PNIRS
PsychoNeuroImmunology
Research Society

Thursday, 23 February 2023 Schedule

Sign in to Zoom by 20:55 GMT!			
21:00-21:05 GMT	Introduction/Move to Breakout Rooms (Main Zoom Room)		
21:05-23:00 GMT	**CNS Disorders & Immune Profiling**	**Immune Challenge**	**Immune Brain Communication**
23:00-23:30 GMT	**Transition to Networking Breakout Rooms**		

1 - CNS Disease/Immune Profiling

Session Chairs: Mark Opp, Rafael Gonzalez-Ricon
Jennifer Felger, Julie Bower

1.1 Family Stress, Socioeconomic Disadvantage, and Inflammation Among Youth
Michelle Chen

1.2 Inflammation & depression in Chronic Kidney Disease
Christophe Clesse

1.3 Placental and fetal blood-brain barrier breakdown during gestational influenza virus infection allows maternally derived molecules to reach the fetal brain.
Rafael Gonzalez-Ricon

1.4 Clearance of senescent-like microglia/macrophages improves remyelination in a mouse model of focal demyelination
Phillip Gross

1.5 Adolescents' friend support buffers the association between family subjective socioeconomic status and low-grade inflammation in adolescents
Tao Jiang

1.6 Social Stress, Inflammatory Reactivity, and Depressive Symptoms
Annelise Madison

1.7 Exploration of Clinical Mechanisms of the Neuroimmune Modulator, Ibudilast, for Alcohol Use Disorder
Lindsay Meredith

1.8 Racial Disparities in Alzheimer's Disease (AD): the associations between adverse childhood experiences and AD
Deborah Rose

2 - Immune Challenge

Session Chair: Adrienne Antonson
Peter Grace, Ilia Karatsoreos, Sarah Spencer

2.1 Inhibition of tryptophan 2,3-dioxygenase exhibits early and long-term neuroprotection in an animal model of sepsis
Lucineia Danielski

2.2 Maternal immune activation and raloxifene alter microglia- and complement-related transcripts in the substantia nigra of female and male rat offspring
Sophie R. Debs

2.3 Microglial alteration in female mice submitted to chronic stress: An imbalance in the CX3CL1:CX3CR1 axis
Alina Díez-Solinska

2.4 Pramipexole modulates pro-plasticity proteins, attenuates inflammation, and improves depressive-like behaviors in female BALB/c mice
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2.5 Maternal antibiotic treatment alters offspring gut microbiota and LPS-induced Neuroinflammation
Abdullah Madany

2.6 Murine influenza A virus disrupts immune profiles in the maternal gut and placenta in a dose-dependent manner
Ashley Otero

2.7 Sex differences in the effect of social isolation on brain circuits and neuroendocrine-immune status in rats
Estherina Trachtenberg

2.8 Body odor disgust sensitivity and concern about COVID-19 pandemics
Marta Zakrzewska

3 - Immune-Brain Communication

Session Chairs: Christoph Rummel, Lina Hansson
Luba Sominsky, Eric Wohleb

3.1 Lung-to-Brain communication: IL-17a in allergies
Emily Allgire

3.2 L1210 Leukemic Cells and Methotrexate Impact the Transcriptional Response of Microglia and Astrocytes from the Prefrontal Cortex
Alyshia Davis

3.3 Stress Neurocircuitry and Airway Inflammation in Asthma
Estelle Higgins

3.4 Taste-associative learning to induce behaviorally conditioned analgesia in an animal model of inflammatory pain
Stephan Leisengang

3.5 Lung-Brain Communication in viral infection onset
Sarah Monroe

3.6 Complement system: A possible link between neonatal status epilepticus and behavioral deficits in mice.
Danielle Santana Coelho

3.7 The cortisol awakening response: A switch for diurnal Th1/Th2 rhythms?
Lennart Seizer

3.8 The walking sick: what predicts the detection of walking sick individuals?
Lina Hansson

Session Abstracts

1 - CNS Disease/Immune Profiling

1.1 Family Stress, Socioeconomic Disadvantage, and Inflammation Among Youth

Michelle A. Chen [a], Shohreh Raeisi [a], Veronica Passarelli [a], Edith Chen [a], Gregory E. Miller [a]
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Introduction

Early life stress is associated with increased inflammation, a key mechanism involved in cardiovascular disease and other health outcomes. In particular, family stress (e.g., poor parent-child relationships, marital problems between parents, or major family transitions) has been associated with poor outcomes among youth. Socioeconomically disadvantaged youth may be particularly vulnerable to the negative consequences of family stress, due to the accumulation of stressors faced by families under financial strain. Thus, we examined the combined roles of family stress and socioeconomic disadvantage on inflammation among adolescents.

Method

We examined the interaction between family stress (assessed on a 1-5 scale via semi-structured interview) and socioeconomic disadvantage predicting inflammation among 275 adolescents. Socioeconomic disadvantage was assessed on a 0-5 scale, with one point for each of the following: an income to poverty ratio less than 1.99, at least one parent with a high school education or less, at least one unemployed parent, living in a single parent household, and receiving government assistance. Inflammation was assessed using a composite index consisting of serum cytokines (IL-6, IL-8, IL-10, TNF-a), CRP, and suPAR and circulating levels of CD14++CD16- classical monocytes, important cellular drivers of inflammation.

Results

Socioeconomic disadvantage exacerbated the relationship between family stress and the inflammation composite (B = 0.07; p = .033) and the relationship between family stress and classical monocytes (B = 6.49; p = .035).

Conclusion

Youth with higher socioeconomic disadvantage may be particularly vulnerable to negative health-related consequences of family stress, potentially due to an accumulation of stressors.

1.2 Inflammation & depression in Chronic Kidney Disease

Christophe Clesse [a,b], Muhammad Magdi Yaqoob [c], Simone Jayakumar [a,b], Kamaldeep Bhui [d,e,f] and Livia A Carvalho [a].

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[b] *Center for Psychiatry and Mental Health, Wolfson Institute of Population Health, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, London, UK*

[c] *Translational Medicine and Therapeutics, William Harvey Research Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, London, UK*

[d] *Department of Psychiatry and Nuffield Department of Primary Care Health Sciences, University of Oxford, London, UK*

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[f] *Health NHS Foundation Trust, Oxford, UK*

Introduction

Research has confirmed the presence of an association between inflammation and depression among patients with chronic kidney disease (CKD). However, little is known about the clinical and psychological phenotype of these patients.

Method

Using a large dataset (UKbiobank) for Chronic Kidney Disease patients (N=41133) and a clinical cohort study for Kidney Failure patients (N=300), we conducted a cross-sectional analysis to investigate the clinical and psychological phenotype of depressed CKD and KF patients. Investigated model included sociodemographic and socioeconomic variables, adverse health behaviours, main aetiological causes of CKD (hypertension, diabetes, glomerular Diseases), main comorbidities (CVD, COPD, autoimmune diseases...), antidepressants and various psychosocial variables.

Results

General Linear models confirm that anxiety (*p.0.026*), pain (*p. 0.015*) fewer frequency of tenseness/restless (*p. 0.050*) and being less unenthusiastic (*p.002*) are also associated with high inflammation in depressed CKD patients.

Longitudinal analysis demonstrates that depressed CKD highly inflamed patients have more risk to develop COPD, diabetes and to die.

Conclusion

This research highlights the clinical and psychological phenotype of depressed CKD and KF patients. These results would be beneficial in future research aiming at evaluating impact of immunotherapy in depressed CKD and KF patients.

1.3 Placental and fetal blood-brain barrier breakdown during gestational influenza virus infection allows maternally derived molecules to reach the fetal brain.

Rafael Gonzalez-Ricon [a], Adrienne Antonson [b]
[a] *University of Illinois Urbana-Champaign, USA*
[b] *University of Illinois Urbana-Champaign, USA*

Introduction

A successful pregnancy requires a finely regulated exchange of nutrients across the placental barrier and ultimately, across the fetal blood-brain barrier (BBB). However, the integrity of these barriers can be compromised during maternal immune activation, causing a cascade of inflammatory signaling within the fetal compartment. Maternal influenza A virus (IAV) infection during pregnancy increases the risk of neurodevelopmental disorders in offspring, yet the importance of placental and fetal brain barriers has not been properly tested in this context. Here, we evaluate whether maternally derived molecules are accessing the fetal compartment and entering the fetal brain during maternal IAV infection.

Method

C57Bl/6NTac pregnant mice were inoculated with mouse-adapted IAV or saline at gestational day 9.5. Fluorescently labeled tracer molecules were administered intravenously to pregnant dams at 7 days post inoculation, and fetal tissues were collected. Sagittal sections of whole fetuses were imaged and fluorescence intensity of each tracer was quantified. Gene expression of tight junction proteins and proinflammatory mediators was assessed in placentas and fetal brains, and presence of clotting factor fibrinogen was assessed in the fetal brain.

Results

Increased dissemination of all tracers was observed within the fetal brains of the IAV group with no differences in the placenta. IAV increased placental *Cldn5* expression, while *Cldn1*, *Ocln,* and *Nos-2* were increased in fetal brain samples.

Conclusion

Maternally derived molecules can reach the fetal brain during IAV infection, potentially by hyperpermeability of placental and fetal BBB structures. Ongoing experiments will determine if fibrinogen may be mediating neuroinflammation in this context.

1.4 Clearance of senescent-like microglia/macrophages improves remyelination in a mouse model of focal demyelination

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[c] *Natl. Inst. of Neurolog. Disorders and Stroke (NINDS), USA*

Introduction

Multiple Sclerosis (MS) is a demyelinating and degenerative disease that is the number one neurological disability among young adults. Myelin degeneration results in denuded axons that consequently conduct signals inefficiently and eventually degenerate. In early stages of the disease, oligodendrocyte progenitor cells (OPCs) can regenerate myelin, resulting in effective remyelination. However, at later stages of the disease and with increasing age, remyelination becomes inefficient, leading to degeneration of axons and worsening symptoms. One of the key characteristics of aging is the accumulation of senescent cells. Here, we hypothesized that the age-associated accumulation of senescent cells limits the ability of OPCs to remyelinate.

Method

To test this, we induced focal demyelinating lesions in both young and aged mice using lysolecithin and used a murine fluorochrome reporter line with expression under the p16INK4a locus (p16-tdt) to measure senescence throughout the process of remyelination. We also used the transgenic INK-ATTAC mouse line to selectively ablate p16INK4a expressing cells throughout remyelination.

Results

We found increased markers of senescent cells present after demyelination and throughout remyelination, with aged mice showing markedly increased markers compared to their young counterparts at both early and late timepoints post lesion. These markers predominantly colocalized with microglia/macrophages. Interestingly, clearance of senescent cells in young and middle-aged mice resulted in increased remyelination in the lesion compared to vehicle-treated controls.

Conclusion

These results suggest the accumulation and subsequent failed clearance of senescent cells with age may contribute to their reduced remyelination, and that therapeutic targeting of cellular senescence might promote remyelination in MS.

