at assessing the potential role of C in the quantification of MS-related tissue damage of T2-visible lesions and NAWM. We obtained dual-echo, T1-weighted and DT-MRI scans from 78 patients with relapsing-remitting (RR), secondary progressive (SP), or primary progressive (PP) MS and from 26 healthy volunteers. We calculated, FA and C of T2-hyperintense lesions, T1-isointense lesions, T1-hypointense lesions and several areas of the NAWM. and FA of the majority of NAWM regions studied from MS patients were different from the corresponding quantities of the white matter from controls. NAWM C from patients was lower than white matter C from controls only for the parietal pericallosal areas. SPMS patients had higher corpus callosum and lower corpus callosum FA and C than patients with either RRMS or PPMS. Average lesion was higher, and average FA and C lower than the corresponding quantities measured in the NAWM. Average T1-hypointense lesion was higher and average FA lower than the corresponding quantities of T1-isointense lesions, whereas average C of these two lesion populations were not different. SPMS had higher average lesion than both PPMS and RRMS patients. NAWM and C of the corpus callosum were moderately correlated with disability. This study confirms the role of DT-MRI metrics to identify MS lesions with different amounts of tissue damage and to detect diffuse changes in the NAWM. It also shows that measuring C enables us to obtain additional information about tissue damage, which is complementary to that given by the analysis of and FA.

PIMD: 11979576

White matter mapping using diffusion tensor MRI.

Diffusion tensor MRI is used to define trajectories that reflect the long-range order of in vivo white matter (WM) fiber tracts. Fiber tracking is particularly prone to cumulative error from noise and partial volume along the length of the trajectory paths, but the overall shape of each path is anatomically meaningful. By considering only the long-range similarity of path shapes, a method of constructing 3D maps of specific WM structures has been developed. A trajectory is first computed from an operator-selected seed voxel, located within the anatomical structure of interest (SOI). Voxels from the same structure are then automatically identified based on the similarity of trajectory path shapes, assessed using Pearson's correlation coefficient. The corpus callosum and pyramidal tracts in 14 patients with multiple sclerosis, and in 10 healthy controls were mapped by this method, and the apparent diffusion coefficient (ADC) was measured. The ADC was significantly higher in patients than in controls, and higher in the corpus callosum than in the pyramidal tracts for both groups. Using this method the different functional structures in the WM may be identified and mapped. Within these maps, MRI parameters can be measured for subsequent comparison with relevant clinical data.

PIMD: 11973459

Axonal lesions and PDGF-enhanced remyelination in the rat corpus callosum after lysolecithin demyelination.

In multiple sclerosis (MS), demyelination is often accompanied by axonal lesions, which largely account for patient disability. We therefore studied the consequences of demyelination induced by lysophosphatidylcholine (LPC) on the axonal cytoskeleton, particularly neurofilaments (NF) and tubulin, in the adult rat corpus callosum. Immunocytochemistry showed that NF immunolabelled fibres decreased by 49% in the LPC injured area at day 15. Since it has been previously demonstrated that PDGF improves remyelination, we performed a comparative study between LPC controls and PDGF-treated (1 microg) animals. In these later animals, immunolabelling for NFL and NFM (NFH subunit excepted) was increased by 142 and 63%, respectively, indicating reduction of axonal abnormalities. These results extend the potential therapeutic role of PDGF in MS.

PIMD: 11949719

Dichotic listening and corpus callosum magnetic resonance imaging in relapsing-remitting multiple sclerosis with emphasis on sex differences.

Twenty-five early-onset relapsing-remitting multiple sclerosis patients (12 women and 13 men) with mild disability were compared with 25 matched controls in a dichotic listening (DL) test under nonforced and forced attentional-shift conditions. Patients showed left ear impairment and no left ear advantage in the forced-left condition. Four corpus callosum (CC) regions were measured in patients on a midsaggital magnetic resonance imaging scan. The right ear score was negatively correlated whereas the left ear score was positively correlated with CC regions (significant only for the nonforced condition). Moreover, in men, the correlations with DL scores were linked mainly to the splenium and posterior isthmus, and in women, they were stronger for anterior isthmus and posterior body. An inverse correlation between months of disease evolution and CC area was found only in women.

PIMD: 11901239

Imaging of white matter lesions.

Magnetic resonance imaging (MRI) is very sensitive for the detection of white matter lesions (WML), which occur even in normal ageing. Intrinsic WML should be separated from physiological changes in the ageing brain, such as periventricular caps and bands, and from dilated Virchow-Robin spaces. Genuine WML are best seen with T2-weighted sequences such as long TR dual-echo spin-echo or FLAIR (fluid-attenuated inversion recovery); the latter has the advantage of easily separating WML from CSF-like lesions. Abnormal T2 signal in MRI is not specific, and can accompany any change in tissue composition. In the work-up of WML in small vessel disease, magnetic resonance angiography can be used to rule out (concomitant) large vessel disease, and diffusion-weighted MRI to identify new ischaemic lesions (amidst pre-existing old WML). The differential diagnosis of WML includes hereditary leukodystrophies and acquired disorders. The leukodystrophies that can present in adult age include metachromatic leukodystrophy, globoid cell leukodystrophy, adrenomyeloneuropathy, mitochondrial disorders, vanishing white matter, and cerebrotendinous xanthomatosis. These metabolic disorders typically present with symmetrical abnormalities that can be very diffuse, often with involvement of brainstem and cerebellum. Only the mitochondrial disorders tend to be more asymmetric and frequently involve the grey matter preferentially. Among the acquired white matter disorders, hypoxic-ischaemic causes are by far the most prevalent and without further clinical clues there is no need to even consider the next most common disorder, i.e. multiple sclerosis (MS). Among the nonischaemic disorders, MS is far more common than vasculitis, infection, intoxication and trauma. While vasculitis can mimic small vessel disease, MS has distinctive features with preferential involvement of the subcortical U-fibres, the corpus callosum, temporal lobes and the brainstem/cerebellum. Spinal cord lesions are very common in MS, but do not occur in normal ageing nor in small vessel disease.

PIMD: 11901003

Sandlike appearance of Virchow-Robin spaces in early multiple sclerosis: a novel neuroradiologic marker.

The distinctive hyperintensity of multiple sclerosis (MS) lesions on T2-weighted brain MR images is well recognized. However, Virchow-Robin spaces (VRSs), especially in early MS, have not been described. Our purpose was to determine the frequency of VRSs in recent-onset MS.Brain MR imaging was performed in 71 patients (mean age, 26.8 years; range, 20-41 years; 47 women, 24 men) within 3 months of MS onset. Proton density-, T2-, and T1-weighted images were obtained. Age-and sex-matched control subjects (mean age, 27.2 years; range, 22-41 years; 38 women, 22 men) who underwent brain MR imaging as a part of headache evaluation, and findings that were interpreted as normal served as controls. On high-convexity images (axial sections above the upper corpus callosum border), VRSs were identified as small (<2-mm diameter) sandlike areas isointense to CSF. VRSs were graded 0-3.VRSs were visualized in high-convexity white matter in 55% of patients and 7% of control subjects (P <.001). In patients, 15% of VRSs were grade 1 (fewer than four), 23% were grade 2 (four to seven), and 62% were grade 3 (more than seven). In control subjects, all identified VRSs were grade 1. Among patients with and those without VRSs, age at onset, neurologic disability, and specific functional system involvement or mono- versus polysymptomatic involvement at onset did not differ.VRSs were more frequent in patients with recent-onset MS than in control subjects. The sandlike appearance of VRSs may be a neuroradiologic marker that reflects early inflammatory changes in MS.

PIMD: 11803584

Cognitive dysfunction and histological findings in adult rats one year after whole brain irradiation.

Cognitive dysfunction and histological changes in the brain were investigated following irradiation in 20 Fischer 344 rats aged 6 months treated with whole brain irradiation (WBR) (25 Gy/single dose), and compared with the same number of sham-irradiated rats as controls. Performance of the Morris water maze task and the passive avoidance task were examined one year after WBR. Finally, histological and immunohistochemical examinations using antibodies to myelin basic protein (MBP), glial fibrillary acidic protein (GFAP), and neurofilament (NF) were performed of the rat brains. The irradiated rats continued to gain weight 7 months after WBR whereas the control rats stopped gaining weight. Cognitive functions in both the water maze task and the passive avoidance task were lower in the irradiated rats than in the control rats. Brain damage consisting of demyelination only or with necrosis was found mainly in the body of the corpus callosum and the parietal white matter near the corpus callosum in the irradiated rats. Immunohistochemical examination of the brains without necrosis found MBP-positive fibers were markedly decreased in the affected areas by irradiation; NF-positive fibers were moderately decreased and irregularly dispersed in various shapes in the affected areas; and GFAP-positive fibers were increased, with gliosis in those areas. These findings are similar to those in clinically accelerated brain aging in conditions such as Alzheimer's disease, Binswanger's disease, and multiple sclerosis.

PIMD: 11733726

In vivo damage of CNS myelin and axons induced by peroxynitrite.

In multiple sclerosis (MS) the mechanisms of injury caused by peroxynitrite remain uncertain. To study histological, ultra structural and molecular alterations caused by peroxynitrite in brain, the peroxynitrite donor 3-morpholinosydnonimine was injected in rat corpus callosum. Peroxynitrite induces strong primary axonal damage with characteristics of primary acute axonopathy, together with severe myelin alteration, myelin vacuolation and demyelination, and nitrotyrosine formation as confirmed by detection of nitrosated target proteins. Administration of the peroxynitrite scavenger uric acid inhibited these effects. In vivo, peroxynitrite leads to a disorganisation of myelin and to axonal damage presenting some similarities to the formation of MS lesions. Understanding the action of peroxynitrite in this process will open new therapeutic strategies by specific inhibition of peroxynitrite formation and action.

PIMD: 11589650

Cognitive correlates of supratentorial atrophy on MRI in multiple sclerosis.

We aimed to investigate associations between neuropsychological indices and normalized volumes of supratentorial structures, and the area of the corpus callosum.We studied 40 patients with clinically definite MS, using 3D-acquired MRI (MPRAGE, Magnetization Prepared Rapid Acquisition Gradient Echo) and stereology. Subjects underwent a neuropsychological battery interrogating multiple cognitive domains, from which a global Cognitive Index Score (CIS) was derived.White matter volumes were significantly correlated with CIS (rho= -0.59, P<0.0001) and with many of the individual cognitive tests. CIS was also significantly correlated with the corpus callosal area (rho= -0.49, P<0.002). Grey matter volumes did not significantly correlate with any cognitive test.These volume/function relationships presumably reflect the effects of subcortical axonal and myelin loss on the neural networks that subserve cognition. If serial MRI volume estimations can index accumulating cognitive deficits, this simple technique may be useful in therapeutic trials.

PIMD: 11464854

Amyotrophic lateral sclerosis with multiple sclerosis: a clinical and pathological report.

We report a 62-year-old woman with a past history of painful central visual loss who developed progressive quadriparesis and bulbar palsy. Neurological examination revealed widespread upper and lower motor neuron signs in the bulbar region and extremities. Electromyography demonstrated widespread active and chronic motor axon loss. Magnetic resonance neuroimaging studies revealed enhancing callosal and periventricular white matter lesions and cervical and thoracic cord hyperintensities. Cerebrospinal fluid analysis was consistent with multiple sclerosis. The patient died of respiratory failure two years after presentation, and autopsy revealed multifocal demyelination involving the corpus callosum, cerebellum and spinal cord as well as pathologic findings typical of amyotrophic lateral sclerosis. A review of the literature confirms the exceedingly unusual combination of amyotrophic lateral sclerosis with multiple sclerosis.

PIMD: 11442439

Correlations of brain MRI parameters to disability in multiple sclerosis.