1.5 Adolescents' friend support buffers the association between family subjective socioeconomic status and low-grade inflammation in adolescents

Tao Jiang [a], Jungwon Kim [a], Hee Moon [a], Edith Chen [a], Gregory E. Miller [a]
[a] *Northwestern University, United States of America*

Introduction

Early-life socioeconomic disadvantage is linked to poor health outcomes across the lifespan. Mounting evidence indicates that strong parental relationships can serve as a buffer against these risks, but it is unclear whether other relationships function similarly. Given the importance of friendships in adolescence, we considered whether peer relationships operated as buffers against low-grade inflammation among teenagers of low socioeconomic status.

Method

277 dyads of adolescents (63.3% female; M_{age} = 13.9) and one of their parents participated in a longitudinal study (two waves approximately two years apart). Parents reported family objective SES (i.e., income, savings, and education) and family subjective SES (i.e., the MacArthur Scale of subjective SES). Adolescents reported perceived friend support. Fasting antecubital blood was drawn from adolescents at both visits. For analyses, low-grade inflammatory activity was represented by: 1) a composite of the biomarkers CRP, IL-6, IL-8, IL-10, TNF-α, and suPAR, measured by immunoassay; and 2) numbers of classical monocytes, key cellular drivers of inflammation, measured by flow cytometry.

Results

Results showed that friend support moderated the associations of family subjective SES with both inflammatory biomarkers and classical monocytes cross-sectionally (at Time 1) and longitudinally (at Time 2). Specifically, lower family subjective SES was associated with higher levels of inflammatory biomarkers and higher numbers of classical monocytes for adolescents who had lower friend support, but these associations were nonsignificant for those with higher friend support. No moderation was observed for objective SES.

Conclusion

The current study suggests that high peer support buffers lower SES adolescents from low-grade inflammation.

1.6 Social Stress, Inflammatory Reactivity, and Depressive Symptoms

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Introduction

These studies test the Social Signal Transduction Theory of Depression and whether omega-3 supplementation impedes this etiological pathway.

Method

Study 1: 76 physically healthy adults and 79 breast cancer survivors completed a laboratory social stressor (a marital conflict or the Trier Social Stress Test, respectively), had their blood drawn to assess inflammatory responsivity, and reported their stress exposure at baseline and their depressive symptoms at baseline and follow-up (one month later or four and eight months later, respectively). Study 2: 138 middle-aged, sedentary adults were randomized to 2.5 g/day of omega-3, 1.25 g/day of omega-3, or placebo for four months. Before and after supplementation, they completed the Trier Social Stress Test and had their blood drawn to assess inflammatory responsivity. Study 3 features secondary analyses from the same RCT to examine whether omega-3 reduced self-reported depressive symptoms among those who reported more social stress.

Results

Study 1: Those who reported more frequent social stress, but not other types of stress, and had greater inflammatory responsivity at baseline had heightened depressive symptoms at follow-up. Study 2: Omega-3 supplementation promoted a more resilient physiological response to acute stress, including lower inflammatory responsivity. Study 3: Omega-3's antidepressant effect was greatest among those who reported frequent social stress.

Conclusion

These data support the Social Signal Transduction Theory of Depression, showing the unique potency of social stress and inflammatory signaling in depression etiology. Omega-3 may promote stress resilience and prevent depression worsening among the socially-stressed.

1.7 Exploration of Clinical Mechanisms of the Neuroimmune Modulator, Ibudilast, for Alcohol Use Disorder

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Introduction

Despite the promising implications for novel immune therapeutics, few clinical trials have tested these therapies for AUD to date. An understanding of how immune pharmacotherapies influence complex AUD profiles to alcohol is very limited. Elevated inflammation, indicated by high levels of C-reactive protein (CRP), represents a possible subtype of AUD, which may be associated with treatment response to ibudilast. Initial findings show that ibudilast reduces rates of heavy drinking and alcohol craving.

Method

This study is a secondary analysis of a two-week clinical trial of ibudilast for AUD. Eligible participants (N = 52) provided blood samples at baseline to assess CRP levels, were randomized to ibudilast or matched placebo, and then completed daily diary assessments (DDAs). Each morning for DDAs, participants retrospectively reported on their previous day's experiences (i.e., craving, mood, alcohol intake). Multilevel and general linear models compared the effects of medication on subjective alcohol response and the internaction of baseline inflammation and medication on drinking.

Results

Ibudilast attenuated alcohol-induced increases in craving compared with placebo (p = .047), but not other subjective response measures. There was a significant interaction between medication and CRP (F = 3.80, p = .03), such that as levels of baseline CRP increased, those randomized to ibudilast but not placebo, showed reduced drinking.

Conclusion

Reductions in alcohol craving may represent a primary mechanism of ibudilast. The ecologically valid nature of DDAs provide a clinically useful window into how individuals experience alcohol's effects with medication. Results suggests that a baseline proinflammatory profile may enhance clinical efficacy of ibudilast.

1.8 Racial Disparities in Alzheimer's Disease (AD): the associations between adverse childhood experiences and AD

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Andy Liu, Duke University Medical Center, Durham, North Carolina, USA

Introduction

Adverse childhood experiences (ACEs) are an important public health concern that predict neuroanatomical changes in development such as decreased prefrontal cortex and hippocampal volumes, and can lead to poor health outcomes in adulthood, including cognitive impairment. Alzheimer's disease (AD) is the most common cause of dementia, and it disproportionately affects racial and ethnic minoritized (REMs) individuals including African Americans and Hispanic Americans compared to non-Hispanic whites. The mechanisms underlying these racial disparities are not fully understood, but research demonstrates that differences in exposure to specific types of early life adversity (i.e. parental remarriage and/or death) may play a role. A significant ACE burden can lead to disruption of the hypothalamic-pituitary adrenal (HPA) axis.

Objective: The goals of this study are to correlate ACEs to AD dementia, mild cognitive impairment (MCI), and normal cognition (NC), and to determine the specific ACE types that are most significantly associated with AD dementia in REM populations.

Method

Correlate HPA axis dysregulation inflammatory biomarkers in association with ACEs (using traditional assays and large-scale proteomics) to AD dementia (cognitive assessments and clinical history) and pathology (plasma phosphorylated tau 181 and phosphorylated tau 217) in a nationally representative, diverse cohort of participants with NC, MCI, and AD dementia.

Results

Research is ongoing.

Conclusion

Literature and preliminary data support that the growing evidence that there is an association between ACEs and the development of cognitive impairment, including AD dementia, later in life.

2 - Immune Challenge

2.1 Inhibition of tryptophan 2,3-dioxygenase exhibits early and long-term neuroprotection in an animal model of sepsis

Lucineia Gainski Danielski[1]; Kiuanne Lobo[2]; Khiany Mathias[3]; Tais Denicol[3]; Thaina Cidreira[4]; Sandra Bonfante[4]; Larissa Joaquim[4]; Anita Pacheco[4]; Marina Goulart[4]; Guilherme Daros[4]; Elisa Lins[5]; Fernanda Belle[5]; Carolina Giassi Alano[1]; Rafaela Tezza Matiola[1]; Isabela da Silva Lemos[1]; Gislane Tezza Rezin[4]; Rafael Bitenourt[4]; Fraciane Bobinski[5]; Emilio Luiz Streck[1]; Gislaine Reus[1]; Tatiana Barichello[6]; Fabricia Petronilho[1].

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Introduction

One pathway that may be related to the progression of neurological damage in sepsis is the kynurenine (KYN) pathway (KP). Critically ill patients may exhibit elevated levels of KYN in the expense of tryptophan (TRP) plasmatic level depletion (Rogers et al., 2014).

Method

Two-month-old male Wistar rats were submitted to the sepsis model by cecal ligation and perforation (CLP). The rats received allopurinol (Allo, 20 mg/kg, gavage) or vehicle, once a daily for 7 days. Sepsis induction increase IL-6, neutrophil infiltrate, nitric oxide formation, increase oxidative stress and lead to energy impairment in 24h after CLP , Allo administration restored these parameters.

Result

TDO activity inhibition reduces hippocampal level of IL-6 after sepsis. TDO activity inhibition reduces neutrophil brain infiltrate after sepsis. TDO activity inhibition reduces brain oxidative stress after sepsis. TDO activity inhibition restores brain mitochondrial energy metabolism after sepsis. TDO activity inhibition protects against behavioral alteration after sepsis

Conclusion

In summary, the TDO inhibition was effective in preventing long-term depressive behavior and memory impairment by reduce acute neuroinflammation, oxidative stress and mitochondrial alteration.

2.2 Maternal immune activation and raloxifene alter microglia- and complement-related transcripts in the substantia nigra of female and male rat offspring

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Introduction

Maternal immune activation (MIA) results in dopamine dysregulation, behavioural abnormalities and midbrain neuroinflammatory changes in adult offspring, similar to schizophrenia. The selective estrogen receptor modulator, raloxifene, benefits those with schizophrenia possibly through modulating neuroinflammation. We investigated how raloxifene alters microglia- and complement-related gene expression in the substantia nigra (SN) in female and male adult offspring of Poly(I:C) exposed dams.

Method

MIA was induced in Wistar dams (GD19) with Poly(I:C) [4mg/kg, tail vein, saline/poly(I:C) n=11/10]. Raloxifene (5mg/kg) was administered to offspring daily (PND58-84, cookie dough) with four groups/sex: vehicle/placebo, vehicle/raloxifene, MIA/placebo, MIA/raloxifene (n=23-30/group/sex; half underwent behavioural tests). Offspring were euthanised (PND83-85), SN dissected and cDNA prepared. Microglia- (Iba1, Tmem119, CD11b, Cd11c, Trem2, Fcrl2) and-complement-related (C1q, C2, C3, C4, C5) mRNAs were measured (RT-qPCR).

Result

CD11c, Trem2 and C3 mRNAs were reduced in female MIA offspring, whereas C1q mRNA was reduced in male MIA offspring. C5 mRNA was increased in female MIA offspring only. Raloxifene-treated male MIA offspring displayed increased CD11c and decreased C4a and Tmem119 mRNAs. Fcrl2 mRNA was reduced in raloxifene-treated female MIA offspring only.

Conclusion

MIA reduces multiple microglial markers in adult female midbrain and induced complement pathway changes in one specific factor in each sex. Raloxifene induced transcriptional changes that were dependent on earlier exposure to MIA and targeted distinct microglia markers in males and females, being more apparent in male MIA offspring. Further work will determine how these findings relate to behavioural abnormalities and microglia morphology.

2.3 Microglial alteration in female mice submitted to chronic stress: An imbalance in the CX3CL1:CX3CR1 axis

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Introduction

Social stress has been shown to induce microglial cell-mediated immune activation in the brain, however, the effects in female mice remain incomplete because they have been understudied. Therefore the aim of this study was to assess the impact of Cronic Social Instability Stress (CSIS) on the activation of the microglia in the striatum and in the hippocampus in OF1 female mice.