The objective was to correlate magnetic resonance imaging (MRI) T2-weighted lesion load and measures of white matter atrophy in the brain to disability in a population-based sample of patients with multiple sclerosis (MS).A well defined cohort of patients was drawn at random from the general MS population by using the Danish Multiple Sclerosis Registry. A semi-automated local thresholding technique was used to quantify T2-weighted lesions on MRI; whereas manual tracing was applied to measure the corpus callosum brain ratio (CCR) and the ventricle brain ratio (VBR).A sample of 86 patients with a mean age of 43.3 years (SD 4.3), mean disease duration of 13.6 years (SD 4.4) and a median Expanded Disability Status Score (EDSS) of 6.0 was identified. The correlation between total lesion area of the brain (TLA) and disability (EDSS) for the whole sample was moderate (Spearman rank correlation coefficient r=0.48, P<0.001). Also correlations of CCR and VBR to disability (r=0.32-0.46) were significant.Correlations of TLA and disability in this study were rather strong. Hence, T2-weighted MRI lesion load in the brain still plays an important role as a surrogate marker of disease and as a secondary outcome measure in phase III treatment trials.

PIMD: 11424636

Water diffusion is elevated in widespread regions of normal-appearing white matter in multiple sclerosis and correlates with diffusion in focal lesions.

Pathological changes in the normal-appearing white matter in multiple sclerosis are well recognised, but their relationship to pathology in focal lesions is not well understood. Magnetic resonance diffusion imaging is sensitive to abnormalities in the integrity, size and geometry of water spaces in brain tissue. This study investigated the anatomical distribution of normal-appearing white matter diffusion abnormalities and their relationship to diffusion in focal lesions in multiple sclerosis (MS). The average apparent diffusion coefficient (ADCav) was measured by three-axis echoplanar diffusion imaging in normal-appearing white matter regions and lesions throughout the brain in 40 patients, and in white matter in 14 matched controls. The correlation between the ADCav in normal-appearing white matter and lesions was determined. In controls and patients, diffusion was highest in the corpus callosum. Patients had a higher mean ADCav than controls in widespread regions including the corpus callosum, cerebellar, temporal and occipital normal-appearing white matter. Mean normal-appearing white matter ADCav correlated strongly with mean lesion ADCav ($r = 0.67$, $P < 0.001$). This study demonstrates that water diffusion is elevated in widespread areas of normal-appearing white matter in MS, and is correlated with diffusion in lesions. These findings suggest that the pathogenetic mechanisms causing tissue damage in lesions and normal-appearing white matter are at least partly linked.

PIMD: 11335699

Central nervous system disease in patients with macrophagic myofasciitis.

Macrophagic myofasciitis (MMF), a condition newly recognized in France, is manifested by diffuse myalgias and characterized by highly specific myopathological alterations which have recently been shown to represent an unusually persistent local reaction to intramuscular injections of aluminium-containing vaccines. Among 92 MMF patients recognized so far, eight of them, which included the seven patients reported here, had a symptomatic demyelinating CNS disorder. CNS manifestations included hemisensory or sensorimotor symptoms (four out of seven), bilateral pyramidal signs (six out of seven), cerebellar signs (four out of seven), visual loss (two out of seven), cognitive and behavioural disorders (one out of seven) and bladder dysfunction (one out of seven). Brain T(2)-weighted MRI showed single (two out of seven) or multiple (four out of seven) supratentorial white matter hyperintense signals and corpus callosum atrophy (one out of seven). Evoked potentials were abnormal in four out of six patients and CSF in four out of seven. According to Poser's criteria for multiple sclerosis, the diagnosis was clinically definite (five out of seven) or clinically probable multiple sclerosis (two out of seven). Six out of seven patients had diffuse myalgias. Deltoid muscle biopsy showed stereotypical accumulations of PAS (periodic acid-Schiff)-positive macrophages, sparse CD8+ T cells and minimal myofibre damage. Aluminium-containing vaccines had been administered 3-78 months (median = 33 months) before muscle biopsy (hepatitis B virus: four out of seven, tetanus toxoid: one out of seven, both hepatitis B virus and tetanus toxoid: two out of seven). The association between MMF and multiple sclerosis-like disorders may give new insights into the controversial issues surrounding vaccinations and demyelinating CNS disorders. Deltoid muscle biopsy searching for myopathological alterations of MMF should be performed in multiple sclerosis patients with diffuse myalgias.

PIMD: 11254774

Demyelinating disorder of the central nervous system occurring in black South Africans.

To investigate the nature and cause in eight black South African patients of a recurrent (multiphasic), remitting, and relapsing demyelinating disease of the CNS.The clinical and laboratory investigations and radiological manifestations of these patients were documented.Each patient had two or more acute attacks of demyelinating disease affecting the CNS. The clinical presentations of the patients were predominantly those of multiphasic neuromyelitis optica (NMO). Brain MRI in these patients showed features consistent with those described for acute disseminated encephalomyelitis (ADEM), as well as lesions that are described in multiple sclerosis. There was involvement of the corpus callosum in addition to typical ADEM lesions. Laboratory investigations excluded all other known causes of multiphasic CNS demyelination. Oligoclonal antibodies were not detected in these patients at any time. The patients were all from a population with a low risk for MS (black South Africans).The patients described here represent a new phenotypic expression of a recurrent (multiphasic), steroid sensitive, inflammatory demyelinating disorder of the CNS occurring in black South Africans. The disorder is either a distinct inflammatory demyelinating disorder of the CNS of as yet unknown aetiology, or a varied form of MS (ADEM/NMO) occurring in a population with a low risk (where the genetic trait and environmental risk factors for MS do not exist) for MS.

PIMD: 11151683

Classification of acquired lesions of the corpus callosum with MRI.

MRI has facilitated diagnostic assessment of the corpus callosum. Diagnostic classification of solitary or multiple lesions of the corpus callosum has not attracted much attention, although signal abnormalities are not uncommon. Our aim was to identify characteristic imaging features of lesions frequently encountered in practice. We reviewed the case histories of 59 patients with lesions shown on MRI. The nature of the lesions was based on clinical features and/or long term follow-up (ischaemic 20, Virchow-Robin spaces 3, diffuse axonal injury 7, multiple sclerosis 11, hydrocephalus 5, acute disseminated encephalomyelitis 5, Marchiafava-Bignami disease 4, lymphoma 2, glioblastoma hamartoma each 1). The location in the sagittal plane, the relationship to the borders of the corpus callosum and midline and the size were documented. The 20 ischaemic lesions were asymmetrical but adjacent to the midline; the latter was involved in new or large lesions. Diffuse axonal injury commonly resulted in large lesions, which tended to be asymmetrical; the midline and borders of the corpus callosum were always involved. Lesions in MS were small, at the lower border of the corpus callosum next to the septum pellucidum, and crossed the midline asymmetrically. Acute disseminated encephalomyelitis and the other perivenous inflammatory diseases caused relatively large, asymmetrical lesions. Hydrocephalus resulted in lesions of the upper part of the corpus callosum, and mostly in its posterior two thirds; they were found in the midline. Lesions in Marchiafava-Bignami disease were large, often symmetrically in the midline in the splenium and did not reach the edge of the corpus callosum.

PIMD: 11147320

[Neuroradiological aspects of encephalitis disseminata].

Magnetic resonance imaging (MRI) has developed without doubt to the most important investigation method in multiple sclerosis. MRI is very sensitive to detect MS lesions but unfortunately of limited specificity. The purpose of this review is 1. to work up the MRI characteristics of MS lesions, 2. to derive recommendations for MRT-protocolls for daily radiological work and 3. to discuss new MR developments. MS lesions in the acute inflammatory stage show first an enhancement of GD-DTPA due to break down of the blood brain barrier and develop a T2-hyperintensity due to an edema. The following disease course is categorized in a phase of reparation and remyelinisation respectively, of gliosis and a defect stage. MS-plaques in the remyelinisation and gliotic phase appear as hyperintens lesions on T2-weighted scans. Chronic MS lesions with a defect are also T2-hyperintens and demonstrate additionally due to severe axonal loss a hypointensity on short TR SE scans. MS lesions exhibit a characteristic distribution. They are found typically periventricular, in the corpus callosum and at the calloso-septal interface, cortico-subcortical and infratentorial. The most important MR criteria to predict conversion from suspected (CSMS) to clinical definite MS (CDMS) are GD-DTPA enhancement and juxtacortical lesion localisation followed by the parameter periventricular and infratentorial localisation. Based on guidelines for the use of MRI in drug studies and on equivalent recommendations for the routine diagnostic we suggest rational and economic MRT protocols for cerebral, spinal, and N. opticus investigations. Such standardised protocols shall help to make MRI investigations more efficient and better comparable. New MR developments include measurement of magnetisation transfer and T2-relaxation, diffusion weighted imaging, proton MR spectroscopy, and quantification of lesion load. These methods can analyse more specifically tissue changes in MS plaques and yet can reveal changes in normal appearing white matter.

PIMD: 11090771

Motor-evoked potentials in response to fatiguing grip exercise in multiple sclerosis patients.

This study examined central and peripheral effects of fatiguing exercise (3 min maximal grip) in healthy controls (n=10) and multiple sclerosis (MS) subjects with weakness, MS-W (n=16) and normal motor function, MS-NM (n=16) in the studied extremity.Transcranial magnetic stimulation (TMS) was used to assess resting and facilitated motor-evoked potentials (MEPs) of abductor pollicus brevis (APB) and flexor carpi radialis (FCR) muscles before and after fatiguing exercise. Exercise-induced depletion and recovery of phosphocreatine (PCr) were measured using (31)P magnetic resonance spectroscopy ((31)PMRS) in FCR.MS subjects demonstrated significantly lower peak force and a faster decline in force than controls. Contralateral muscle activation (hand grip) before the fatigue protocol resulted in significantly increased MEP amplitudes in all groups. Contralateral hand grip following fatiguing exercise resulted in significantly higher MEP amplitudes in controls and MS-NM subjects, but not MS-W subjects. Fatiguing exercise resulted in prolonged central motor conduction time (CMCT) in MS subjects, but not controls. No group differences in PCr depletion or resynthesis were observed. All groups demonstrated significant post-exercise depression (PED) of MEP amplitude that persisted beyond the time course of PCr recovery, indicating fatigue was central in origin. MS subjects were less able than controls to increase cortical excitability using contralateral muscle activation following fatiguing exercise, possibly indicating impaired conduction in the corpus callosum.

PIMD: 11085872

Interferon-gamma protects against cuprizone-induced demyelination.

Evidence suggests that interferon-gamma (IFN-gamma), a proinflammatory cytokine secreted by activated T lymphocytes, contributes a deleterious effect to immune-mediated demyelinating disorders such as multiple sclerosis and experimental autoimmune encephalomyelitis (EAE). Nevertheless, mouse strains that are normally resistant to EAE induction become susceptible when the gene encoding either IFN-gamma or its receptor is mutated, demonstrating that the role that this cytokine plays in demyelinating disorders is complex. We have examined the effect of IFN-gamma in a chemically induced model of CNS demyelination. Mice that receive through their diet the copper chelator cuprizone display extensive demyelination of the corpus callosum. Remarkably, transgenic mice that ectopically express low levels of IFN-gamma in the CNS did not display evidence of demyelination when treated with cuprizone, nor did they shows signs of oligodendroglial death, astrogliosis, or microgliosis, which are typically seen in treated animals. Myelin protein gene expression was, however, dramatically reduced in both the treated control and the transgenic animals, indicating that demyelination is not an obligatory consequence of a large diminution of myelin protein synthesis. Interestingly, the CNS of the IFN-gamma-expressing mice contained elevated levels of insulin-like growth factor I, which has been demonstrated to have a protective effect against the demyelinating action of cuprizone.

PIMD: 11018243

In vivo evaluation of remyelination in rat brain by magnetization transfer imaging.

The aim of this work was to assess quantitatively and qualitatively the ability of magnetization transfer imaging to follow in vivo remyelination. Demyelination lesions were induced in rats by the injection of L-alpha-lysophosphatidylcholine stearoyl into the corpus callosum and imaging was performed in vivo on a 4.7-Tesla system at different time points. The percentage of magnetization transfer ratio (MTR) decrease was calculated for each animal. To evaluate the MTR findings for remyelination, myelin was quantitated by histological analysis of the lesion size and counting the number of remyelinating axons. An MTR decrease was observed when demyelination was present at 7 days after injection. During the remyelinating phase between day 30 and 40 after injection, contralateral values almost complete returned to normal, thus indicating remyelination. Histologically, at days 30 and 40 after injection, the lesion area was reduced in size and the axons were surrounded by a thin myelin sheath, indicating the remyelination process. Statistical analysis showed that the profile of MTR values was significantly correlated with the course of remyelination. All the MTR changes show a correlation with both myelin damage and repair. In conclusion, the study of the MTR profile in this myelin lesion model demonstrates in vivo the loss of myelin and the presence of spontaneous remyelination. This methodological approach which can also be applied to multiple sclerosis patients to show demyelination, should prove helpful to determine the degree of spontaneous and therapeutically induced remyelination in multiple sclerosis lesions, and thus to validate therapeutic treatments for myelin repair.

PIMD: 10960048

Regional axonal loss in the corpus callosum correlates with cerebral white matter lesion volume and distribution in multiple sclerosis.

Previous imaging studies have suggested that there is substantial axonal loss in the normal-appearing white matter (NAWM) of brains from multiple sclerosis patients and that this axonal loss may be an important determinant of disability. Recently, substantial axonal loss in the NAWM has been confirmed directly in post-mortem tissue. Whether the NAWM changes occur as a consequence of damage to axons traversing lesions or to a more diffuse injury process is uncertain. Using formalin-fixed brains of eight multiple sclerosis patients and eight age-matched controls, we examined the relationship between demyelinating lesion load in three volumes of the cerebral white matter and the loss of axons in NAWM of the corresponding three projection regions (anterior, middle, posterior) in the corpus callosum (CC). There was a significant loss of calculated total number of axons crossing the CC in each of the three regions relative to the non-multiple sclerosis controls. Strong correlations were found between the regional lesion load and both the axonal density (r = -0.673, P: = 0.001) and the total estimated number of axons crossing the corresponding projection area in the CC (r = -0. 656, P: = 0.001) for the patients. This suggests that Wallerian degeneration of axons transected in the demyelinating lesions makes a major contribution to the substantial, diffuse loss of axons in the NAWM in multiple sclerosis. These findings emphasize the need to consider the consequences of multiple sclerosis lesions in terms of both local and distant effects in functionally connected regions of the brain.

PIMD: 10934726

[A case of Marchiafava-Bignami disease demonstrated by MR diffusion-weighted image].

A Case of Marchiafava-Bignami disease demonstrated by MR diffusion-weighted image (DWI) was reported. A 55-year-old male with chronic alcoholism demonstrated dysarthria, disorientation and apraxia of left-hand. Sagittal view on MRI showed a swelling of the corpus callosum. The body and splenium of the corpus callosum showed symmetrically iso-intensity in T1 WI and hyperintensity in T2 WI, and remarkable hyperintensity in fluid attenuated inversion recovery images. DWI showed a definite hyperintensity area on the corpus callosum and the apparent diffusion coefficient (ADC) map presented the decreased water self-diffusion. These findings differed from the other demyelinating diseases, such as multiple sclerosis. We considered these DWI findings were the initial changes on MBD which preceded the demyelination. To our knowledge, this is the first report of DWI that was used in a case of Marchiafava-Bignami disease.

PIMD: 10727693

Brain atrophy in relapsing-remitting multiple sclerosis: relationship with 'black holes', disease duration and clinical disability.

Recent MRI studies in multiple sclerosis have highlighted the potential role of brain atrophy evaluation as a putative marker of disease progression. In the present study, we evaluated the supratentorial and infratentorial brain volume in patients with relapsing remitting multiple sclerosis (RR MS) and in healthy subjects. Moreover, we determined whether brain volumes of MS patients are associated with different aspects of brain MRI abnormalities and clinical findings. Two-dimensional acquired MRI was performed on 52 relapsing-remitting multiple sclerosis and 30 healthy subjects. The volume of supratentorial and infratentorial structures was measured in selected representative slices. Gd-enhancement, T2 hyperintense, T1 hypointense (i.e. 'black holes') total lesion load, as well as the area of corpus callosum was calculated in the MS group and related to brain volume measures. Correlations between MRI parameters and clinical features were also considered. MS patients had significantly lower supratentorial, infratentorial brain volume and corpus callosum area than healthy subjects ($P<0.01$). Supratentorial brain volume was significantly related to corpus callosum area ($r=0.58$; $P<0.01$) and T1 hypointense lesion load ($r=0.48$; $P<0.01$), but not with T2 hyperintense lesion load. Infratentorial/supratentorial ratio was significantly associated with disease duration and EDSS score ($r=-0.34$; $P=0.02$ and $r=-0.49$; $P<0.01$, respectively). This study documents that brain atrophy is an early MRI finding in RR MS and it is closely related to 'black holes' burden. The use of relative values (infratentorial/supratentorial ratio) may increase the conspicuity of correlation between clinical and MRI findings.

PIMD: 10716264

Quantitative pathological evidence for axonal loss in normal appearing white matter in multiple sclerosis.

We assessed axonal loss in the normal appearing white matter of the corpus callosum in postmortem brains of patients with multiple sclerosis, using quantitative measures of both axonal density and white matter atrophy. The calculated total number of axons was reduced significantly (mean +/- SD, 5.4 x 10(7) +/- 3.1 x 10(7)) compared with normal controls (11.6 x 10(7) +/- 2.2 x 10(7), p = 0.001) with a reduction both in axonal density (median, 34%; range, 16-56%; p = 0.004) and area (mean +/- SD: multiple sclerosis, 584 +/- 170 mm2; controls, 871 +/- 163 mm2; p = 0.004). These results confirm substantial axonal loss in the normal appearing white matter and demonstrate that measures of both axonal density and white matter volume are necessary to appreciate the full extent of axonal loss.

PIMD: 10553988

Intraventricular transplantation of oligodendrocyte progenitors into a fetal myelin mutant results in widespread formation of myelin.

Transplantation of myelin-forming cells is a promising strategy for the treatment of myelin disorders. In this study, transplantation of glial cell progenitors into the cerebral ventricles of the embryonic myelin-deficient rat, a model of Pelizaeus-Merzbacher disease, was performed to assess the ability of these cells to incorporate into the developing brain and produce myelin. The donor cells migrated into the white and gray matter and produced myelin at widespread sites ranging from the corpus callosum and optic nerve to the cerebellum. These data suggest that myelin repair might be achieved by intraventricular delivery and transependymal incorporation of myelin-producing cells. Because these cells were genetically transduced to express a reporter gene, similar ex vivo manipulation with genes known to promote survival, migration, or proliferation of the transplanted cells could be used to enhance repair. Such a therapeutic strategy may be feasible in patients with inherited myelin disorders or in multiple sclerosis, particularly where the lesions are periventricular.

PIMD: 10516773

Magnetisation transfer of normal appearing white matter in primary progressive multiple sclerosis.

Patients with primary progressive multiple sclerosis may develop severe disability despite a paucity of lesions on conventional magnetic resonance imaging, raising the possibility that intrinsic changes in normal appearing white matter (NAWM) contribute to disability. This study has measured magnetisation transfer ratio (MTR), an index of tissue damage, of NAWM in 52 patients with primary progressive multiple sclerosis and 26 healthy controls. Absolute values of MTR were obtained from the genu of the corpus callosum and pons, and mean values were calculated from bilateral regions in the centrum semiovale, frontal white matter, parieto-occipital white matter and posterior limb of the internal capsule. The median MTR was lower in all regions in patients compared to controls. Median values (per cent units) were significantly lower in corpus callosum (39.73 vs 40.63; P=0.01), frontal white matter (39.11 vs 39.59; P=0.01) and centrum semiovale (37.21 vs37.82; P<0.05). This study has demonstrated small but widespread decreases in MTR in NAWM in primary progressive multiple sclerosis supporting the hypothesis that there are intrinsic changes in NAWM which may contribute to disability in this patient group.

PIMD: 10408550

A longitudinal study of brain atrophy in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG).

To determine if progressive brain atrophy could be detected over 1- and 2-year intervals in relapsing MS, based on annual MR studies from the Multiple Sclerosis Collaborative Research Group (MSCRG) trial of interferon beta-1a (Avonex).All subjects had mild to moderate disability, with baseline expanded disability status scores ranging from 1.0 to 3.5, and at least two relapses in the 3 years before study entry. Atrophy measures included third and lateral ventricle width, brain width, and corpus callosum area.Significant increases were detected in third ventricle width at year 2 and lateral ventricle width at 1 and 2 years. Significant decreases in corpus callosum area and brain width were also observed at 1 and 2 years. Multiple regression analyses suggested that the number of gadolinium-enhancing lesions at baseline was the single significant contributor to change in third ventricle width. Atrophy over 1 and 2 years as indicated by enlargement of the third and lateral ventricle and shrinkage of the corpus callosum was greater for patients entering the trial with enhancing lesions. Greater disability increments over 1 and 2 years were associated with more severe third ventricle enlargement.In patients with relapsing MS and only mild to moderate disability, significant cerebral atrophy is already developing that can be measured over periods of only 1 to 2 years. The course of cerebral atrophy in MS appears to be influenced by prior inflammatory disease activity as indicated by the presence of enhancing lesions. Brain atrophy measures are important markers of MS disease progression because they likely reflect destructive and irreversible pathologic processes.

PIMD: 10391075

[A clinico-pathological study of so-called "acute multiple sclerosis" mimicking a brain tumor on the MRI findings].

We are reporting an autopsy case of so-called "acute multiple sclerosis" that was difficult to differentiate from a brain tumor on MRI findings. This case was a 69-year-old man, whose initial symptoms consisted of headache and unsteadiness in walking. Neurological findings included mild ataxia of the left upper extremity and positive Romberg sign. T 2-weighted MRI showed high intensity areas in the posterior limb of the right internal capsule and white matter near the posterior horn of the right lateral ventricle. Although the headache improved, the unsteadiness was exacerbated and the patient became unable to keep standing. Psychiatric symptoms and left hemiparesis were added to the clinical picture. The following MRI proved expansion of the previous lesions and the diffusely enhanced lesion spreading into the contralateral side through the corpus callosum. Stereotaxic biopsy showed the perivascular accumulation of small lymphocytes and a large number of bizarre astrocytes. Primary brain malignant lymphoma was diagnosed and radiation therapy was carried out. However, he developed perforation of the intestinal tract and died. Autopsy findings revealed scattered and disseminated small lesions in the cerebral white matter and the corpus callosum. There were a large number of lipid-laden macrophages, no stainable myelin and preserved axis cylinders in those lesions. Thus, those were interpreted as demyelinting lesions. They were scattered and multiple. This case was radiologically characterised by the diffusely enhanced, expanding butterfly-shaped lesion in bilateral cerebral hemisphere through the corpus callosum, and pathologically proven to be acute demyelination associated with severe perivascular infiltration of inflammatory cells. Multiple sclerosis may mimic neoplastic processes as trans-callosal hyperplastic neuroimage on neuroimaging like the present case.

PIMD: 10378748

Demyelination and axonal degeneration in corpus callosum assessed by analysis of transcallosally mediated inhibition in multiple sclerosis.

Following focal transcranial magnetic cortex stimulation (fTMS), inhibition of voluntary EMG activity in the ipsilateral first dorsal interosseus (FDI) muscle was studied, in order to assess the functional integrity of the corpus callosum in patients with multiple sclerosis (MS).Thirty-four patients suffering from definite MS and 12 healthy, age-matched normal subjects were examined. In mid-sagittal slices, 29 patients showed lesions within the truncus corporis callosi in T2-weighted MRI. In 20 patients, all areas (anterior, middle and posterior parts), in one both the anterior and posterior part, in 3 exclusively the anterior, in 4 the middle and in one the posterior area were affected. In 5 patients, lesions of corpus callosum were lacking. In normal subjects, fTMS elicited a transient inhibition (TI) of preactivated (50% of maximal force) isometric voluntary ipsilateral FDI muscle activity. Mean onset latencies of TI were 35.5+/-5.4 ms in right and 36.1+/-4.2 ms in left FDI. Mean duration of TI amounted to 23.0+/-8.4 ms for right and 24.6+/-8.4 ms for left FDI. In the MS group, TI latencies were significantly increased in 23 and TI durations in 16 cases, whereas a lack of TI was found in 5 patients bilaterally and in 6 unilaterally. In patients, mean onset latencies of TI were 40.4+/-13.8 ms in right and 43.3+/-14.4 ms in left FDI, TI duration amounted to 30.5+/-17.4 ms for right and 31.0+/-25.2 ms for left FDI. Increase of onset latencies and durations of TI were positively correlated with the summed area of lesions of corpus callosum in representative mid-sagittal MRI slices. Significant correlations between TI onset latencies and duration on the one hand, and central motor conduction latencies along corticospinal tracts (CML) on the other hand, were not found.The present investigation indicates that measurement of TI elicited by fTMS seems to be a sensitive method for an assessment of demyelination and axonal degeneration within corpus callosum in MS patients.