Method

To this purpose, subjects (n=91) were divided into 2 groups, the stressed (n=52) and the non-stressed (n=39) ones. The stressed group was submitted to CSIS model for 28 days. The hippocampus and striatum dissection took place immediately after the experimental procedure. Samples were then processed and the resulting cDNA was analyzed through Real-Time RT–PCR.

Results

Stressed mice showed no differences in the CX3CL1 mRNA gene expression levels neither in hippocampus nor in the striatum ($F [1,86] =0.293$; $p =0.590$; $\eta2 =0.003$; and $F [1,86] =2.829$; $p =0.096$; $\eta2 =0.032$ respectively). However, differences were observed in CX3CR1 expression. The stressed mice showed higher CX3CR1 expression levels in both, in the hippocampus ($F [1,86] =53.579$; $p =0.000$; $\eta2 =0.384$) and the striatum ($F [1,86] =66.940$; $p=0.000$; $\eta2 =0.438$). This increase resulted in a lower CX3CL1:CX3CR1 ratio in hippocampus and striatum ($F [1,87] =12.833$; $p =0.001$; $\eta2 =0.129$; and $F [1,87] =20.913$; $p =0.000$; $\eta2 =0.194$ respectively).

Conclusion

These data demonstrate that CSIS has an effect on the microglia in the two stress-sensitive brain structures measured. This suggests that microglial activation could intervene in adapting to a stressful condition.

2.4 Pramipexole modulates pro-plasticity proteins, attenuates inflammation, and improves depressive-like behaviors in female BALB/c mice

Karli Gilbert, M.S. [a], Katherine Conant, M.D. [a]
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Introduction

Pramipexole (PPX) is a dopamine 2/3 receptor agonist that has been recently explored as a potential antidepressant, although its mechanism(s) of action have yet to be fully established. Previous studies utilizing PPX in rodents found a D3R-dependent improvement in depression-like behavior after treatment. We hypothesized that PPX would induce an antidepressant-like phenotype in female *BALB/c* mice, which display anxiety-like behavior, by modulating pro-plasticity kinases, increasing dendritic arborization, and decreasing inflammation.

Method

Mice were treated with PPX for 4 weeks (1 mg/kg) in their cage drinking water vs controls. Behavioral tests (OF, EPM, NSF, SPT, FC, T-maze) were performed during the last 2 weeks of treatment. Mice were then sac'd and brains hemisected for IHC and protein analysis of the hippocampus, PFC, and striatum.

Results

We found a significant increase for sucrose preference (baseline: p=0.0013, test: p=0.019), an increase in working memory in the T-maze (alternations: p=0.0078), and decrease in neophobic behaviors compared to controls (T-maze no choice: p=0.056; exploration: p=0.0056). Results from fear conditioning, novelty suppressed feeding, social interaction, and elevated plus maze results did not indicate a treatment effect, but rather a spectrum of behavioral responses among both treatment groups.

Conclusion

Our pilot data indicate that Pramipexole has anti-inflammatory and pro-plasticity effects in the PFC and Striatum of female *Balbc* mice. Pramipexole alleviates anhedonia in BALB/c female mice and improves working memory, which may correlate with proteomic changes that are favorable to increasing LTP.

2.5 Maternal antibiotic treatment alters offspring gut microbiota and LPS-induced Neuroinflammation

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Introduction

Studies have shown that maternal infections and/or inflammation cause dysbiosis, with an increased risk of neurodevelopmental disorders such as Autism Spectrum Disorders (ASD) in children. Therefore, we hypothesized that prenatal maternal antibiotics (ABX) use which also causes dysbiosis, could induce long-term gut microbiota and immunological effects on the offspring, which leads to increased susceptivity and severity of the dysbiotic and immunological response. This study aimed to investigate the influence of an acute ABX-treatment of pregnant murine dams on the long-term neuroimmunity of the offspring.

Method

A broad-spectrum ABX-cocktail consisting of (vancomycin, ampicillin, and neomycin), or vancomycin alone, was administered ad-lib orally to elicit a dysbiotic environment. To determine the long-term effects, we analyzed the gut microbiota of offspring and their immune responses in the periphery and the brain of the C57BL/6J mice during infancy, early adolescence, and adulthood. We first performed 16s rRNA sequenced, then analyzed computationally predicted metabolic pathways. Next, serum and brain cytokine levels were determined.

Results

ABX-treatment can have several adverse effects on the gut microbiota, including reduced diversity, altered metabolic activity, and immune function. We show that the maternal ABX-treatment significantly alters the gut microbiota diversity, composition, and potential metabolic pathways from infancy well into adulthood despite not coming in direct contact with ABX. Lower levels of neuronal chemokines and inflammatory cytokines in offspring were also seen.

Conclusion

This study shows that the gut microbiome is altered by maternal ABX-treatment, and the extent of the alteration is determined by the antibiotic regimen, age, and sex of offspring.

2.6 Murine influenza A virus disrupts immune profiles in the maternal gut and placenta in a dose-dependent manner

Ashley Otero [a], Adrienne Antonson [a]
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Introduction

Maternal immune activation (MIA) during pregnancy is linked to neurodevelopmental disorders in offspring. To elucidate the mechanisms behind this link, we utilize live influenza A virus (IAV) infection in pregnant mice, which activates both innate and adaptive immune responses. We seek to characterize downstream immune responses to IAV infection and determine whether there is an infection severity threshold for fetal brain abnormalities. Respiratory IAV infection is known to cause immune dysregulation in the intestine through IL-17-producing RORγt+ T helper (Th) 17 lymphocytes. While IL-17-producing cells have been implicated in MIA-mediated fetal brain abnormalities, the maternal RORγt+ cell landscape has never been examined in IAV-induced MIA models.

Method

Pregnant C57BL/6NTac mice received 10^3 or 10^4 $TCID_{50}$ H3N2 IAV strain X31, or mock-inoculation with saline. Maternal blood, lungs, and intestine, placentas and fetal brains were collected on gestational day 11.5 or 16.5, two or seven days post inoculation (dpi).

Results

At 2 dpi, respiratory IAV infection upregulated genetic markers and proteins of Th17 cells in the intestine only at the high viral titer. Placental immune transcripts were also altered in a dose-dependent manner. Notably, numbers of fetal macrophages and microglia were no different. Ongoing studies are evaluating maternal lamina propria RORγt cells across gestation.

Conclusion

A higher infectious dose of IAV is necessary to induce downstream immune changes in the maternal gut and placenta during acute infection, confirming the use of live pathogens in MIA modeling to evaluate the complete immune response and improve translation to the clinic.

2.7 Sex differences in the effect of social isolation on brain circuits and neuroendocrine-immune status in rats

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Introduction

Social isolation (SI) is a risk factor for malignancy, morbidity, and mortality and is associated with immune suppression and neuroendocrine perturbations. Here we investigated the effects of SI on gene expression in the Nucleus Accumbens (NAc), the Bed Nucleus of the Stria Terminalis (BNST), and on peripheral neuroendocrine immune responses.

Method

Female and male F344 rats were assigned to six weeks of SI. Brain and plasma samples were collected. Relative expression levels of OXTR, CRFR1, CRFBP, 5-HTR, and D1R genes were assessed. Plasma levels of corticosterone (CORT), IL-6, and TNFa were quantified using ELISA.

Results

In the NAc, SI females showed increased levels of OXTR and 5HTR mRNAs ($p=0.02$; $p=0.01$), whereas SI males showed decreased levels of 5HTR ($p=0.03$) and increased levels of D1R mRNAs ($p=0.04$). In the BNST, female rats showed a significant increase of CRFR1 ($p=0.001$) and a marginal increase in CRFBP ($p=0.07$), whereas males showed no significant differences. In the periphery, both sexes exhibited higher levels of plasma IL-6 in isolated rats ($p=0.03$). Plasma TNFa levels were significantly higher ($p=0.002$) in isolated females but significantly lower ($p=0.006$) in isolated males, and CORT levels were significantly increased only in isolated females ($p=0.004$).

Conclusion

SI affected the expression of key genes related to social neurocircuits in the NAc and the BNST. SI also altered peripheral cytokines and CORT levels. These neuronal and immune alterations were sex-dependent, and associated with a pro-inflammatory state in females. Our ongoing studies address the influence of the social environment on neuro-immune pathways.

2.8 Body odor disgust sensitivity and concern about COVID-19 pandemics

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Introduction

The COVID-19 pandemic has drastically changed the way we interact with each other. Research on disease avoidance behaviors showed that they are related to several individual characteristics, one of them being disgust sensitivity. Interestingly, disgust sensitivity to body odors in particular (body odor disgust sensitivity, BODS) has recently been studied in more detail and seems to be important for avoidance behaviors. This is understandable as olfaction helps in recognizing and evading the (often invisible) threat of disease.

Method

In this project, we used online surveys to investigated the relationship between BODS and disease avoidance during salient pathogen threat (COVID-19 pandemics). We collected data in three waves between April 2020 and June 2022, in various locations around the world: wave 1 (N=2068) in Italy and Sweden; wave 2 (N=4595) in Canada, Chile, Hong Kong, Kenya, Nigeria, Mexico, New Zealand and the United Kingdom (UK); wave 3 (N=2893) in Australia, Colombia, India, Italy, Nigeria, Sweden and UK. Participant completed the BODS questionnaire and answered questions about importance of behaviors related to COVID-19 (e.g., wearing masks, avoiding contact with strangers etc.).

Results

We used Bayesian parameter estimation and model comparison. In all waves, the best model showed that participants who reported greater body odor disgust sensitivity were also more concerned about COVID-19 pandemics.

Conclusion

Our findings support the idea that body odor disgust is somewhat relevant to disease avoidance by showing that it is related to attitudes about disease spread limiting behaviors during a salient pathogen threat situation.

3 - Immune-Brain Communication

3.1 Lung-to-Brain communication: IL-17a in allergies

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Introduction
Allergic asthma is a prominant source of childhood inflammation, which has been associated with posttraumatic stress disorder. Of note, asthma severity correlates to PTSD symptom score. Asthma severity is influenced by T helper 17 cells/IL-17a which is increased in a subset of patients with PTSD. To explore the mechanisms of this relationship, we've utilized a mouse model (House Dust Mite) of both mild and severe asthma. In this model, we've demonstrated extinction deficits in the severe, but not mild/moderate phenotype. Here, we sought to explore the role and route of Th17/IL-17a.

Method
To investigate the role of Th17/IL-17a in lung-brain communication in allergic asthma, we conducted: (1) Necessity of IL-17a in severe asthma-mediated extinction deficits via IP αIL-17a throughout allergen exposure. (2) identify neuronal recruitment in blood-brain barrier compromised circumventricular organ, the subfornical organ (SFO), via direct administration of recombinant IL-17a. (3) Analysis of T-cell and leukocyte presence in lung, meninges, SFO, and prefrontal cortex (PFC) via flow cytometry in control, mild/moderate, and severe airway inflammation.