PIMD: 10377832

[Magnetic resonance imaging in multiple sclerosis].

Useful characteristics of MRI finding of multiple sclerosis (MS) include the distribution of lesions such as a strictly periventricular, infratentorial, or juxtacortical location, involvement of the corpus callosum and the presence of ovoid lesions with long axis directed to lateral ventricles. Our MRI-diagnostic criteria improved the sensitivity and specificity and is clinically useful. New sequences, such as fast spin echo, turbo spin echo or fluid attenuated inversion recovery have improved the detection of lesions. The presence of contrast enhancement in some but not all lesions--that is, evidence of both old and new lesions--provides additional diagnostic support. Enhanced lesions with more than 1 cm diameter often become ring-shaped. Strong correlations were found between the number and volume of enhancing lesions with changes of T 2 and magnetization transfer (MT) lesion loads in patients with secondary progressive MS. The degree of hypointensity of so called black holes on moderately T1-weighted spin echo images correlates with loss of magnetisation transfer, a marker of destruction of matrix and axon, and shows correlation with disability. One of spectroscopic indices of axonal loss is N-acetylaspartate. Atrophy is a process closely linked with the progressive phase of MS and worsening disability. Detection of the reduction in cord cross-sectional area or spinal cord atrophy over time makes an important contribution to the evaluation of therapeutic efficacy, especially in primary progressive disease.

PIMD: 10210877

Neurological complications to vaccination against Japanese encephalitis.

Japanese encephalitis (JE) vaccine has been used for childhood immunization programmes in Asia since the 1960s. Also, travellers from other parts of the world have been vaccinated before travelling to Asian countries. Some JE vaccines are produced from infected mouse brains and contain small amounts of myelin basic protein. Neurological side effects in larger vaccine trials in Asia have been reported in 1-2.3 per million vaccinees. Statens Serum Institut is the only distributor of JE vaccine in Denmark, delivering 384 000 doses from 1983-96. In 1996, evaluation of initial symptoms and findings in 10 adult travellers from Denmark, who developed moderate-severe neurological symptoms within a few weeks of JE vaccination, was performed as well as follow-up magnetic resonance imaging (MRI) and clinical neurological examination. Three patients initially had symptoms varying from severe encephalitis-like illness to paraesthesia, double vision or parkinsonian gait disturbance. MRI showed severe atrophy of the corpus callosum with altered signal intensity indicating gliosis in one patient, another patient had several hyperintense spots located periventricularly in the white matter, while a third patient had spots with increased signals in the pons, the right substantia nigra and the occipital region. Acute disseminated encephalomyelitis (ADEM) is a possible explanation for these MRI changes, although multiple sclerosis is an alternative diagnosis in one or two of the patients. Another three patients had long-lasting headache, concentration difficulty or intellectual reduction. One man had afebrile convulsions, another gait instability and depression and one parkinsonism. A woman developed myelitis. If these findings are due to JE vaccination the frequency of neurological reactions to the vaccine is considerably higher than previously reported and in the future any minor neurological complaints occurring shortly after vaccination should lead to neurological examination and acute MRI scan should be considered.

PIMD: 9875266

Changes of NGF presence in nonneuronal cells in response to experimental allergic encephalomyelitis in Lewis rats.

We recently reported that the cerebrospinal fluid (CSF) of patients affected by multiple sclerosis (MS) and the brain tissues of rats with experimental allergic encephalomyelitis (EAE) contain elevated levels of nerve growth factor (NGF). In the present study, we demonstrate that astrocytes and oligodendrocytes particularly localized in the white matter, including corpus callosum, overexpress NGFmRNA and produce NGF protein in the CNS of EAE affected rats. These findings indicate that the increased NGF found in the brain of EAE rats and most probably also in the CSF of patients affected by MS is produced by activated glial cells. It is hypothesized that the enhanced production of NGF by glial cells is necessary to compensate for the effect of axonal and/or neuronal cell body injury occurring in EAE. The possible functional significance of these findings in demyelinating diseases is discussed.

PIMD: 9647277

Unenhanced and enhanced magnetic resonance imaging in the diagnosis of multiple sclerosis.

Initial enthusiasm about the role of magnetic resonance imaging (MRI) in the diagnosis of multiple sclerosis decreased substantially with the notion that (a) lesions of various pathological origins may resemble demyelinating plaques and (b) a dissemination of lesions throughout the brain is not unique for multiple sclerosis but may even be a "normal" finding. Current experience still does not allow the identification of the aetiology of a single hyperintensity but has identified multiple features of multiple sclerosis related signal abnormalities which, in combination, provide rather high diagnostic accuracy. Useful characteristics include the distribution of lesions such as a strictly periventricular, infratentorial or juxtacortical location, and involvement of the corpus callosum. The presence of contrast enhancement in some but not all lesions-that is, evidence of both old and new lesions-provides additional diagnostic support. Improved instrumentation for imaging of the spine further extends the diagnostic options. Intramedullary signal abnormalities are detected with increased sensitivity and may disclose the presence of multiple lesions even in patients with an equivocal or a negative MRI of the brain. The high sensitivity to plaques and the opportunity to simultaneously rule out other gross morphological damage justifies the use of MRI as the primary diagnostic modality in the evaluation of multiple sclerosis.

PIMD: 9553845

Functional correlates of callosal atrophy in relapsing-remitting multiple sclerosis patients. A preliminary MRI study.

In multiple sclerosis (MS), periventricular lesions produce atrophy of the corpus callosum (CC), as evidenced by magnetic resonance imaging (MRI). We investigated whether CC atrophy in relapsing-remitting MS patients is related to functional deficits. We compared 14 mildly disabled (mean Expanded Disability Status Scale score 2.7) relapsing-remitting MS patients with 14 age- und sex-matched controls. CC size was determined using sagittal T1-weighted MRI. The function of the CC was studied using a neuropsychological battery and neurophysiological evaluation based on visual stimulation using a divided visual field paradigm. The total area of the CC in patients (mean 5.3 cm2) was significantly (P = 0.002) smaller than in controls (mean 6.6 cm2). Patients showed left ear extinction using the dichotic listening test and impaired name learning, which was correlated with atrophy of the splenium. There were no differences in interhemispheric transfer time between patients and controls. Marked atrophy of the CC can be encountered in relapsing-remitting MS patients. The associated cerebral disconnection correlated with atrophy of expected regions of the CC, thus supporting topographical organization.

PIMD: 9501242

Proliferation and phenotype regulation in the subventricular zone during experimental allergic encephalomyelitis: in vivo evidence of a role for nerve growth factor.

Proliferating cells in the subventricular zone (SVZ) of adult rat brain could provide a source of cells for repair attempts during degenerative diseases. However, very few reports dealt with the spontaneous regulation of this cell population during experimental conditions. In this paper, we describe an increase in the proliferation activity in the SVZ during experimental allergic encephalomyelitis, a demyelinating disease widely used as an experimental model for human multiple sclerosis. Moreover, p75(LNGFR)-immunoreactive elements in the SVZ were larger in experimental allergic encephalomyelitis compared with control groups, and they also showed multiple and branched elongations. Finally, a selective uptake of 125I-nerve growth factor was observed in the SVZ in neonatal rats, and positive elements migrated in the corpus callosum within a few days. These data indicate that cell populations in the SVZ are regulated during inflammatory conditions and degenerative diseases involving oligodendrocytes and neurotrophins, including nerve growth factor, could participate in these phenomena.

PIMD: 9449478

Alternate finger tapping test in patients with migraine.

Migraine patients are thought to show some cognitive dysfunction and slight structural abnormalities in the white matter of the brain, whereas most patients with multiple sclerosis (MS) are known to have numerous white matter lesions, often affecting the corpus callosum. To demonstrate psychomotor dysfunction, an alternate finger tapping task (a-FTT) on a PC was administered to controls (n = 41), migraine patients (n = 25), and multiple sclerosis patients (n = 22). Five MS patients with secondary callosal atrophy detected by MRI were also investigated as a separate group. Significant slowing was demonstrated in migraine (P = 0.0005) and MS (P<0.0001). The poorest test results were found in patients with callosal atrophy. In summary, a-FTT on a PC is able to detect minimal psychomotor dysfunction in migraine.

PIMD: 9296149

[Familial multiple sclerosis: study of 2 cases of a northern African family].

We report two cases of multiple sclerosis (MS) beginning in a mother and her daughter at 40 years of age. The diagnosis of MS was certain for both patients (Poser et al., 1983). Clinical features, evolution and response to treatment are comparable in both cases. Cerebral and medullar cord MRI and/or CT Scan showed characteristic lesions of demyelination on periventricular white matter, corpus callosum and brainstem.

PIMD: 9106120

A magnetization transfer study of white matter in siblings of multiple sclerosis patients.

In this study, we evaluated magnetization transfer ratio values in the brain white matter of siblings of multiple sclerosis (MS) patients and compared them to those obtained in sex- and age-matched normal controls. No statistically significant difference was found between the two groups for all the white matter areas studied (frontal and occipital lobes, centrum semiovale, periventricular white matter, internal capsule, genu and splenium of the corpus callosum).

PIMD: 9292200

Minimal surface: a useful paradigm to describe the deeper part of the corpus callosum?

The aim of this magnetic resonance imaging study was to find a geometrical characterization of the deeper part of the corpus callosum. Its shape was studied in 12 middle-aged persons free of white matter pathology. Profiles of curvatures were measured showing that this surface was close to a minimal one, especially at the genu and near the splenium. To assess the effect of a white matter pathology on these geometrical features, the same measurements were performed in an extra group of nine patients with definite multiple sclerosis. The hypothesis of curvatures profiles parallelism for the two groups could be rejected at the 0.05 confidence level for the mean curvatures but not for the Gaussian ones. Curvatures profiles may give indications on balance between the cortex and the fiber bundles growth rates during the development and on large scale modifications co-occurring with multilocular white matter pathologies.

PIMD: 9022652

Brain mercury in neurodegenerative disorders.

Trace element neurotoxicity has long been invoked as an etiologic factor for Alzheimer's disease. This study was conducted to determine the concentrations of mercury in seven different brain regions from deceased patients histologically confirmed with Alzheimer's disease or multiple sclerosis as compared to control subjects without known central nervous system and renal disorders. Brain mercury concentrations in all deceased subjects can arise from amalgam restorations, diet, and the working environment.Autopsy frozen specimens (control, Alzheimer's disease and multiple sclerosis) from seven brain regions, which included frontal cortex, temporal cortex, occipital cortex, putamen, hippocampus, corona radiata and corpus callosum were assayed for the concentrations of selenium using instrumental neutron activation analysis and mercury using radiochemical neutron activation analysis.We found that the concentrations of mercury and the mercury/selenium molar ratios were significantly lower in the hippocampi of multiple sclerosis patients as compared to aged-matched controls. However, no statistically significant differences were detected for the concentrations of mercury and the mercury/ selenium molar ratios for the remaining six brain regions among these groups.Since brain mercury concentrations from deceased subjects with either Alzheimer's disease or multiple sclerosis are not significantly higher than controls, the present study provides no scientific support that mercury plays a significant role in the pathogenesis of these neurologic disorders.

PIMD: 9046854

[A case of adult type adrenoleukodystrophy with an acute onset and repeated episodes of ataxic dysarthria].