Results
We identified that blocking IL-17a recovered the extinction deficit observed in our model of severe airway inflammation. Furthermore, direct administration of IL-17a increased cFos recruitment in the SFO. Analysis of flow cytometry data is ongoing.

Conclusion
Overall, in addition to mechanistic information on asthma-PTSD association, our work provides novel insights on lung-brain communication in regulating behavior of relevance to other prevalent airway pathologies.

3.2 L1210 Leukemic Cells and Methotrexate Impact the Transcriptional Response of Microglia and Astrocytes from the Prefrontal Cortex

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Introduction

Acute Lymphoblastic Leukemia (ALL) is one of the most prevalent childhood cancers, with survival rates over 90%, however, long term cognitive deficits occur in 40% to 70% of these survivors. Reducing the incidence of long-term side effects like cognitive deficits in survivors is a priority. Our preliminary studies have indicated that neuroinflammatory responses due to MTX treatment may be related to the deficits seen in ALL survivors.

Method

To investigate the roles of microglia and astrocytes in early life cancer+chemotherapy exposed animals, we have created a mouse model that incorporates both cancer and chemotherapy exposure which leads to cognitive deficits. C57BL/6 x DBA F1 mice were randomly assigned to an injection of cultured L1210 mouse leukemic cell line, or saline on postnatal day (P) 19. Starting on P21 cancer exposed mice began a 4-cycle chemotherapy using MTX, vincristine, and leucovorin; the control group received saline. One day following the final chemotherapy exposure, prefrontal cortex (PFC) was dissected and microglia and astrocytes were isolated from the PFC using a Percoll density gradient and fluorescence activated cell sorting (FACS). RNA isolated from the sorted cells was used for RNA-sequencing to identify gene expression changes in both sexes.

Results

While the full bioinformatic analysis is ongoing, preliminary results show that significantly more genes are changed in females versus males, and significantly more genes are changed in astrocytes versus microglia.

Conclusion

Collectively, these data will identify pathways of interest that may contribute to cancer + chemotherapy associated cognitive deficits.

3.3 Stress Neurocircuitry and Airway Inflammation in Asthma

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Introduction

Asthma is a highly prevalent inflammatory airway disease marked by recurrent respiratory symptoms and increased prevalence of psychopathology. Psychological stress intensifies airway inflammation, likely contributing to individual differences in asthma pathobiology and treatment resistance. However, the neural mechanisms and descending pathways that underlie these interactions are incompletely understood.

Method

To identify the brain circuits engaged by psychosocial stress that may impact airway inflammation, we measured [F-18]fluorodeoxyglucose (FDG) binding using positron emission tractography (PET) following the Trier Social Stress Test (TSST). Cortisol levels in saliva were used to quantify physiological stress responses. Provocation with inhaled whole-lung allergen challenge (WL-AG) followed PET imaging and airway inflammatory response was assessed before and 24hr post-challenge.

Results

Salivary cortisol area under the curve (AUC) was significantly greater during the TSST, relative to control condition ($t(24) = -2.9$, $p = .008$). Stress-evoked cortisol AUC was positively correlated with glucose metabolism in the bilateral insulae, anterior cingulate cortex (ACC), R amygdala, and cerebellum. Importantly, stress-evoked neural activity in bilateral amygdalae predicted increased expression of IL-23A mRNA in sputum following WL-AG.

Conclusion

Results confirm that a greater physiological stress response is associated with increased activity in stress- and emotion-responsive brain regions. Moreover, correlations between stress-evoked bilateral amygdalae activation and subsequent WL-AG-induced IL-23A mRNA expression support our hypothesis that stress-evoked neural activity in emotion-related circuits predicts an enhanced airway inflammatory response to allergen. These results provide insight into brain-to-lung signaling pathways that underlie mind-body interactions in asthma, and may ultimately suggest novel targets for asthma management.

3.4 Taste-associative learning to induce behaviorally conditioned analgesia in an animal model of inflammatory pain

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Introduction

While the phenomenon of placebo analgesia is well-documented in humans, the translation into a reliable animal model is still challenging. In this study, we aim to apply an established protocol of taste-associative learning to induce behaviorally conditioned analgesia.

Method

We use a rat model of Complete Freund's Adjuvant (CFA)-induced paw edema to induce symptoms of inflammatory pain. From day 2 after CFA-injection, rats are repeatedly treated with ibuprofen (100 mg/kg, i.p.) or morphine (2 mg/kg, s.c.). Application of analgesic drugs (*unconditioned stimulus*, US) will be paired to a novel sweet taste (*conditioned stimulus*, CS) in an initial acquisition phase. In the following retrieval phase, rats are re-exposed to the taste to induce a conditioned response, mimicking pharmacological effects. We assess spontaneous (Open-Field-Test) and induced pain-related behaviors (Von-Frey-Test, Plantar-Heat-Test) and examine inflammation-associated changes in structures of the afferent nociceptive system.

Results

Intraplantar injection of CFA induces a robust paw edema for eight days, accompanied by a consistently enhanced mechanical and thermal sensitivity compared to saline injected controls. Activity, water consumption and weight gain are reduced for 24h but return to baseline from day 2. Repeated intraperitoneal injection of ibuprofen on every other day results in a drug-induced analgesia.

Conclusion

After having established a reliable model of inflammatory pain with drug-induced short-term analgesia, we will be able to apply a taste-associative learning paradigm in rodents in order to analyze mechanisms of learned analgesic effects, which might form the basis for developing conditioned analgesic responses in humans.

3.5 Lung-Brain Communication in viral infection onset

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Introduction

Society faces increasing incidence of respiratory immune challenge including air pollution and novel respiratory virus. Respiratory viral infection with influenza A strain PR8 causes local inflammation as well as a neuroinflammatory response in hippocampal neurons and microglia. Vagally innervated pulmonary neuroendocrine cells (PNECs) mount a secreted immune response to respiratory challenge, recruiting immune cells to lung tissue. However, it is unknown whether PNEC signaling contributes to the microglial response to influenza A infection. This project investigates potential rapid immune signaling mechanisms from PNECs to microglia through the vagus nerve during influenza A infection.

Method

P60 mice were infected with the influenza strain PR8 and tissues were collected at 24 and 72 hours post infection. Gene expression in homogenized lung tissue was measured by RTqPCR. Brains were post fixed sectioned; sliced were immunohistochemically stained. Using the softwares UNet and WholeBrain, region-specific counts of cFos positive cells were obtained.

Results

Cytokine upregulation occurred at 72 hours but not at 24 hpi. Brain region analysis showed neuronal suppression occurred as early as 24 hours in the cortex and other regions. By reactivating influenza infection responsive neurons, it is possible to examine whether this neural activity drives microglial changes. Future experiments will directly manipulate PNECs to determine how their signaling impacts the response to PR8 infection.

Conclusion

Brain activity is rapidly altered in a region specific manner during the acute phase of influenza infection. It is possible that vagal signals from the lung are influencing this activity prior to robust cytokine upregulation.

3.6 Complement system: A possible link between neonatal status epilepticus and behavioral deficits in mice.

Danielle Santana Coelho[a], David A. Narvaiz[a], Srikhar Chilukuri[a], Joaquin N. Lugo[a]
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Introduction

Seizures during the neonatal period can have deleterious consequences on brain development leading to behavioral deficits later in life. The mechanisms by which neonatal seizures disrupt neurodevelopment are unclear. Synaptic pruning is an important developmental process that can be altered in developmental disorders such as autism spectrum disorder and schizophrenia. The pruning of synapses occurs during development in synapses that are tagged by the complement proteins C1q and C3. These complement proteins are increased in response to status epilepticus (SE) in adult rodents. Thus, we hypothesize that neonatal SE leads to the upregulation of the complement system. This increase in complement signaling can alter synaptic pruning and lead to behavioral deficits later in life.

Method

Mice were treated with 2 mg/kg kainic acid intraperitoneally at postnatal day 10 to induce SE. Following SE, hippocampal microglial activation was assessed at 1- 5 days, 2 weeks, and 1 month after SE using flow cytometry to quantify MHCII+ myeloid cells. Expression and levels of the complement system proteins C1q, C3, and C4 were measured at 1 day, 2 days, and 2 weeks after SE.

Results

Microglial activation was increased by SE with the highest activation occurring at one- and two-days post-SE. C4 expression was decreased one day after SE, and increased in females 2 weeks after SE. C3 and C1q expression and protein levels were not altered at the time points we measured.

Conclusion

Microglial activation and complement system expression was altered after SE in a time-dependent manner.

3.7 The cortisol awakening response: A switch for diurnal Th1/Th2 rhythms?

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Introduction

Immune system activity is subject to diurnal rhythms that appear to be regulated by circadian variations in cortisol. Particularly, it has been proposed that the steep cortisol increase upon awakening (cortisol awakening response, CAR) is associated with a switch from Th1 to Th2 activity. In this project we aim to evaluate the influence nightly Th1 immune activation has on the CAR in the morning.

Method

To do so, for 30 days, 10 subjects will collect their entire urine overnight, including the first morning sample, to determine neopterin levels (HPLC). Further, they collect three saliva samples at 0-, 30- and 45-minutes post-awakening to determine cortisol levels and the CAR. A common source of error in CAR estimations is delayed sampling by the probands, thus, the probands wear an EEG-headband during the night to quantify the lag between actual awakening and first saliva sampling.

Results

So far, the collections of two subjects are finished (total of 60 sampling days). In this preliminary data, we found a significant positive correlation between nightly neopterin levels and the cortisol awakening response, i.e. a high Th1 activation overnight was associated with a stronger CAR the following morning.

Conclusion

If the CAR plays a role in the regulation of diurnal immune activation, it may have implications on the interpretation of its use as a measure of HPA axis activity. However, before firm conclusions can be drawn, the results need to be replicated in more subjects.

3.8 The walking sick: what predicts the detection of walking sick individuals?

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Background

Humans can detect sick individuals from various cues, such as body odors and facial appearance. We have recently demonstrated that walking sick individuals can also be detected solely from their walking pattern. Here, we investigate which factors that may predict this detection.

Methods

In two studies, raters watched video recordings and point-light displays (i.e. dots depicting the body joints) of walking individuals who were either experimentally sick (after injection with lipopolysaccharide at 2.0 ng/kg bw) or healthy (after a placebo injection). In study 1, 106 raters classified each walking individual as either sick or healthy. In study 2, 106 other raters graded health of the stimuli on a visual analogue scale. We assessed the predicting effect on sickness detection (study 1) and apparent health (study 2) of walking parameters and sickness responses.

Results

In study 1, shorter steps was the only predictor of the detection of sick individuals from video recordings ($B=0.712(0.257)$, $p=0.02$). In the point-light displays, slower, wider, stiffer and shorter steps, all predicted a better sickness detection ($B=0.0003(0.0001)-0.415(0.126)$, $p<0.05$).