We report a 30-year-old man with adult type adrenoleukodystrophy (ALD) who manifested an acute onset and repeated episodes of ataxic dysarthria. He noticed a moderate dysarthria after a high grade fever in February of 1995; however, two weeks later his symptom disappeared completely. Three months later, he noticed the dysarthria again and he was referred to our hospital for further examination. General physical findings on admission revealed a dark skin color, pigmentation of gingivae and reduced body hair. Neurologically he was normal except for a moderate ataxic dysarthria. Cranial T2-weighted MRI showed multiple high intensity lesions in the subcortical white matter of frontal lobe, bilateral peritrigonal white matter, splenium of the corpus callosum and bilateral cerebellar white matter. Only cerebellar lesions responsible for his symptom were enhanced on MRI after gadolinium administration. Initially we diagnosed him with multiple sclerosis (MS) based upon the clinical course and MRI findings, and then started corticosteroid treatment. His dysarthria was slightly improved after the treatment and bilateral gadolinium-enhanced lesions of cerebellar white matter on MRI disappeared. Multimodality evoked potentials such as short latency somatosensory evoked potentials, brainstem auditory evoked potentials and pattern-reversal visual evoked potentials, disclosed a prolonged central conduction time associated with bilaterally symmetric individual interpeak latencies. These findings, which supported diffuse and bilateral subclinical demyelinating lesions in the central nervous system, were unusual for MS; therefore his plasma very-long-chain fatty acids (VLCFA) were assayed for ALD. Finally, he was diagnosed with adult type ALD because of the high ratio of C26: 0/C22: 0 (0.075; normal 0.033). It is very difficult to clinically distinguish the early stage of adult type ALD especially in patients like this from MS. Therefore it is useful and important to evaluate not only the level of plasma VLCFA, but also to evaluate multimodality evoked potentials.

PIMD: 8874592

Visual form agnosia in multiple sclerosis.

We report a case of multiple sclerosis with visual form agnosia and callosal syndromes. Initially, the patient's visual recognition of object form was severely disturbed at the perceptual stage, in association with left-sided ideomotor apraxia and agraphia. Magnetic resonance imaging showed large white matter lesions in the bilateral frontal and occipital lobes, the latter extending to the occipitotemporal junction, and widespread corpus callosum lesions. Over the course of one year follow-up, neuropsychological examinations indicated that the patient's visual recognition defects occurred not only at the early substage of form perception, but also at the stage of reproducing the shape of objects from visual memory store. The present case suggests that neural connections between the striate cortex and occipitotemporal visual areas are crucial for both the perceptual and associative stages of visual object recognition.

PIMD: 8725904

Characterization of glial cultures from rapid autopsies of Alzheimer's and control patients.

We have developed isolated and mixed cultures of microglia, astrocytes, and oligodendrocytes from rapid (mean of 2 h 55 min) autopsies of nondemented elderly patients and patients with Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Cultures were derived from both the corpus callosum (CC) and superior frontal gyrus (SFG). Cultured microglia phagocytosed latex beads, were reactive for Dil-acetylated low density lipoprotein, were immunoreactive for CD68 and major histocompatibility complex II markers, and were not immunoreactive for fibroblast, astrocyte, or oligodendrocyte markers. Cultured astrocytes included fibrous and protoplasmic types, were immunoreactive for GFAP, and were not immunoreactive for fibroblast, microglia, or oligodendrocyte markers. Cultured oligodendrocytes were poorly adherent, were slow to develop, were immunoreactive for galactocerebroside, and were not immunoreactive for fibroblast, microglia, or astrocyte markers. Because they are readily manipulated under controlled experimental conditions, and because they permit immediate access to individual cells and sets of cells from patients who have actually suffered the disease, these cultures may provide an important new tool for unravelling the etiology and pathogenesis of human CNS disorders.

PIMD: 8787171

The value of magnetic resonance imaging in diagnosis and monitoring of treatment in multiple sclerosis.

We analysed MR examinations of 277 patients with multiple sclerosis. White matter hyperintensities in brain were found in 270 of them. The most frequently they were found in periventricular white matter (in 100% of cases), in subcortical localization (52.2%) and in the corpus callosum (44.4%). MR examination allows to estimate the activity of the disease on the basis of the presence of oedema around the plaques and their contrast enhancement with gadopentetate dimeglumine (Gd-DTPA). 17.8% of all cases showed the signs of the acute phase of MS. About one-third of all cases were accompanied by cortical brain atrophy (the most often seen in frontal lobes), subcortical brain atrophy was less frequent (one-sixth). In about two-third of all cases the corpus callosum atrophy was found. The analysis of follow-up MR examinations of 83 patients taking part in a double-blind placebo-controlled trial of a new immunosuppressive drug cladribine showed that patients from the placebo group were more compliant to any changes of the plaques. Decrease of the plaques size was found mainly in women. No correlation between the patients age and the plaques changes was established.

PIMD: 8746750

Reversal of alexia in multiple sclerosis by weak electromagnetic fields.

The occurrence of cognitive deficits in patients with multiple sclerosis (MS) has been recognized since 1877 when Charcot first observed "enfeeblement of memory" in his patients. Cognitive deficits have been reported in almost 50% of patients with a relapsing-remitting course and in a significantly higher percentage of patients with a chronic progressive course leading to intellectual disability which is often severe enough to preclude employment. MS is considered a form of subcortical dementia and the occurrence of classical cortical disorders such as aphasia, agnosia and apraxia is reported to be rare in the disease. However, in my experience alexia, a reading impairment unrelated to visual acuity or visual field defects, is common in patients with MS. Recently, I reported that treatment with picotesla range electromagnetic fields (EMFs) is an efficacious modality in the management of both the motor and cognitive symptoms of MS. Three patients with MS who developed alexia as a manifestation of the disease are presented. In all patients the alexia was reversed several months after they began treatment with EMFs. Since alexia usually reflects a disconnection syndrome whereby lesions involving the left visual cortex and the splenium of the corpus callosum disconnect language association areas from visual association areas, it is suggested that reversal of the alexia in these patients by EMFs was related to improved interhemispheric transcallosal transmission of visual information. In addition, it is conceivable that changes in the metabolism of monoamines, which are involved in visual information processing and reading comprehension, may have been important in causing reversal of the alexia. This report further supports the unique efficacy of this treatment modality in reversing specific cognitive deficits in MS.

PIMD: 7677014

MR findings in adult-onset adrenoleukodystrophy.

To describe the MR findings of brain and spinal cord in adult-onset adrenoleukodystrophy.One hundred sixty-four adult patients ranging from 19 to 74 years of age (119 men and 45 women) with clinically and biochemically proved adrenoleukodystrophy underwent MR of the brain. In 30 patients the spinal cord also was evaluated with MR.The brain MR findings were abnormal in 54 of 119 males and in 9 of 45 female heterozygotes and consisted of varying degrees of demyelination of the cerebral white matter in 40 patients, corpus callosum in 25 patients, corticospinal tracts in 46 patients, visual tracts in 31 patients, and auditory tracts in 18 patients. The thoracic spinal cord showed diffuse atrophy in 18 of 20 men and in 8 of 10 women.It is important to recognize the MR findings of adult-onset adrenoleukodystrophy, because not uncommonly the clinical and MR findings of adrenoleukodystrophy are misdiagnosed as multiple sclerosis, olivopontocerebellar or spinocerebellar atrophy, amyotrophic lateral sclerosis, or dementia. Analysis of the MR findings and correlation of the clinical findings has permitted a tentative subdivision of adult-onset adrenoleukodystrophy population into four subtypes that appear to differ in respect to prognosis and possibly pathogenesis. MR evaluation of the brain in adrenoleukodystrophy also is helpful in patient selection for experimental therapy, which is most effective if offered in the early stage of the disease.

PIMD: 7591490

The neuropsychiatry of multiple sclerosis.

This article examines the cognitive and psychiatric features of multiple sclerosis. MS can manifest as a neuropsychiatric disturbance even in the absence of physical disabilities.Two MS patients with predominant behavioral symptoms are described, and the literature is reviewed.The first patient had an interhemispheric disconnection syndrome, and the second patient had cognitive fatigue and depression. Other patients have slowed information processing speed, memory retrieval difficulty, frontal-executive dysfunction, and visuospatial difficulty.MS results in specific cognitive deficits and mood disorders. These two patients had organic mental disorders from cerebral demyelination particularly affecting the corpus callosum. Our patients have neuropsychiatric symptoms from extensive demyelination of prefrontal-subcortical circuits. Evaluation and management strategies are discussed.

PIMD: 7603740

Pineal-hypothalamic tract mediation of picotesla magnetic fields in the treatment of neurological disorders.

The objective of this study is analysis of the clinical efficacy of picotesla magnetic fields in the treatment of epilepsy, Parkinson's disease and multiple sclerosis. The method utilized involved the exogenous application of physiologic, very weak magnetic fields to the brain by Sandyk, Anninos, Derpapas and Tsagas. The magnetic device produced a magnetic field ranging from about 5 x 10(-8) gauss to about 2.5 x 10(-7) gauss at frequencies of 2 to 7 Hertz. The wave form was sinusoidal and the device was positioned about the posterior portion of the corpus callosum most specifically to influence the pineal gland. Direct correlation of melatonin production with magnetic field stimulation was established. Amelioration or palliation of the neurological conditions was observed over an extended period of time in most cases. It appeared that a resonance situation was established between the magnetic field and melatonin which could be explained with Jacobson Resonance. These studies begin to point to the explanation of the mechanism of interaction between non-ionizing electromagnetic radiation and biological systems. Furthermore, the evaluation of the pineal gland as an magneto-sensitive gland may help us understand fundamental conditions in magneto-receptors of biological systems in terms of their piezoelectric nature.

PIMD: 8158186

Dementia in two histologically confirmed cases of multiple sclerosis: one case with isolated dementia and one case associated with psychiatric symptoms.

During the past 10 years, considerable attention has been devoted to cognitive impairment in multiple sclerosis. Occasionally this impairment may be so severe that multiple sclerosis presents as a dementia associated with only minor neurological signs and symptoms. The cases of two women affected by multiple sclerosis who presented with a pure dementia are reported. In the first patient, a progressive apragmatic behavioural disturbance with reduced short term memory and learning abilities were the main clinical features. Neuropathological examination of the brain disclosed numerous plaques in the periventricular white matter, with severe atrophy of the corpus callosum. Plaques were also seen in the white matter of both hippocampus and in the columns of the fornix. The impairment of short term memory could be linked to these lesions. Behavioural changes were probably related to the bilateral lesions of the long associative bundles that disconnected the frontal lobes from other parts of the cerebral hemispheres. In the second patient, visual hallucinations were associated with cognitive dysfunction. MRI showed large plaques in the white matter of both left frontal and temporal lobes. Smaller plaques were also present in the periventricular white matter of the occipital lobes, the nature of which were confirmed by a stereotactic biopsy.

PIMD: 8178661

Correlates of cognitive impairment and depressive mood disorder in multiple sclerosis.

The psychopathological status of 25 inpatients suffering from clinically definite multiple sclerosis (MS) according to Poser criteria was assessed by using standardized methods (Structured Clinical Interview for DSM-III-R, Inpatient Multidimensional Psychiatric Scale, Hamilton and Montgomery-Asberg Depression Rating Scales and the Structured Interview for the Diagnosis of Alzheimer Dementia and Dementias of other Aetiology (SIDAM). Magnetic resonance (MRT) (0.5 T; T2-weighted sequence) of the brain was analysed by measuring the ventricular brain ration (VBR), the area of the corpus callosum (CC) and the extension of hyperintense lesions of the brainstem, the temporal lobes and the brain at all. Six of 25 (24%) of these moderately disabled patients (mean Extended Disability Score (EDSS) 3.3) were diagnosed to suffer from depressive mood disorder (major depression or dysthymia); 2 were demented. In correlation analysis, depression was unrelated to age, gender, duration of illness, status of disability (EDSS) or the results of cognitive assessment. No relationship between the depression scores and the different MRT measures could be identified. The presence or absence of gadolinium enhancement was also uncorrelated to depressive symptoms. Fatigue as measured by the Fatigue Severity Scale was unrelated to depression or subcortical brain atrophy (increased VBR) but significantly correlated to the area of hyperintense MRT changes in brainstem and midbrain. Cognitive impairment (decreased SIDAM scores) was correlated to the total area of hyperintense MRT changes of the brain parenchyma. The type of clinical course (relapsing-remitting vs chronic progredient) was not found to influence the affective or cognitive state in our MS patient's sample.

PIMD: 8156087

Correlation of dementia, neuropsychological and MRI findings in multiple sclerosis.

Twenty patients diagnosed as having multiple sclerosis (MS) were examined by MRI and 9 neuropsychological scales: MMSE, BCRS, RMB, SDMT, BNT, VM, FAS, Benton and Hamilton. The number and distribution of the lesions, and cerebral and corpus callosum atrophy were evaluated by MRI. MR images were generated by a 0.5 Tesla instrument utilizing T1WI, PD and T2WI imaging techniques. The results reveal (1) that patients with MS are impaired in a broad range of cognitive functions but mainly memory is affected; (2) number of lesions in the corona radiata, insula and hippocampus is correlated with cognitive impairment, and (3) enlargement of the IIIrd ventricle is an indicator of memory impairment in MS patients.

PIMD: 8170575

Callosal disconnection in multiple sclerosis.

A patient with MS demonstrated a striking callosal disconnection syndrome. MRI revealed callosal atrophy and extensive bilateral white matter changes. Of 15 comparison patients with clinically definite MS, only one had minimal callosal disconnection. Callosal disconnection in MS may be due to pathology of the corpus callosum as well as extensive white matter disease.

PIMD: 8477079

[The importance of magnetic field strength in the MR diagnosis of multiple sclerosis: a comparison of 0.5 and 1.5 T].

The value of magnetic resonance (MR) to establish the diagnosis of multiple sclerosis (MS) is well known. This study was undertaken to compare MR imaging of the brain of MS patients at high (1.5T) and mid (0.5T) field strength. 25 patients with MS underwent two consecutive MR studies within one hour, each consisting of axial proton density and T2-weighted spin-echo images. Lesions in the supratentorial white matter and corpus callosum and those in the brain stem and cerebellum were separately counted. At 1.5T significantly more lesions were seen than at 0.5T ($p < 0.05$). Although T2-weighted images at 1.5T added significant information compared to images obtained at 0.5T, in none of our 25 patients the diagnosis was missed at 0.5T. However, at 1.5T dissemination in space was better demonstrated, suggesting MR scanning with high field-units to be favourable in patients with clinically suspected MS.

PIMD: 8340796

Brain magnetic resonance imaging correlates of cognitive impairment in multiple sclerosis.

We evaluated the correlations between cognitive impairment, clinical and brain magnetic resonance imaging (MRI) findings in 100 patients with multiple sclerosis (MS). The performance on one or more neuropsychological tests was abnormal in 47% of the 64 patients who completed the entire neuropsychological battery; the cognitive impairment was mild in 14 (22%) and severe in 16 (25%). Performance on any single neuropsychological test was unrelated to clinical parameters (age, duration of the disease, disability). The neuropsychological performance of relapsing-remitting patients was better than in patients with a chronic-progressive disease. The mean scores for almost all the neuropsychological tests were significantly lower in patients with severe ventricular dilatation and corpus callosum atrophy than in patients in whom these structures were little affected. Mean scores for WMS, performance Intelligence Quotient (IQ), total IQ and Token Test (TT) were also significantly correlated with the widening of cortical sulci and total lesional scores. Our data support the contention that the involvement of pathways that are critical for a given cognitive process as well as the progression of the axonal degeneration and sclerosis seem to play important roles in the pathophysiology of cognitive dysfunction in MS.

PIMD: 8340793

Neuropsychology and multiple sclerosis: diagnostic and rehabilitative approaches.

The frequency of cognitive deficits in multiple sclerosis (MS) patients is rather high and the estimates vary between 43% and 72% depending on the patient samples studied as well as on the methods of cognitive assessment. Despite the great impact of cognitive dysfunction on several aspects of the quality of life, the importance of accurate assessment and rehabilitation of neuropsychological deficits in MS patients has long been ignored. In this article, we first describe tests for the assessment of impairments, disabilities and handicaps. We emphasize that after screening with brief assessment instruments, detailed testing of the basic target deficits is mandatory for the planning of special cognitive training programs. Second, the correlation of certain cognitive deficit patterns with important magnetic resonance imaging (MRI) variables such as total lesion area, size of the corpus callosum and specific lesion location is outlined in detail. Third, some recommendations are made with regard to general rehabilitation principles such as restitution, compensation and adaptation as well as for special rehabilitation techniques including cognitive retraining of basic deficits and/or training of activities of daily living. Finally, we emphasize that there is a need for the development of tailor-made neuropsychological rehabilitation techniques for MS patients, which take into account the course and stage of the disease as well as the specific psychosocial problems of the individual patient.

PIMD: 8427077

Midsagittal MR measurements of the corpus callosum in healthy subjects and diseased patients: a prospective survey.

To determine quantitatively a possible corpus callosum (CC) involvement in normal aging and white matter diseases.Midsagittal size and signal of CC were recorded prospectively from 243 routine MR brain examinations. A midline internal skull surface (MISS) and subcutaneous fat signal intensity were measured to calculate CC/MISS and CC/fat ratios. Four groups of subjects were studied: 124 apparently healthy subjects, 45 patients with multiple sclerosis, 13 patients with a noncerebral cancer under chemotherapy, and 37 AIDS patients.Mean surface area of CC in controls was 6.36 cm2. It was significantly larger in men than in women ($P < .05$), but CC/MISS ratio was not. Elderly controls > 70 years and AIDS patients displayed significant CC atrophy, as well as multiple sclerosis subjects with long-standing disease or with a severe chronic progressive form.CC substance loss identification should not be based on visual inspection or on absolute area, but by means of a CC/MISS ratio.

PIMD: 8412020

Inborn errors and demyelination: MRI and the diagnosis of white matter disease.

The progress and extent of myelination can be assessed using magnetic resonance imaging (MRI). Myelination is delayed or diminished in several inherited metabolic abnormalities presenting in early life. Only minimal myelination of the CNS occurs in Pelizaeus-Merzbacher disease. Dysmyelination tends to produce fairly symmetrical lesions affecting white matter. In many mitochondrial enzyme and some lysosomal defects, the grey matter is also involved. The appearances and in particular the distribution on MRI and/or CT are characteristic in some conditions and the diagnosis is limited in others. Demyelination due to inflammatory disorders typically causes multifocal white matter lesions, recurrent in multiple sclerosis, monophasic in acute disseminated encephalomyelitis, extending in progressive multifocal leukoencephalopathy and classically involving the pons or corpus callosum in myelinolysis. Hypoxic ischaemic lesions may be metabolically induced and simulate primary demyelinating disorders. Mitochondrial enzyme defects in particular may present with stroke-like appearances. In many of these conditions, diagnosis is biochemical, but imaging has a significant role in suggesting the diagnosis, and documenting progression, response to therapy or complications.

PIMD: 1345734

Cognitive and brain imaging measures of multiple sclerosis.

In this review we will describe the cognitive deficiency in Multiple Sclerosis (MS) and analyze the relationship between the performance on neuropsychological tests and the anatomofunctional findings assessed by neuroimaging techniques. Memory, abstract reasoning, and visuospatial abilities impairments are correlated with lesion extension and with corpus callosum atrophy, quantified on MRI. On the other hand, in MS patients with cognitive disturbance, PET and SPET studies show metabolic alterations and perfusion deficits at the cortical level, particularly in the left hemisphere and in the frontal and temporal lobes.

PIMD: 1469440

Relationship between corpus callosum atrophy and cerebral metabolic asymmetries in multiple sclerosis.

Corpus callosum (CC) atrophy by magnetic resonance imaging (MRI) is a common finding in multiple sclerosis (MS). In order to examine the relationship between CC atrophy and cortical brain metabolism, we compared the cerebral metabolic rates for glucose (CMRglc), measured by positron emission tomography (PET), of 8 MS patients with evidence of CC atrophy on midsagittal MRI, 8 MS patients without CC atrophy and 10 healthy controls. Results showed no significant differences in supratentorial CMRglc absolute values between the three groups, although a slight metabolic reduction was observed in both MS groups compared with normal controls. By contrast, only patients with CC atrophy showed greater directional metabolic asymmetry than normals, the left frontal, temporal and parietal association cortices being significantly lower than the right. Predominant left hemispheric metabolic reductions were not accompanied by a corresponding left-sided predominance in the extent of MRI-detected demyelinating lesions. Therefore our data suggest that CC atrophy interfers more with left than with right metabolic function.

PIMD: 1522265

Volume T1-weighted gradient echo MRI in multiple sclerosis patients.

Three-dimensional (3D) volume turbo fast low angle shot (FLASH) techniques have become available which produce heavily T1-weighted images, similar to inversion recovery scans, utilizing the appropriate flip angle and inversion time. The purpose of this study was to compare the sensitivity of a rapid volume gradient echo technique [3D magnetization prepared rapid acquisition gradient echo (MP RAGE)] in identifying multiple sclerosis (MS) plaques with a conventional T2-weighted spin echo (SE) sequence. Ten patients with clinical MS were evaluated. Patients underwent a routine examination consisting of an axial T2-weighted SE sequence (2,500,22/90) and a coronal 3D MP RAGE, 10/4/10, acquired as 128 two mm partitions. In six patients, area measurements of 22 plaques were determined on both the axial T2-weighted SE examinations and the axial reformatted MP RAGE examinations. The overall number of plaques utilizing each technique was approximately the same. One hundred twenty-two plaques were visualized for the 3D MP RAGE sequence, and 128 plaques for the T2-weighted SE sequence. There were differences in detection of plaques in different regions, with plaques in gray matter better demonstrated utilizing the conventional T2-weighted SE sequence. Plaques in the corpus callosum, pons, and brachia pontis were better demonstrated utilizing 3D MP RAGE. No significant difference was found between the areas measured on the MP RAGE sequence and on the T2-weighted SE sequence. Three-dimensional MP RAGE provides a sensitive and complementary method to conventional T2-weighted SE sequences in the evaluation of patients with MS.

PIMD: 1620336

Neuropsychological and structural brain lesions in multiple sclerosis: a regional analysis.

Quantified lesion scores derived from MRI correlate significantly with neuropsychological testing in patients with multiple sclerosis (MS). Variables used to reflect disease severity include total lesion area (TLA), ventricular-brain ratio, and size of the corpus callosum. We used these general measures of cerebral lesion involvement as well as specific ratings of lesion involvement by frontal, temporal, and parieto-occipital regions to quantify the topographic distribution of lesions and consequent effects upon cognitive function. Lesions were heavily distributed in the parieto-occipital regions bilaterally. Neuropsychological tests were highly related to all generalized measures of cerebral involvement, with TLA being the best predictor of neuropsychological deficit. Mean TLA for the cognitively impaired group was 28.30 cm2 versus 7.41 cm2 for the cognitively intact group (p less than 0.0001). Multiple regression analyses revealed that left frontal lobe involvement best predicted impaired abstract problem solving, memory, and word fluency. Left parieto-occipital lesion involvement best predicted deficits in verbal learning and complex visual-integrative skills. Analysis of regional cerebral lesion load may assist in understanding the particular pattern and course of cognitive deficits in MS.

PIMD: 1627976

Magnetic resonance imaging correlates of neuropsychological impairment in multiple sclerosis.

The authors examined whether specific neuropsychological abnormalities in multiple sclerosis (MS) are associated with focal lesion areas detected by MRI. Lesion area, regardless of distribution, correlated with performance on the vast majority of neuropsychological procedures. No significant difference appeared between groups with normal/mild and moderate overall cognitive impairment on any of the MRI measures. However, patients with severe cognitive impairment had greater lesion area, regardless of location, and had significant atrophy of the corpus callosum compared with the other two groups. These results suggest that severe atrophy of the corpus callosum reflects global disease and provides a relatively focal morphological marker of severe cognitive impairment in MS.