In study 2, lipopolysaccharide-induced slower, shorter and stiffer steps ($B=5.214(1.888)-6.385(2.083)$, $p<0.01$), as well as higher interleukin-6 concentrations ($B=0.051(0.020)$, $p=0.01$), predicted worse health ratings of sick individuals in the video recordings. In the point-light displays, lipopolysaccharide-induced slower, shorter and stiffer steps, and more head tilting, predicted worse health ratings of sick individuals ($B=4.185(1.892)- 6.701(2.092)$, $p<0.05$).

Conclusion

The results imply that specific changes in walking parameters may aid in sickness detection, possibly regulating approach-avoidance behaviors towards sick peers.

PNIRS
PsychoNeuroImmunology
Research Society

Friday, 24 February 2023 Schedule

Sign in to Zoom by 14:55 GMT!			
15:00-15:05 GMT	Introduction/Move to Breakout Rooms (Main Zoom Room)		
15:05-17:00 GMT	**CNS Disorders & Immune Profiling**	**Immune-Brain Communication/Immune Challenge**	**Nutrition/Gut-Brain/Drug Use**
17:00-17:30 GMT	**Transition to Networking Breakout Rooms**		

4 - CNS Disorders & Immune Profiling

Session Chair: Bart Ford
Neil Harrison, Ebrahim Haroon

4.1 Immune signature of multiple sclerosis-associated depression
Jelena Brasanac

4.2 Masked 40Hz light therapy rescues cognitive decline and associated neuropathology in a mouse model of Alzheimer's disease
Madison F Browne

4.3 Comparison of ImageJ-based microglial morphology quantification techniques
Tabitha R.F Green

4.4 Clustering of 237 probands with DSM-IV diagnoses reveals three groups based on immune markers
Jonas Hagenberg

4.5 Complement genes are differentially methylated in the prefrontal cortex of individuals with schizophrenia: a meta-analysis
Carolin Hoffmann

4.6 A Systematic Review and meta-analysis of the Evidence on Inflammation in Depressive Illness and Symptoms in Chronic and End Stage Kidney Disease
Simone Jayakumar

4.7 Temporal stability of circulating and stimulated cytokines among older adults
Molly A. Wright

4.8 Elevated Systemic Inflammation is Associated with Reduced Corticolimbic White Matter Integrity in Depression
Haixia Zheng

5 - Nutrition/Gut-Brain/Drug Use

Session Chairs: Jean-Christophe Delpech, Michael Bailey
Lauren Osborne, Aniko Korosi

5.1 The Central Executive Network Mediates the Relationship Between Post-traumatic Stress Symptom Severity and Gastrointestinal Issues
Kia Howard

5.2 Effects of immunization with Mycobacterium vaccae ATCC 15483, a bacterium with stress resilience properties, on high-fat/high-sugar "Western" diet-induced weight gain, adiposity, neuroinflammation, and behavior in adolescent male mice
Desmond, L.W.

5.3 Peptidoglycan Levels in Healthy Murine Brain Fluctuate with Sleep, Sleep Loss, and Activity Cycles
Erika L. English

5.4 Microglia exosomes participation in brain inflammation and cognitive impairment following omaga-3 deficiency.
Ivan Marnique

5.5 Offspring alterations - induced by a maternal dietary n-3 polyunsaturated fatty acids (PUFAs) deficiency - are partially protected by the genetic restoration of n-3 PUFAs levels during development
Flore Marchaland

5.6 Is Low-Grade Inflammation a Shared Mechanism of Obesity and Depression Development During Adolescence?
Meital Mashash, PhD

5.7 Alcohol Use Disorder is Associated with Enhanced Sensitivity to Cellular LPS Challenge
Elizabeth M. Burnette

5.8 Autophagy-inducer effect as an underlying mechanism for Cannabidiol action on microglia: relevance for its antidepressant-like effect
Adriano M. Chaves-Filho

6 - Immune-Brain Communication/Immune Challenge

Session Chair: Teresa Reyes
Julie Lasselin, Andrew Steelman

6.1 Measuring fetal neuroarchitecture in germ-free mice in response to maternal IL-17A administration.
Izan Chalen

6.2 HIV, SARS-CoV-2 and Methamphetamine Use in Sexual Minority Men
Jennifer V. Chavez

6.3 Toll-like receptor 4 mediates SARS-CoV-2 Spike protein long-term memory impairment
Gabriel G. Fernandes

6.4 SARS-CoV-2 specific sIgA in saliva increases after disease-related video stimulation
Judith K. Keller

6.5 Characteristics of asymptomatic neuroinvasive coronavirus infection in outbred mice
Catherine LaCourse

6.6 Distinct biobehavioral characteristics of low- versus high-grade ovarian carcinoma
Mackenzie Lemieux

6.7 Sleep Deprivation Differentially Alters Physiological Responses to Repeated Stressors
Kirsie R. Lundholm

6.8 Investigation of the glymphatic system as a potential mediator of adverse outcomes following blast trauma and alcohol use
Makenzie C. Patarino

4 - CNS Disorders & Immune Profiling

4.1 Immune signature of multiple sclerosis-associated depression

Jelena Brasanac [1], Caren Ramien [2], Stefanie Gamradt [3], Aline Taenzer [3], Laura Glau [4], Kristin Ritter [3], Kostas Patas [5], Agorastos Agorastos [6], Klaus Wiedemann [7], Cüneyt Demiralay [7], Felix Fischer [8], Christian Otte [3], Judith Bellmann-Strobl [9], Manuel A Friese [2], Eva Tolosa [4], Friedemann Paul [9], Christoph Heesen [2], Martin Weygandt [9], Stefan M Gold [10]

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Introduction

Multiple neurobiological pathways have been implicated in the pathobiology of major depressive disorder (MDD). The identification of reliable biological substrates across the entire MDD spectrum, however, is hampered by a vast heterogeneity in the clinical presentation, presumably as a consequence of heterogeneous pathobiology. One way to overcome this limitation could be to explore disease subtypes based on biological similarity such as "inflammatory depression". As such a subtype may be particularly enriched in depressed patients with an underlying inflammatory condition, multiple sclerosis (MS) could provide an informative disease context for this approach. Few studies have explored immune markers of MS-associated depression and replications are missing.

Method

We performed immunophenotyping by flow cytometry in two independent case-control studies on immune signatures of MS-associated depression, conducted at two different academic MS centers with an overall sample size of n = 132.

Result

Using a stepwise data-driven approach, we identified $CD4^{+}CCR7^{low}T_{CM}$ cell frequencies as a robust correlate of depression in MS. This signature was associated with core symptoms of depression and depression severity (but not MS severity per se) and linked to neuroinflammation as determined by

magnetic resonance imaging (MRI). Furthermore, exploratory analyses of T cell polarization revealed this was largely driven by cells with a T_H1-like phenotype.

Conclusion

Our findings suggest (neuro)immune pathways linked to affective symptoms of autoimmune disorders such as MS, with potential relevance for the understanding of "inflammatory" subtypes of depression.

4.2 Masked 40Hz light therapy rescues cognitive decline and associated neuropathology in a mouse model of Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is one of the greatest global unmet medical needs, but the development of effective therapies has proven challenging. Gamma oscillations (20-50Hz), indicative of coordinated hippocampal and cortical neuronal firing required for healthy cognition, are dampened with AD, suggesting network-wide desynchrony. Recent findings revealed that visual stimulation with 40Hz light enhances hippocampal gamma rhythmicity and improves cognition and microglial phagocytosis of extracellular amyloid-beta plaques. However, 40Hz white-light stimulation is stroboscopic and has potential side effects of administration (i.e., migraine, seizures) in vulnerable individuals.

Method

Our group developed a novel lighting device that produces 40-Hz 'invisible' spectral flicker (ISF) that appears as static white light by presenting two color-matched light sources in antiphase. We first confirmed that ISF lighting produced a robust 40Hz cortical response comparable to stroboscopic light. We then we exposed 5-month-old 5XFAD and WT mice to 1 h a day of ISF light, stroboscopic light, or static light for one month.

Result

Chronic treatment with 40Hz ISF light induces comparable plaque clearance, preservation of cognition, and neuroimmune modulation to that of 40Hz stroboscopic lighting. We also observed reduced plaque load and increased gliosis and microglial clustering around plaques, mirroring improvements to cognition and flexibility behavior. Additionally, both 40Hz treatments preserve extracellular matrices that selectively stabilize parvalbumin inhibitory interneuron synapses critical for the generation of 40Hz rhythms.

Conclusion

These findings not only enhance our understanding of neuroinflammation and cognitive decline in AD, but also provide foundational preclinical data for comfortable, non-invasive treatment of AD.

4.3 Comparison of ImageJ-based microglial morphology quantification techniques

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Introduction

Microglial morphology is often used to measure neuroinflammation and pathology. For reliable inference, it is critical that microglial morphology is accurately quantified and that results can be easily interpreted and compared across studies and laboratories. The process through which microglial morphology is quantified is a key methodological choice and little is known about how this choice may bias conclusions.

Method

We used hierarchical generalized linear mixed models to compare five common ImageJ-based methods for quantifying microglial morphology, which allowed for direct comparisons of results generated using these methods. Using Ionized calcium-binding adapter molecule 1 (Iba1) stained sections from mice with manipulated microglia and controls, we compared percent coverage/stain intensity of Iba1, and full photomicrograph skeletal analysis (average number of branches, branch endpoints, and branch length among cells per photomicrograph). Additionally, we used three techniques that quantify microglial ramification at the single cell level. Fractal analysis was used to quantify the spatial complexity of the individually isolated microglia. Single cell skeletal analysis was used to quantify microglial ramification and cell body size. Sholl analysis, which uses intercepts on concentric circles around the cell body, was applied to determine the extent of microglial branching.

Result

We found a lack of comparability across methods that analyzed full photomicrographs, with significant discrepancies in results among the five methods. We found that single cell skeletal analysis had larger effect sizes than the other methods tested.

Conclusion

We conclude that combinations of quantitative methods to analyze microglial morphology may give the most biologically accurate representation.

4.4 Clustering of 237 probands with DSM-IV diagnoses reveals three groups based on immune markers

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Introduction

In the last years, it was shown that a part of depressed patients has low grade inflammation. However, studies with deep phenotyping, an extensive cytokine panel and multiomics measurements to better characterize subgroups are missing.

Method

237 probands from two inhouse studies with a diagnosis according to the Composite International Diagnostic Interview (depression, dysthymia, panic disorder, phobia, post-traumatic stress disorder, generalised anxiety disorder, obsessive compulsive disorder, bipolar disorder or substance dependency) were selected. A cytokine panel with 43 cytokines and RNA expression was measured in blood. The probands were clustered based on the cytokine and RNA expression data corrected for age, sex and body mass index.

Result

The clustering leads to a three cluster solution. The most important variables are the gene expression data showing distinct patterns across the clusters, whereas the cytokines are only weakly separated by the clusters. However, we do not find differences in the Beck Depression Inventory II between the clusters.

Clustering on the cytokine data alone leads to a two cluster solution, where one cluster has higher cytokine levels than the other. The most important cytokines are IL-7 and TNF-alpha, while CRP and IL-6 are not well separated between the clusters.

Conclusion

We do not find that the previously described cytokines CRP and IL-6 are important for separating clusters of probands. Also, the gene expression data seem to contain additional information not included in the cytokine data. In a next step, we plan to analyze the patterns in the gene expression data.

4.5 Complement genes are differentially methylated in the prefrontal cortex of individuals with schizophrenia: a meta-analysis

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Introduction

Schizophrenia is considered a neurodevelopmental disorder with elusive etiology. Genes from the complement system, i.e. C4 and CSMD1 have been associated with schizophrenia. Several complement genes have been identified as risk locus and/or are differentially expressed in blood and brain of patients. The complement system is traditionally known for its function in innate and adaptive immune responses, but several components are also implicated in neurogenesis, from embryo until adulthood, neuronal migration and synaptic pruning. Whether epigenetic mechanisms play a role in regulating complement genes in Schizophrenia is not yet known.

Method

We identified open-source data from whole-genome methylation analysis using the 450k Illumina platform and tissue from the prefrontal cortex of individuals with schizophrenia (GSE61107, GSE61380, GSE61431, GSE74193, and Viana et al. doi: 10.1093/hmg/ddw373). Normalized and pre-processed beta values or summary statistics were extracted and CpGs within the HGNC curated complement gene-set (N=56) were selected. Differentially methylation positions (DMPs) within complement genes were determined by estimating surrogate variables and performing linear regression for each study, followed by meta-analysis.

Result

A meta-analysis of DMPs revealed that 54 CpGs within 16 complement genes are differentially methylated in schizophrenia. Nine of these genes are known to be risk genes for Schizophrenia (GWAS-locus). Four of these genes were found to be also differentially methylated during fetal brain development.

Conclusion

We report for the first time that methylation of complement genes is altered in individuals with Schizophrenia. It remains to determine genetic and environmental drivers acting on regulating these complement genes.

4.6 A Systematic Review and meta-analysis of the Evidence on Inflammation in Depressive Illness and Symptoms in Chronic and End Stage Kidney Disease

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Introduction

Depression affects approximately 27% of adults with chronic kidney disease (CKD) and End Stage Kidney Failure (ESKF). Depression in this population is associated with impaired quality of life and increased mortality. The extent of inflammation and the impact on depression in CKD/ESKF is yet to be established. Through a systematic literature review and meta-analysis, we aim to understand the relationship between depression and inflammation in CKD/ESKF patients.

Method

We searched nine electronic databases for published studies up to January 2022. Titles and abstracts were screened against an inclusion and exclusion criteria. Data extraction and study quality assessment was carried out independently by two reviewers. A meta-analysis was carried out where appropriate, otherwise a narrative review of studies was completed.

Result

Sixty studies met our inclusion criteria and entered the review (9481 patients included in meta-analysis). Meta-analysis of cross-sectional associations revealed significantly higher levels of pro-inflammatory biomarkers; C-reactive protein (CRP); Interleukin 6 (IL-6) and Tumor necrosis factor alpha (TNF-a) in patients with depressive symptoms (DS) compared to patients without DS. Significantly lower levels of anti-inflammatory cytokine Interleukin 10 (IL-10) were found in patients with DS compared to patients without DS. Considerable heterogeneity was detected in the analysis for most inflammatory markers.

Conclusion

We found evidence for an association of higher levels of pro-inflammatory and lower anti-inflammatory cytokines and DS in patients with CKD/KF. Clinical trials are needed to investigate whether anti-inflammatory therapies will be effective in the prevention and treatment of DS in these patients with multiple comorbidities.

4.7 Temporal stability of circulating and stimulated cytokines among older adults

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Introduction

Circulating and stimulated cytokines are often utilized as markers of overall inflammation status. However, the temporal stability of such measures in older adults is not well understood.

Method

The present study examined the stability of circulating and stimulated cytokines in a sample of 227 older adults (aged 70 to 90 years, M=76.7) between two blood draws spaced approximately two weeks apart. Intraclass correlation coefficients (ICCs) obtained from linear mixed models (controlling for days between measurements, age, gender) were calculated as a measure of temporal stability (reliability) for a panel of circulating and lipopolysaccharide (LPS)-stimulated cytokines (interleukin [IL]-1β, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-alpha [TNF-α]). Sensitivity analyses were employed that re-examined ICCs in individuals reporting high vs. low subjective health (determined by the PROMIS physical functioning scale).

Result

A composite measure of circulating cytokines exhibited strong reliability (ICC: 0.854), with individual cytokines exhibiting moderate (>0.5) to very high reliability (>0.9). The stimulated cytokine composite had moderate reliability (ICC: 0.552), with individual cytokines having low (<0.5) to moderate reliability. Considerably lower reliability was seen for the stimulated composite measure for individuals with low (ICC: 0.457) vs. high (ICC: 0.631) subjective health; this difference was most pronounced for TNF-α and IL-6.

Conclusion

Across two weeks in older adults, circulating cytokines had moderate to excellent stability whereas stimulated cytokines exhibited relatively low stability. Individuals with lower subjective health exhibited the greatest variability in stimulated cytokines, suggesting that higher fluctuation in inflammatory responsivity may reflect suboptimal health in older adults.

4.8 Elevated Systemic Inflammation is Associated with Reduced Corticolimbic White Matter Integrity in Depression

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Introduction

Growing evidence indicates that inflammation can induce neural circuit dysfunction and plays a vital role in the pathogenesis of major depressive disorder (MDD). Nevertheless, whether inflammation affects the integrity of white matter pathways is only beginning to be explored.

Method

We computed quantitative anisotropy (QA) from diffusion magnetic resonance imaging as an index of white matter integrity and regressed QA on C-reactive protein (CRP), controlling for age, sex, and BMI, in 176 participants with MDD.

Result

The QA values of several white matter tracts were negatively correlated with CRP concentration (standardized beta coefficient = −0.22, 95%CI = −0.38–−0.06, FDR < 0.05). These tracts included the bilateral cortico-striatal tracts, thalamic radiations, inferior longitudinal fasciculi, corpus callosum (the forceps minor portion and the tapetum portion), cingulum bundles, and the left superior longitudinal fasciculus III. Importantly, the association remained robust after regressing up to twelve potential confounders. The bilateral fornix and a small portion of the thalamic radiationshowed a positive association with CRP levels, but these associations did not remain significant after adjusting for confounders.

Conclusion

Peripheral inflammation may contribute to the etiology of MDD by impacting the microstructural integrity of brain corticolimbic white matter pathways.

5 - Nutrition/Gut-Brain/Drug Use

5.1 The Central Executive Network Mediates the Relationship Between Post-traumatic Stress Symptom Severity and Gastrointestinal Issues

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Introduction

Although the majority of adults experience at least one traumatic event in their lifetime, a smaller proportion go on to be diagnosed with post-traumatic stress (PTS) disorder. Studies show PTS disorder diagnoses are associated with a higher propensity to develop gastrointestinal (GI) disorders. However, the extent to which subclinical reports of PTS correspond to the incidence of GI disease is unclear. This paper aims to explore whether and how frontal lobe function may mitigate the allostatic effects of stress exposure on GI complaints in non-clinical populations.

Method

Data were acquired from the Enhanced Nathan Kline Institute-Rockland Sample. Data collection involved self-reported medical history, neuropsychological assessments, and resting-state fMRI. GI issues were indexed by endorsement of current GI complaints. PTS was measured using the Trauma Symptom Checklist-40 (TSC-40).

Result

A total of 378 individuals were included. TSC-40 was positively associated with GI disorders, b=-.038, SE=.009, p<.001. The interaction between TSC-40 scores and resting-state functional connectivity (rsFC) of the central executive network (CEN) was significant on total count of GI issues after controlling for demographic, cardiometabolic and immune measures, b=-.031, SE=.016, p<.05.

Conclusion

Greater connectivity within the CEN was associated with lower association between TSC-40 scores and GI issues. Inversely, below average CEN rsFC was associated with a stronger effect for PTS on GI issues. Our findings suggest that that greater resting state connectivity of the CEN may mitigate downstream stress reactivity processes that contribute to gut dysbiosis and GI complaints.

5.2 Effects of immunization with Mycobacterium vaccae ATCC 15483, a bacterium with stress resilience properties, on high-fat/high-sugar "Western" diet-induced weight gain, adiposity, neuroinflammation, and behavior in adolescent male mice

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Introduction

Evidence suggests that inflammation and the prevalence of stress-related psychiatric disorders are increasing in modern urban societies. A possible explanation for the rise of inflammation in modern urban societies is the lack of exposure to certain immunoregulatory microbes, "Old Friends," that humans have coevolved with. In this study we investigated the effects of an "Old Friend", *Mycobacterium vaccae* , with anti-inflammatory, immunoregulatory, and stress resilience properties, on "Western-style" diet-induced weight gain, adiposity, neuroinflammation, and behavior in.

Method

Mice were randomly divided into either a Western diet group (*N* = 24) or a control diet group (*N* = 24). Within these groups, mice received a subcutaneous injection of *M. vaccae* ATCC 15483 (s.c., 0.1 mg in 0.1 ml sterile borate-buffered vehicle, weekly starting on day –77 and ending on day –7) or vehicle, resulting in a 2 x 2 design with *n* = 12 per group. Mice were assessed in the elevated plus-maze (EPM) on day 3 and euthanized on day 4 for assessment of adiposity and collection of tissues.

Result

Exposure to a Western diet resulted in increased body weight gain, visceral adiposity, and increased anxiety-like behavior in the EPM. Immunization with *M. vaccae* ATCC 15483 prevented Western diet-induced body weight gain and visceral adiposity. In addition, *M. vaccae* ATCC 15483 had a main effect to decrease anxiety-like defensive behavioral responses in the EPM.

Conclusion

These data support the hypothesis that *M. vaccae* has potential for protection against adverse outcomes associated with exposure to a Western diet.

5.3 Peptidoglycan Levels in Healthy Murine Brain Fluctuate with Sleep, Sleep Loss, and Activity Cycles

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Introduction

Microbiomes influence host physiology. Host behavioral changes, including altered sleep, can perturb the microbiome and associated circulating bacterial products. Bacterial product detection via host pattern recognition receptors induces inflammatory and sleep regulatory cytokines. Bacterial cell wall peptidoglycan (PG) and its muramyl peptide (MP) constituents are extensively characterized sleep promoting substances and found in healthy murine brain. A quantitative description of brain PG/MPs is lacking as is whether brain PG changes with sleep.