PIMD: 1303556

[Interhemispheric transfer in multiple sclerosis. Morphofunctional correlations].

Signs of cerebral disconnection, especially left ear suppression to dichotically presented verbal stimuli, have been reported in multiple sclerosis patients and found to be correlated to morphological atrophy of the corpus callosum on magnetic resonance imaging. To reinvestigate this issue, 26 patients satisfying criteria for definite multiple sclerosis were proposed 3 tasks aimed at evaluating interhemispheric function: a dichotic listening task, a motor finger-tapping task and a sensory transfer task. Performance at these tasks suggested impaired callosal function in MS patients, compared to normal controls. Callosal morphology was assessed on midsagittal MRI sections using a digitalised method of partition of the callosal area into 6 subregions and automatized surface measurements. Results of correlations between task performance and callosal areas showed a significant correlation between total callosal atrophy and severity of interhemispheric impairment on each functional task. Moreover, impaired motor transfer was specifically related to atrophy of the anterior callosal regions. These results suggest that MS patients may constitute a suitable population to studying interhemispheric transfer of information through the callosal commissure and that this approach may be useful in the clinical management of MS patients.

PIMD: 1743039

Anterior corpus callosum atrophy and verbal fluency in multiple sclerosis.

To determine whether different portions of the corpus callosum (CC) are responsible for transferring the information of specific cognitive modalities, eighteen females with relapsing-remitting Multiple Sclerosis (MS) were studied using neuropsychological procedures and Magnetic Resonance Imaging (MRI). Measures of both anterior and posterior CC areas were obtained in patients with MS as well as in eighteen age and sex matched healthy controls. MRI scans were additionally analyzed for each patient in order to evaluate the extent of demyelinating lesions in both periventricular and subcortical areas. Patients with MS exhibited a significant decrease in both the anterior and posterior CC areas compared with normal subjects. The results of statistical analysis showed that, even when the effect of demyelinating lesions was taken into account within a regression equation, the atrophy of anterior CC area strongly affected the performance on verbal fluency task. These data emphasize the importance of the anterior CC area for the interhemispheric transfer of cognitive information associated with verbal fluency.

PIMD: 2052698

Abnormal corpus callosum: a sensitive and specific indicator of multiple sclerosis.

The authors investigated whether identification of corpus callosal (CC) involvement might increase the specificity of magnetic resonance (MR) imaging in differentiating multiple sclerosis (MS) from other periventricular white matter diseases (PWDs). They prospectively evaluated 42 patients with MS and 127 control patients with other PWDs. Ninety-three percent of the MS patients demonstrated confluent and/or focal lesions involving the callosal-septal interface (CSI). These lesions characteristically involved the inferior aspect of the callosum and radiated from the ventricular surface into the overlying callosum. CSI lesions were optimally demonstrated on sagittal long repetition time (TR)/short echo time (TE) images and frequently (45% of cases) went undetected on axial images. Only 2.4% of the control patients had lesions of the CC. The authors conclude that midsagittal long TR/short TE images are highly sensitive and specific for MS and that callosal involvement in MS is more common than previously reported.

PIMD: 2052684

Multiple sclerosis and imaging of the corpus callosum.

No abstract

PIMD: 2026793

Axial vs sagittal T2-weighted brain MR images in the evaluation of multiple sclerosis.

Axial and sagittal proton density and T2-weighted MR images (TR 2,500-3,000 ms, TE 15-22 and 85-90 ms) were performed in 50 patients with multiple sclerosis (MS) on a 1.5 T superconductive system. The number of plaques on the axial and sagittal images in the periventricular white matter, the corpus callosum, the brain stem, the cerebellum, and the basal ganglia were counted separately by two independent observers. A total of 858 lesions (mean 17.40 +/- 21.57) were seen on the axial series and 1,196 (mean 24.32 +/- 26.22) on the sagittal scans. More lesions were visualized on sagittal images in the periventricular region (mean 18.79 +/- 21.69 versus 13.34 +/- 16.45; p less than 0.001) and the corpus callosum (mean 3.00 +/- 2.72 versus 0.57 +/- 1.19; p less than 0.001). In the brain stem more lesions were visualized on the axial images (mean 1.55 +/- 2.55 versus 0.87 +/- 1.20; p less than 0.05). In the cerebellum and basal ganglia, scans in the two planes were equivalent (p greater than 0.5). In three patients lesions were seen on the sagittal series, while the axial scans were normal. Sagittal T2-weighted images appear to demonstrate significantly more MS plaques than transverse images, especially in the periventricular region and the corpus callosum. This is explained by partial volume averaging, by the orientation of some cerebral structures (e.g., corpus callosum) with regard to the section plane, and by the longer diameter of the lesions in the axial plane.

PIMD: 2006091

[Disseminated sclerosis: organic basis for mental disorders and cognitive dysfunction].

The MRI-(magnetic resonance imaging) scanner has improved the knowledge of the organic basis of cognitive defects in multiple sclerosis. Recent studies demonstrated a correlation of MRI-verified single lesions, atrophy of the corpus callosum and cognitive defects; but failed to demonstrate the convincing correlation between psychic symptoms and MRI-verified lesions.

PIMD: 1817029

Cognitive function in adult adrenoleukodystrophy: comparison with leukoaraiosis and multiple sclerosis.

Cognitive evaluation of 6 cases of adult adrenoleukodystrophy (ALD) included in a brain magnetic resonance (MR) study are reported: 2 males with adrenomyeloneuropathy and 4 women heterozygous for ALD. Cognition was normal in 4 and MR scan in 2 of them. In the 2 others, there were mild modifications of the white matter. One patient suffered of visual retention disturbances with abnormalities of the white matter in MR scan. In the last, cognitive decline was observed; MR scan showed atrophy of cortex and corpus callosum and periventricular high signal areas. Comparison with leukoaraiosis in healthy adults and with multiple sclerosis suggests that there is probably a relationship between cognition and extension of brain MR abnormalities. Time of appearance and frequency of cognitive dysfunction might be explained by the natural history of each of these diseases.

PIMD: 2300013

Magnetic resonance imaging in clinically-definite multiple sclerosis.

Forty-two patients with clinically-definite multiple sclerosis were examined by magnetic resonance imaging using a 1.5-T instrument. Magnetic resonance imaging detected an abnormality in 90% of patients. In four patients, no lesions were demonstrated. The number, size and site of the lesions by magnetic resonance imaging were compared with the patients' clinical status and other variables. The Kurtzke disability status scale score increased in patients with corpus callosum atrophy, and brainstem and basal ganglia lesions, and correlated with the total number of lesions. No correlation was shown between the findings of magnetic resonance imaging and disease duration, age, sex or pattern-reversal visual-evoked potentials. This article highlights the variety of magnetic resonance images that is obtained in patients with clinically-definite multiple sclerosis.

PIMD: 2757533

Cerebral disconnection in multiple sclerosis. Relationship to atrophy of the corpus callosum.

Left ear suppression to dichotically presented verbal stimuli has been observed in patients with multiple sclerosis (MS). Rubens and coworkers have suggested that a disconnection of the auditory callosal pathways may account for this finding. To examine this proposal, we compared the performance of 28 MS patients with significant corpus callosum atrophy (CCA) on midsagittal magnetic resonance scans, 16 MS patients without significant CCA, and 64 demographically matched normal control subjects on two laterality tasks: verbal dichotic listening (consonant-vowel syllables) and tachistiscopic object-naming latency. Results indicated that left ear suppression was found only in the MS patients with CCA. Likewise, patients in the MS group with CCA were slow in responding to stimuli presented in the left visual field; this effect was not observed in patients without CCA. These findings support the hypothesis that efficiency of cross-callosal information flow is reduced in MS patients with CCA.

PIMD: 2761662

[Multiple sclerosis: atrophy of the corpus callosum and psychosyndrome].

Examination with magnetic resonance imaging of 176 patients with multiple sclerosis showed that corpus callosum (CC) atrophy is common. The thinning of the CC depends on the extension of the coalescent periventricular white matter changes. A highly significant association was found between CC-atrophy and, the severity of organic mental disorder.

PIMD: 2915783

Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis.

Previous research has suggested that cerebral lesions observed on magnetic resonance imaging (MRI) of MS patients are clinically "silent." We examined the validity of this assertion by correlating neuropsychological test performance with MRI findings in 53 MS patients. We used a semiautomated quantitation system to measure three MRI variables: total lesion area (TLA), ventricular-brain ratio (VBR), and size of the corpus callosum (SCC). Stepwise multiple regression analyses indicated that TLA was a robust predictor of cognitive dysfunction, particularly for measures of recent memory, abstract/conceptual reasoning, language, and visuospatial problem solving. SCC predicted test performance on measures on mental processing speed and rapid problem solving, while VBR did not independently predict cognitive test findings. These findings suggest that cerebral lesions in MS produce cognitive dysfunction and that MRI may be a useful predictor of cognitive dysfunction.

PIMD: 3171594

Magnetic resonance imaging and clinical correlations in multiple sclerosis.

We examined the relationship between magnetic resonance imaging (MRI) cerebral findings and clinical evaluations in 66 patients with clinically definite multiple sclerosis (MS). MRI observations included total number and location of lesions visualized, degree of periventricular involvement, degree of degeneration of the corpus callosum, and extent of generalized parenchymal atrophy. Overall physical disability was evaluated by the Kurtzke Expanded Disability Status Scale (EDSS) and individual symptoms were rated according to the Kurtzke Functional Systems (FS) scale. Our results suggest that MRI brain abnormalities are significantly related to the overall severity of disease, but MRI is not particularly useful to predict the presence or absence of individual symptoms. These findings do suggest that the MRI may provide useful information to monitor clinical progression of patients with MS, but the lesions visualized need not always be symptomatic nor are we sure that all symptomatic lesions, particularly in the spinal cord and optic nerves, will be visualized.

PIMD: 3171618

Structural brain correlates of anterograde memory deficits in multiple sclerosis.

Progressive decline of anterograde memory functions has been increasingly recognized as a frequent symptom in chronic multiple sclerosis. In order to investigate the brain structures involved, magnetic resonance imaging was performed in 20 patients. Neuropsychological assessment included the WAIS and WMS subtests information, picture completion, similarities, digit span, logical memory, and paired associate learning. All patients with severely impaired memory functions (n = 5) showed bilateral lesions in the medial temporal lobe, whereas in those patients with moderate (n = 10) or no measurable impairment of memory testing (n = 5) either no lesions were seen in the medial temporal lobes or these lesions were restricted to one side. A post hoc cluster analysis strikingly confirmed these results. The differences could not be related to the age of the patients, the disease duration, or the level of education. Extensive lesions in the white matter of the frontal lobes, thinning and lining of the corpus callosum, and bilateral involvement of the anterior cingulate gyrus had no bearing on the neuropsychological results. These findings indicate that bilateral demyelination in the hippocampal regions is the most likely explanation for the impairment of anterograde memory in such patients.

PIMD: 3226533

Multiple sclerosis and corpus callosum atrophy: relationship of MRI findings to clinical data.

Among 110 patients (45 men, 65 women), aged 15 to 66, with clinical and/or biological diagnosis of multiple sclerosis (MS), severe to moderate corpus callosum (CC) atrophy was observed in 67 (60%) patients. Correlation between CC atrophy, brain atrophy, duration and severity of clinical symptoms, and high signal white matter areas, was carried out in 90 patients. Mean age was 46 years for patients with severe CC atrophy, and 33 years for those without atrophy. Mean duration of the disease was 14 years in patients with severe atrophy, and 5 years in patients without atrophy. Severity of clinical symptoms is more pronounced in patients with severe CC atrophy. Numerous or large white matter high signal areas are observed in patients with severe CC atrophy on T2-weighted images. CC atrophy appears earlier than brain atrophy in the course of MS.

PIMD: 3593063

Magnetic resonance imaging correlates of dementia in multiple sclerosis.