Method

WT mice acclimated to standard lab conditions were euthanized at times corresponding to the light to dark transition, peak rest and activity, and mid-way through the rest period, *i.e.,* at Zeitgeber time (ZT) 3, ZT6, ZT12, and ZT15. Additional groups were euthanized at ZT3 and ZT15 following 3h of sleep deprivation (SD). A non-invasive PiezoSleep system recorded sleep.

Result

Compared to control mice, sleep increased following SD from ZT0-3, but not following ZT12-15. Brain stem (BS), hypothalamus (HT), somatosensory cortex (Sctx), and olfactory bulb (OB) PG levels were determined (as ng PG per mg tissue) using a commercial ELISA. In all brain areas PG levels varied with time of day and were lowest at ZT12. Control PG values for BS (8.6), HT (3.6), and Sctx (3.7) were altered with SD from ZT0-3. BS and HT PG (7.5 and 3.0) decreased significantly ($p < 0.05$) while Sctx PG (4.8) increased significantly ($p < 0.01$).

Conclusion

We conclude, PG in healthy murine brain fluctuates with rest and activity and is altered with SD. These data suggest symbiotic microbe-host interactions influence host neurobiology.

5.4 Microglia exosomes participation in brain inflammation and cognitive impairment following omaga-3 deficiency.

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Introduction

Western diet is shown to have a decrease in omega-3 polyunsaturated fatty acids (n3-PUFAs) intake. A deficit in n-3-PUFAs is linked with an alteration of microglia towards an inflammatory phenotype and a memory deficit in mice. In the past decades, exosomes got increasing shred of interest. Those small cargos of 40-110 nm allow them to be studied within the brain but also in the blood. They contain lipids, protein, mRNA, micro-RNA; are part of the extracellular vesicles family and participate to cell-to-cell communications in a targeted way. Interestingly, microglia exosomes participate in the spreading of inflammation but also to some neurodegenerative diseases such as Alzheimer or Parkinson.

Method

The aim of this study is to understand the implication of microglial exosomes in the effect of n-3 PUFAs deficiency on cognitive decline and neurodegeneration in adult mice. To do so, the first part of the project assesses memory and emotional behaviour in n-3 PUFAs deficient adult mice of 3 months followed by electrophysiological recording in the hippocampus.

Result

Our characterization confirm the impact of the n-3 PUFAs deficiency on spatial memory and emotional alteration in n-3 PUFAs deficiency. Moreover, intrinsic and/or extrinsic excitability properties in the pyramidal neuron of the CA1 in the hippocampus are altered.

Conclusion

By the characterization of brain inflammation impact on cognition and microglia exosomes found in blood, we are looking for new biomarkers present in those exosomes to predict the cognitive and inflammation stage of the subject.

5.5 Offspring alterations - induced by a maternal dietary n-3 polyunsaturated fatty acids (PUFAs) deficiency - are partially protected by the genetic restoration of n-3 PUFAs levels during development

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Introduction

N-3 PUFA are essential fatty acids brought exclusively by the mother to the developing brain. Recent changes in dietary habits led to a reduction in n-3 PUFA intake with an increase in n-6 PUFA intake. Several studies, including ours, highlighted the deleterious effects of a maternal dietary deficiency in n-3 PUFA on the offspring brain development: it has been shown to alter synaptic refinement, neuritogenesis, and neurotransmission, leading to the emergence of neurodevelopmental disorders. Notably, we showed that it disrupts the activity of the offspring brain microglia, a key regulator of brain homeostasis and neural networks formation, associated with neural circuits establishment alterations and hippocampo-dependent memory deficits.

Herein, we aim to determine whether increasing n-3 PUFA levels in the developing brain can protect against the deleterious effects induced by a maternal n-3 PUFA deficient diet.

Method

To do so, we use transgenic fat-1 mice allowing the *in vivo* conversion of n-6 PUFA into n-3 PUFA. We use fat-1 mice pups from wild-type mother fed with a n-3 PUFA deficient diet to allow the preservation of n-3 PUFA levels in a n-3 PUFA deficiency environment.

Result

Our first results show an increase of cerebral n-3 PUFA in the offspring and an improvement of hippocampal-dependent working memory abilities. We are currently exploring microglia phenotypes and functions.

Conclusion

These results highlight the key role of n-3 PUFA during development and pave the way for microglial contribution during this critical life period.

5.6 Is Low-Grade Inflammation a Shared Mechanism of Obesity and Depression Development During Adolescence?

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Introduction

Depression and obesity frequently co-occur, yet, the casual mechanisms are poorly understood. Research with adults suggests low-grade inflammation as a potential shared mechanism. However, few studies examined this hypothesis in a prospective longitudinal manner in younger populations, and existing findings are inconsistent.

Method

We examined bidirectional associations between adiposity, inflammation, and depressive symptoms from pre-adolescence to early adulthood (at ages 9, 15, 17, and 24) using data from ALSPAC (*N*=6,558). Fat Mass Index (FMI) was used to measure general adiposity. C-reactive protein (CRP) was used as a marker of systemic inflammation. Depressive symptoms were assessed by the Short Mood and Feelings Questionnaire.

Result

Findings from a 3-level, 4-wave cross-lagged analysis revealed concurrent and longitudinal positive associations between FMI and CRP across all waves, demonstrating that adiposity is a robust predictor of CRP during adolescence. Subsequent multiple groups comparison analysis indicated that preadolescents with elevated depressive symptoms may be at greater risk for increasing adiposity, and for girls, increasing inflammation, in the transition into adolescence. Null and inverse associations were found between CRP and depression at different points in development.

Conclusion

These findings demonstrate that the mechanisms underlying the link between adiposity, inflammation, and depression differ in adolescents compared to adults. There is no evidence that systemic inflammation increases the risk for obesity and depression during adolescence; instead, adiposity appears to drive later inflammation, and both seem to be consequences rather than antecedents of adolescent-onset depression. Further research is needed to elucidate when, how, and for whom these associations emerge.

5.7 Alcohol Use Disorder is Associated with Enhanced Sensitivity to Cellular LPS Challenge

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Introduction

Inflammation is implicated in alcohol use disorder (AUD). A novel method to characterize AUD-related immune signaling is by probing monocyte production of intracellular cytokines (ICCs) after *in vitro* stimulation with lipopolysaccharide (LPS). This study evaluated relationships between alcohol use and monocyte ICC production following LPS challenge.

Method

Blood samples from 36 participants (AUD N=14; Controls N=22), collected across five timepoints, were assessed for monocyte ICC expression at baseline and after LPS challenge (10 repeated measures/participant). Markers of interest included tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interferon (IFN). For each marker, a linear mixed model was constructed with AUD status and LPS stimulation status as fixed effects (BMI and timepoint as covariates), allowing for random slope and intercept. Alcohol x stimulation was included as an interaction term.

Result

For TNF-α, alcohol, stimulation, and alcohol x stimulation effects were seen (i.e. individuals with AUD had greater baseline TNF-α levels and were more responsive to LPS stimulation). While no alcohol or alcohol x stimulation effects were seen for IL-6 expression, alcohol, stimulation, and interaction effects were observed in TNF-α and IL-6 co-expressing monocytes, driven by the effects from the TNF-α model. Similar alcohol, stimulation, and alcohol x stimulation interaction effects were found for IFN levels.

Conclusion

Results indicate that AUD is associated with enhanced sensitivity to LPS challenge. This finding is supported by studies showing that alcohol dependence promotes systemic IFN response in mice, and that chronic alcohol consumption increases plasma TNF-α levels in rodents and humans.

5.8 Autophagy-inducer effect as an underlying mechanism for Cannabidiol action on microglia: relevance for its antidepressant-like effect

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Introduction

Cannabidiol (CBD) is a non-euphoric component of *Cannabis sativa*. Abnormal inflammation is recognized as a contributing factor to depression, and autophagy is a key mechanism for microglia anti-inflammatory polarization. This study aimed to investigate the role of (macro)-autophagy for CBD effects in microglia, and its influences on CBD antidepressant-like action.

Method

Human microglia HMC3 were exposed to lipopolysaccharide (LPS, 0.1 µg/mL) and treated with CBD (1,10 and 100 µM) for 24 hours. Hydroxychloroquine (HCQ) 10 µM was used as autophagy inhibitor. Nitrite, cytokines, autophagy-related genes (ATGs), LC3BI-II conversion and the formation of acidic vesicles (AVOS) were determined through immunoassays, real-time PCR, western blot and flow-cytometry. Mice were injected with LPS (0.5 mg/kg,IP), and 24 hours later, with CBD (10 mg/kg, IP) with or without HCQ (100 mg/kg).

Result

CBD rescued LPS-induced increase in nitrite, TNFα and IL-1β ($P<0.001$) and restored IL-4 ($P<0.05$). HCQ diminished CBD effect in TNFα and IL-4 ($P<0.01$). CBD increased the % of AVOS, which was blocked by HCQ ($P<0.05$). CBD showed a non-significant tendency to increase LC3BII ($P=0.1154$). CBD increased the ATG12 and p62 mRNA compared to LPS ($P<0.05$). In mice, CBD reduced the latency to grooming ($P<0.05$) and increased the grooming duration ($P<0.05$) compared to LPS. CBD reduced the feeding latency compared to LPS ($P<0.01$). HCQ blocked these CBD effects ($P<0.05$).

Conclusion

This study demonstrates the participation of autophagy in CBD action on microglia and for its antidepressant-like effect. Autophagy-inducers can be promising strategies for neuroinflammatory disorders, such as depression.

6 - Immune-Brain Communication/Immune Challenge

6.1 Measuring fetal neuroarchitecture in germ-free mice in response to maternal IL-17A administration.

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Introduction

Infection-induced maternal immune activation (MIA) during pregnancy has been linked to neurodevelopmental disorders in the offspring. Through epidemiological data and animal models, it has been established that schizophrenia and autism are among the primary psychiatric disorders associated with MIA. The molecular pathways responsible for pathogenic abnormalities in the developing brain are still unclear. Some have suggested strong links between the maternal IL-17A pathway and the development of autism-like phenotypes in the offspring. It is important to consider that IL-17A is linked to the maternal microbiota, and that maternal microbial metabolites can also impact prenatal neurodevelopment. Whether IL-17A alone is capable of causing fetal brain abnormalities in the absence of microbes has not been determined.

Method

Pregnant germ-free mice were sterilely injected with either recombinant mouse IL-17A or vehicle daily during gestational day (GD)10.5 through GD15.4, with sacrifice performed on GD16.5. Fetuses were collected and fixed in 10% neutral buffered formalin. Fetal brains were sectioned coronally and immunohistochemically stained for cortical layer development and structure.

Result

Mapping of cortical layer development and structure, via expression of transcription factors CTIP2, SATB2, and TBR1, is ongoing.

Conclusion

These data will help disentangle the effects of IL-17A production from those of maternal microbial disruption on fetal neurodevelopment trajectories.

6.2 HIV, SARS-CoV-2 and Methamphetamine Use in Sexual Minority Men

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Introduction

People diagnosed with HIV who are treated with ART have a life expectancy approaching that of the general population. However, there is residual immune dysregulation and inflammation that can be further complicated by SARS-CoV-2 infection and methamphetamine use.

Method

Banked peripheral blood mononuclear cell (PBMC) samples from 65 sexual minority men (SMM) recruited through the COVID-19 Research for Understanding Substance Use and HIV (CRUSH) cohort will be assessed via flow cytometry to identify distinct profiles of T-cell activation (CD8+38+, CD45, CD25, HLA-DR+), and exhaustion (PD-1, CTLA-4, TIM-3, LAG-3, TIGIT) among SMM with HIV, METH users and those with evidence of recent SARS-CoV-2 infection.

Result

Characterization of the distinct and additive effects of HIV, METH use and SARS-CoV-2 on T-cell activation and exhaustion will elucidate more specific targets for pharmacologic interventions to mitigate the deleterious immunologic consequences of these intersecting epidemics. We anticipate that greater immune dysregulation will be observed in individuals affected by these 3 intersecting epidemics (HIV, METH use and SARS-CoV-2 infection).

Conclusion

Upregulated T-cell activation and exhaustion can accelerate cellular aging and upregulate transcription factors associated with HIV persistence, amplifying risk for clinical HIV progression. Expanded efforts are needed to identify potentially modifiable biological and behavioral factors that could be targeted to alter T-cell activation and exhaustion in people with HIV.

6.3 Toll-like receptor 4 mediates SARS-CoV-2 Spike protein long-term memory impairment

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Introduction

Although initially described as a respiratory disease, the coronavirus disease 19 (COVID-19) is now recognized to affect multiple organs, including the brain. Regarding the latter, several reports pointed out that SARS-CoV-2 (etiological agent of COVID-19) infection may predispose to develop neuropsychiatric disorders, such as anxiety, depression and cognitive impairment. In this direction, our lab has made efforts in order to better understand the long-term effects induced by SARS-CoV-2 spike protein, the main protein involved in viral infection, in the brain. We observed that intracerebroventricular administration of Spike protein induces long-term memory impairment, accompanied by microgliosis, synapse losses through microglial pruning and neuroinflammation.

Method

To further comprehend the mechanism involved in the aforementioned observations, we applied pharmacological (TAK-242, 2mg/kg, i.p. 7 days) and genetic (TLR4 KO mice) tools in order to address the involvement of toll-like receptor 4 (TLR4) on long-term behavioral and neuroplastic abnormalities induced by Spike protein.

Result

In this sense, we observed that the long-term cognitive impairment and neuroplastic alterations previously observed were blocked by the absence of TLR4 signaling. Besides, we also analyze the genotype of individuals that suffered from cognitive impairment following COVID-19, and we observed a higher susceptibility to develop cognitive impairment in individuals carrying a single polymorphism nucleotide that functionally induces an overexpression of TLR4 following Spike protein exposure.

Conclusion

These results provide evidence that strongly suggests that TLR4 mediates Spike protein long-term neurological alterations.

6.4 SARS-CoV-2 specific sIgA in saliva increases after disease-related video stimulation

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Introduction

Secretory immunoglobulin A (sIgA) in saliva is the most important immunoglobulin fighting pathogens in the respiratory tract and may thus play a role in preventing SARS-CoV-2 infections. Previous studies showed that visual perception of disease cues causes an increase in total sIgA in saliva, which suggests a proactive immune response that may also correlate with associated aversive feelings. To gain a better understanding of the plasticity of SARS-CoV-2-specific mucosal antibodies, we investigated this proactive change to visual disease cues in spike- as well as RBD-specific sIgA.

Method

Using a within-subject design, we showed 45 participants either a disease video displaying people with respiratory symptoms resembling realistic situations of increased airborne contagion risk, or a control video of healthy people. Furthermore, we recorded self-reported trait and state feelings of perceived disgust, contagion risk and interoception.

Result

The disease video triggered an increase in spike-specific sIgA, which was absent after the control video. This increase further correlated inversely with revulsion and aversive feelings elicited by the disease video. In contrast, the receptor-binding domain-specific sIgA did not increase after disease stimulation.

Conclusion

The results indicate differential roles of the two salivary antibodies in response to visual predictors of airborne contagion. The observed plasticity of spike-specific salivary antibody release after visual simulation of enhanced contagion risk suggests a role in immune exclusion. Furthermore, the inverse correlation of spike-specific sIgA with self-reported feelings are in line with the hypothesis of a compensatory relationship between behavioral and physiological responses to situations with increased contagion potential.

6.5 Characteristics of asymptomatic neuroinvasive coronavirus infection in outbred mice

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Introduction

We are establishing a model to investigate potential long-term neurological complications resulting from childhood infection with human Coronavirus-OC43 (OC43), a common cause of respiratory infections. Although a majority of children contract OC43 before the age of four, little is known about the long-term effects of infection on neurodevelopment and behavior.

Method

We infected juvenile CD-1 mice with low doses of OC43 to model mild neuroinvasive infection. Four cohorts of male and female mice were inoculated through the natural intranasal route at postnatal day 19 with $3x10^5$ $TCID_{50}$ of OC43 and observed for sickness behavior for up to nine days. At 4- and 9-days post-infection (dpi), two cohorts of mice were euthanized, brains were dissected by region, and viral RNA (vRNA) was extracted and quantified by RT-qPCR. At 13 days, 1 month, and 2 months post-infection, the remaining mice were tested in Open Field.

Result

No sickness behavior or significant weight change was observed. There was evidence of neuroinvasion throughout the olfactory system (olfactory bulb, olfactory tract, piriform cortex) and hippocampus. Females had less vRNA in the olfactory bulb at 9 than 4 dpi, suggesting viral clearance. Males had significantly more vRNA in the olfactory tract than females regardless of day, suggesting heightened susceptibility. Behavioral testing showed no apparent effects of infection on total locomotion, peripheral or central zone locomotion, or rearing.

Conclusion

We have demonstrated neuroinvasion by a coronavirus in an asymptomatic context in outbred mice. These studies provide a tool to model long-term complications of mild infections in young children.

6.6 Distinct biobehavioral characteristics of low- versus high-grade ovarian carcinoma

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Introduction

High-grade (HGOC) and low-grade ovarian carcinoma (LGOC) are distinct malignancies with different biologic pathways, treatment paradigms, and life expectancy. However, differences in quality of life (QOL), sleep, and depressive symptoms have not been examined according to grade, and it is unknown whether inflammatory profiles associated with these symptoms differ between patients with LGOC and HGOC. Here we aim to characterize QOL and inflammatory signatures according to OC grade.

Method

Participants included women with HGOC (N=518) or LGOC (N=81). Prior to surgery or initial treatment, participants completed assessments of psychosocial factors including depressive symptoms, sleep, and QOL, and contributed saliva for cortisol (3 consecutive days) and blood for serum interleukin-6 (IL-6) quantification. Tumor samples were collected intraoperatively to quantify tumor cortisol.

Result

Women with HGOC reported greater vegetative depression (p=0.038) and sleep disturbances (p=0.049), but there was no significant difference in depressive mood (p=0.085) or QOL (p=0.526) compared to those with LGOC, adjusting for age and disease stage. Women with HGOC also showed trends towards higher levels of nocturnal cortisol (p=0.156), tumor cortisol (p=0.078), and serum IL-6 (p=0.352) compared to LGOC, although differences were not significant, likely due to low power.

Conclusion

Here we report unique differences in patient reported outcomes of women with LGOC and HGOC. While differences in biomarkers according to grade were not statistically significant, the observed trends suggest that a more highly powered analysis might reveal differences in inflammatory physiology according to grade in OC and provide a better understanding of potential mechanisms underlying symptom burden.

6.7 Sleep Deprivation Differentially Alters Physiological Responses to Repeated Stressors

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Introduction

Stressful stimuli activate several physiological systems. Sleep deprivation (SD) interferes with these systems, but the mechanisms are poorly understood. We previously demonstrated that SD blunts the sympathetic nervous system (SNS) response to repeated stressors. Using salivary cortisol (sC), we investigated how SD impacts the hypothalamic-pituitary-adrenal (HPA) axis response to repeated stressors.

Method

N=10 healthy adults (ages 28.3±5.78; 5f) completed a 38h in-lab SD study preceded by and followed by 10h sleep opportunities. On days 2 (baseline) and 3 (SD), participants completed two sessions in a high-fidelity shooting simulator with a 30-min break between. During each session, civilian participants verbally de-escalated emergency response scenarios and decided if (simulated) deadly force was necessary for neutralizing assailants. Seven saliva samples were collected each day: pre-stressor, 0-mins, 15-mins, and 30-mins after each session. Samples were assayed using a sC enzyme immunoassay.

Result

Post-simulation samples, normalized to pre-stressor, were analyzed using mixed-effects ANOVA, with fixed effects for day, sample, and their interaction, with a random intercept over subjects. Planned comparisons revealed a significantly blunted sC peak during SD compared to baseline ($t[99]=2.84$, $p=0.006$) following the first session; no sC peak was observed following the second session, regardless of day.

Conclusion

As expected, the sC response to a single stressor was blunted during SD. However, sC continued to decline following exposure to another stressor after a 30-min rest, potentially indicating a HPA axis refractory mechanism. These results demonstrate that the SNS and HPA axis respond differently to repeated acute stressors.

6.8 Investigation of the glymphatic system as a potential mediator of adverse outcomes following blast trauma and alcohol use

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Introduction

Alcohol use disorder (AUD), mild traumatic brain injury (mTBI), and Alzheimer's Disease and related dementias (ADRD) are distinct diagnoses, but are all linked with neuroinflammation. While AUD and mTBI are associated with increased risk of dementia, the potential interaction of mTBI and AUD in the development of ADRD remains understudied. We hypothesize that a possible mechanism for synergistic effects of mTBI and AUD on ADRD is the glymphatic system–which bidirectionally affects neuroinflammation. Glymphatic function is disrupted after mTBI or heavy alcohol use alone, and changes in glymphatic function have been implicated in the development of ADRD. This study investigates how alcohol use after blast-induced mTBI affects ADRD behaviors and neuropathology, and whether these effects are associated with impaired glymphatic clearance.

Method

To model blast-induced mTBI, male mice undergo repetitive (3x) blast or sham exposures using a well-established shock tube. Mice have intermittent access to alcohol in social consumption cages for two distinct 4-week periods post blast exposure. Behavioral outcomes (spatial memory, thermal sensitivity, conditioned aversion, acoustic startle) are assessed at three time points pre/post blast and/or alcohol. Five months post blast, brain metabolism (FDG-PET) and glymphatic function (whole brain clearing/light sheet microscopy) are assessed, brain and blood are collected for cytokine analysis.

Result

While the study is ongoing, initial results show altered drinking patterns and behavioral differences across sham, blast, and alcohol exposed groups.

Conclusion

Completion of the study will reveal new insights about how the glymphatic system affects chronic outcomes after heavy alcohol use following blast-induced mTBI.