Thirty-two patients with clinically definite multiple sclerosis were evaluated with neuropsychological procedures and magnetic resonance imaging (MRI). Neuropsychological evaluation included assessment of language, memory, cognition, visuospatial skills, and depression. Significant impairment in any three areas, compatible with diagnosis of a dementia syndrome, was observed in 28% of these patients, and lesser or no cognitive impairment characterized the remaining patients. Magnetic resonance imaging was used to evaluate the number and distribution of lesions as well as the presence of cerebral atrophy and atrophy of specific anatomic structures such as the corpus callosum. Results suggest that neither the number of lesions, the distribution of lesions, nor the extent of generalized cerebral atrophy was significantly greater in demented compared with non-demented patients. The primary finding was that atrophy of the corpus callosum was significantly more extensive on MRI scans in demented patients. Although the callosum itself may not be implicated directly in the pathogenesis of dementia, the presence of callosal atrophy on MRI scans should alert the physician to the possible occurrence of dementia in patients with multiple sclerosis.

PIMD: 3113196

Quantitative determination of MS-induced corpus callosum atrophy in vivo using MR imaging.

To quantitate the extent of corpus callosum atrophy in multiple sclerosis, midsagittal corpus callosum areas were determined in 48 controls with normal MR scans and 41 patients with definite multiple sclerosis. The mean midsagittal corpus callosum area was 601 mm2 (range 405-791), 641 mm2, and 561 mm2 for all adult controls, for adult males, and for adult females, respectively. Control values were significantly greater than the means determined for all multiple sclerosis (MS) patients (508 mm2, range 281-758), for MS men (528 mm2), or for MS women (498 mm2). The degree of corpus callosum atrophy paralleled the estimated volume of periventricular and corpus callosum high-signal lesions, suggesting a possible cause-effect relationship. The results indicate that corpus callosum atrophy occurs commonly in patients with typical clinical forms of multiple sclerosis.

PIMD: 3726114

Corpus callosum and subcallosal-periventricular lesions in multiple sclerosis: detection with MR.

Examination with magnetic resonance imaging of 40 patients with confirmed diagnoses of multiple sclerosis showed that corpus callosum involvement is common. Thirty percent of the patients had focal callosal lesions similar to those described in the pathology literature. Long, inner callosal-subcallosal lesions were found in 55% of patients. These lesions had signal characteristics similar to those of noncallosal periventricular lesions. Diffuse moderate to severe atrophy of the corpus callosum was noted in 40% of patients, with one exception concurrent with inner callosal lesions. The nature of the inner callosal lesions is not known, since these lesions are not typically described in the literature. These lesions may represent demyelination or increased water content and may be the precursor to atrophy that progresses from the ependymal surface toward the outer fibers of the corpus callosum.

PIMD: 2980501

The spectrum of multiple sclerosis lesions using a multiple spin echo pulse sequence and a high field strength.

Seventy-one patients having clinical laboratory findings consistent with multiple sclerosis (MS) were imaged with a 1.5 tesla MR instrument using multiple spin echo sequences (TR = 2,000 ms and TE = 30, 60, 90, 120 ms). Multiple spin echo is a sensitive method for detecting MS lesions. Sixty-seven patients (94%) demonstrated lesions consistent with MS. With the exception of those located in the cortex, optic nerve and chiasm the lesions detected correlated with pathologic data. Lesions of the cerebral hemispheres, corpus callosum and cerebellum were generally multiple while lesions of the brain stem and optic tracts were generally singular. The majority of the lesions were associated with the white matter tracts of the cerebral hemispheres and brain stem.

PIMD: 4089407

[Cerebral lymphoma associated with lesions of multiple sclerosis].

A 24 year-old man experienced a left retrobulbar neuritis which improved completely after 2 months of non-steroid antiinflammatory therapy. One month after the end of the treatment he developed a Korsakoff-like amnestic syndrome. Three months later he complained of horizontal diplopia. A CT Scan showed a diffuse enhancement of the periventricular areas, corpus callosum and fornix. Diplopia and CT scan abnormalities disappeared after the administration of tetracosactide. Subsequently a progressive worsening of the neurological condition developed, including a 1 1/2 syndrome of Fisher. In C.S.F. proteins ranged from 35 to 66 mg/dl, gammaglobulins from 4 to 5 per cent, cells from 2.2 to 6.8 per mm3 without abnormal cells. Rounded areas of enhancement were observed on CT scan in pons and right occipital lobe. Usual biological tests, abdominal echography and lymphography were normal. Death occurred 15 months after the onset of symptoms. Neuropathological examination showed: 1) a cerebral lymphoma of probable B origin with distinct masses in right occipital lobe and pontine tegmentum and a more diffuse perivascular infiltration on the left side in the amygdaloid nucleus, fourth temporal gyrus, sublenticular area, hypothalamus and in the right internal capsule; 2) multiple small clear-cut foci of demyelination with myelin-axonal dissociation bilaterally in the optic pathways, periventricular regions, corona radiata, cerebral and cerebellar white matter, sublenticular areas, temporal lobes, splenium of the corpus callosum and fornices with secondary atrophy of the mamillary bodies. Both recent and old plaques were observed. Inflammatory perivascular cuffing, when present, consisted of small nontumoral lymphocytes.(ABSTRACT TRUNCATED AT 250 WORDS)

PIMD: 7083846

Computed tomography of gliomatosis cerebri.

Two cases of gliomatosis cerebri which underwent serial CT-examination with contrast enhancement and histological examination of autopsy material are presented. No one single CT showed all the lesions discovered on neuropathological examination, the lesions in the brainstem, basal ganglia and cerebellum being isodense. The presentation of the lesions on CT was in both cases different. In one case there were several hypodense areas predominantly scattered throughout the white matter of both hemispheres, in the other the main lesion was a "tumor' of the corpus callosum, which lead to the decision for operation. Both cases showed periventricular enhancement expressing the histologically verified periventricular spread of tumor cells. Contrast enhancement appeared in the late stages of the diseases. In the different diagnosis, pseudotumor cerebri, multiple sclerosis, encephalitis and multiple brain metastases are considered. Bearing the possibility of gliomatosis cerebri in mind, CT would help limit the differential diagnosis, especially on the basis of serial CT examinations and in combination with the clinical course.

PIMD: 7339773

[Asymptomatic multiple sclerosis - 3 cases (author's transl)].

Multiple Sclerosis (MS) cases found at autopsy in patients who had died from other diseases and in whom no sign or symptom could be related to MS are called "asymptomatic". Three cases are reported. The first patient was a 62 year old man who presented with a slowly progressive disturbance of gait, incontinence and deterioration of intellectual function. A falx meningioma was surgically removed. The patient died 3 years later with an acute respiratory illness. Examination of the brain disclosed evidence of the operation and numerous old plaques disseminated through the cerebral hemispheres (centrum semi-ovale, periventricular regions, internal thalamus and junction between cortex and white matter) and in the brain stem. The second case, a 77 year old woman with diabetes mellitus and hypertension, presented with cortical blindness and disturbances of memory of acute onset. She died one year later. Examination of the brain showed multiple infarcts involving the territories of both posterior cerebral arteries and the left middle cerebral artery. Numerous old plaques were seen in the periventricular regions, in the corpus callosum and in the left middle cerebellar peduncle. The third case, a 60 year old woman with mitral and aortic stenosis, presented with cortical deafness and transient right hemiparesis. She died 5 years later. Brain examination showed infarcts involving both middle cerebral artery territories. There was also many old plaques in the periventricular areas, thalamus, internal capsule, centrum semi-ovale, brain stem and right nucleus dentatus. In the 3 cases, the optic tracts were normal. The spinal cord, examined only in the first case, was also normal. The asymptomatic character of these MS cases can be explained first by the location of the plaques and the lack of spinal cord and optic tract involvement. It could also be due to the small size of the plaques and to axonal preservation. Such features are rare since our 3 observations have been selected from a pathological collection of 125 MS cases and 9,300 general neuropathological records. Six other cases have been previously reported by other authors.

PIMD: 7359171

The influence of the ground substance on the extracellular water of normal and edematous human brain: focal edema and the demyelinating diseases, including multiple sclerosis.

The presence of a ground substance in brain provides a mechanism by which edema localized to one region of the white matter might occur without spreading diffusely into the adjacent tissues. The most common such localization is the sparing of the arcuate white matter when the deeper white matter is markedly edematous. This may be related to the higher concentration of mucopolysaccharides in the former. Petechial hemorrhages in the white matter may be surrounded by a zone free of edema, although the hemorrhagic zone itself is almost certainly edematous. This, and the presence of a central zone within some of the petechiae forming a ring hemorrhage may reflect the influence of the ground substance. Focal lesions of the dorsum of the corpus callosum and similar lesions of the basal surface of the pons, these probably due to traumatization by the contiguous falx or arteries, are characterized by myelin loss and axon preservation, a characteristic of edema; the surrounding tissues are not edematous. Severe hypertension is sometimes associated with the presence of clusters of focal perivenous demyelinating lesions in the white matter, the axons being preserved. These resemble the lesions of acute disseminated encephalomyelitis and may be due to edema; they are surrounded by nonedematous white matter. It is suggested that the same concept may apply to the focal demyelinating lesions of acute disseminated encephalomyelitis, multifocal leukoencephalopathy, central pontine myelinolysis and of multiple sclerosis, i.e. the "true" demyelinating diseases, just as has already been suggested for diffuse sclerosis.

PIMD: 390102

A search for antibodies against glial cells in the serum and cerebrospinal fluid of patients with multiple sclerosis and Guillain-Barré syndrome.

We have used indirect immunofluorescence to examine the binding of immunoglobulin in sera from patients with multiple sclerosis, Guillain-Barré syndrome, other neurological diseases, and normal subjects to marker-identified glial cells in dissociated primary cell cultures of neonatal rat corpus callosum and sciatic nerve. In corpus callosum cultures all the sera tested showed weak surface staining of oligodendrocytes and of a small percentage of astrocytes and bright staining of fibroblasts. The cerebrospinal fluid from one patient with multiple sclerosis showed the same pattern of staining while the cerebrospinal fluid from other patients with multiple sclerosis and pathological controls only showed weak staining of fibroblasts. None of the sera stained the cytoplasm of oligodendrocytes in frozen sections of adult rat optic nerve. In sciatic nerve cultures all sera showed weak staining of Schwann cells and fibroblasts. Thus we were unable to distinguish patients with demyelinating diseases from normal individuals or from patients with other neurological diseases in terms of serum or cerebrospinal fluid anti-glial cell antibodies.

PIMD: 568753

The capillaries in acute and subacute multiple sclerosis plaques: a morphometric analysis.

Two patients, one with multiple sclerosis (MS) and the other with a glioma of the splenium of the corpus callosum, were biopsied with the aid of CAT. Light microscopy, histochemistry, electronmicroscopy and morphometric analysis of counts of mitochondria, dense bodies, and pinocytotic vesicles within the capillary endothelial cells was done. Examination of the MS plaque showed endothelial cell tight junctions to be closed, basal lamina to be thinned, but endothelial cell mitochondria to be the same as in a patient without MS. Pinocytotic vesicles were markedly increased in endothelial cells in MS. Despite intense inflammation in the surround, endothelial lysosomes were as few as in a control.

PIMD: 4457618

Corpus callosum in multiple sclerosis.

A neuropathological study of 20 multiple sclerosis brains using celloidin-embedded slices was carried out to assess the extent of changes in the corpus callosum. Severe atrophy of the callosum was found in cases with marked hydrocephalus. Demyelination of the callosum varied in extent from slight involvement (with a few small plaques) to almost total myelin loss. A clinical history of mental deterioration was usual in the cases with severe callosal lesions, but no symptoms were recorded that indicated a specific disconnection syndrome. The ventricular enlargement noted in this series could not be explained either on the basis of obstruction to the flow of cerebrospinal fluid, or by the effects of shrinkage of the white matter.

PIMD: 14083218

THE RELATIONSHIP BETWEEN ENZYME ACTIVITY AND NEUROGLIA IN THE PRODROMAL AND DEMYELINATING STAGES OF CYANIDE ENCEPHALOPATHY IN THE RAT.

No abstract