NeuroImage 54 (2011) 2557–2562

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Men and women are different: Diffusion tensor imaging reveals sexual dimorphism in the microstructure of the thalamus, corpus callosum and cingulum ☆

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ARTICLE INFO

Article history:
Received 15 July 2010
Revised 4 November 2010
Accepted 8 November 2010
Available online 16 November 2010

Keywords:
Gender
Brain
Sex differences
Structure
Volume
Thalamus
DTI
MRI
Corpus callosum

ABSTRACT

Introduction: Numerous magnetic resonance imaging (MRI) studies have addressed the question of morphological differences of the brain of men and women, reporting conflicting results regarding brain size and the ratio of gray and white matter. In the present study, we used diffusion tensor imaging (DTI) to delineate sex differences of brain white matter.
Methods: We investigated brain microstructure in 25 male and 25 female healthy subjects using a 3 T MRI scanner. Whole-head DTI scans were analyzed without a-priori hypothesis using Tract-Based Spatial Statistics (TBSS) calculating maps of fractional anisotropy (FA), radial diffusivity (RD, a potential marker of glial alteration and changes in myelination) and axial diffusivity (AD, a potential marker of axonal changes).
Results: DTI revealed regional microstructural differences between the brains of male and female subjects. Those were prominent in the thalamus, corpus callosum and cingulum. Men showed significantly ($p<0.0001$) higher values of fractional anisotropy and lower radial diffusivity in these areas, suggesting that the observed differences are mainly due to differences in myelination.
Discussion: As a novel finding we showed widespread differences in thalamic microstructure that have not been described previously. Additionally, the present study confirmed earlier DTI studies focusing on sexual dimorphism in the corpus callosum and cingulum. All changes appear to be based on differences in myelination. The sex differences in thalamic microstructure call for further studies on the underlying cause and the behavioral correlates of this sexual dimorphism.
Future DTI group studies may carefully control for gender to avoid confounding.

Introduction

Neuropathological and MRI studies have shown that brains of men and women significantly differ in absolute brain size (Allen et al., 2003; Ankney, 1992; Cosgrove et al., 2007; Shin et al., 2005), in total gray and white matter volumes (Allen et al., 2003; Gur et al., 1999; Paus et al., 1996) and in the gray/white matter ratio, with women having a higher percentage of gray matter and men of white matter (Allen et al., 2003; Goldstein et al., 2001; Gur et al., 1999).

Diffusion tensor imaging (DTI) is a MRI technique that is used to characterize the microstructure of large white matter tracts in physiological and pathological conditions which has successfully been used to evaluate brain alterations in a range of neurological disorders (Abe et al., 2002; Knake et al., 2010; Unger et al., 2010). The method is based on the measurement of molecular diffusion and its directionality which is influenced by the structure of the surrounding brain tissue. Fractional anisotropy (FA) is an unspecific indicator of alterations in white matter microstructure. It reflects the anisotropy or directionality of the diffusion (Peled et al., 1998), which can be further characterized using the measures axial diffusivity (AD) and radial diffusivity (RD). Axial diffusivity measures the diffusivity along the primary diffusion direction and is assumed to contribute information regarding the integrity of axons (Glenn et al., 2003) or changes in extra-axonal/extracellular space (Beaulieu and Allen, 1994). In contrast, RD represents the diffusivities along directions that are orthogonal to the primary diffusion direction and is assumed to characterize changes associated with myelination or glial cell morphology (Song et al., 2002, 2003, 2005).

The influence of age on DTI measures is well described: A reduction of FA with increasing age was observed (Salat et al.,

☆ Disclosure: The authors report no financial interest or conflicts of interest related to the manuscript.

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doi:10.1016/j.neuroimage.2010.11.029

2005) and studies investigating DTI changes across groups need to carefully account for the influence of age. However, little is known about the effect of sex on DTI measures. Existing studies describe sex differences in predefined, selected Regions of Interest (ROI) like the corpus callosum (Oh et al., 2007; Shin et al., 2005; Westerhausen et al., 2003; Westerhausen et al., 2004), the frontal white matter (Szeszko et al., 2003) or the midcingulum bundle (Huster et al., 2009).

The aim of the present study was to investigate microstructural white matter differences in the brain of male and female subjects using an unbiased hypothesis free automated whole-head analysis approach without a priori selection of regions of interest in order to evaluate the need to account for sex as a stratification factor in future DTI studies.

Subjects and methods

Subject selection

Fifty right-handed healthy subjects, 25 males (mean age 31.8 ± 8.6 years) and 25 females (mean age 31.1 ± 10.6 years) were included in the study. Two additional subjects, one female and one male, were excluded due to artefacts. Exclusion criteria comprised the diagnosis or history of any neurological disease, abnormalities on neurological examination or structural abnormalities on brain MRI as well as a history of any birth complications including preterm birth or hypoxia. None of the subjects showed abnormalities on routine brain MRI after visual inspection. There were no significant age differences between the two groups (two sample *t*-test: $P = 0.86$). All subjects had a high school diploma or a higher educational level. There were no educational differences (χ^2-test: $P = 0.75$). The study was approved by the local IRB. All subjects gave written informed consent to participate in the study.

Methods

Microstructural brain tissue integrity was assessed using DTI measures FA, AD and RD.

MR-imaging

The DTI scans were collected on a 3-T MRI scanner (Trio, Siemens Medical Solutions, Erlangen, Germany), using an eight-channel surface coil. A single shot echo planar imaging with a twice-refocused spin echo pulse sequence, optimized to minimize eddy current-induced image distortions (Reese et al., 2003) was performed on all subjects with the following parameters: TR/TE = 8500/88 ms, Flip Angle = 90°, b = 1000 s mm^2, 128 × 128 × 60 matrix, voxel size 1.9 × 1.9 × 1.9 mm. One T2 b0 image and 30 DWI b1000 images were collected during one scan. To minimize movement artefacts, the head of the subject was firmly fixed with cushions. All images were investigated to be free of motion, ghosting, high frequency and/or wrap-around artefacts at the time of image acquisition.

DTI preprocessing and analysis

Diffusion volumes were motion corrected and averaged using FLIRT (FMRIB's Linear Image Registration Tool; http://www.fmrib.ox.ac.uk/analysis/research/flirt/) with mutual information cost function to register each direction to the minimally eddy current distorted T2-weighted b0 DTI volume that had no diffusion weighting. Eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and Eigenvectors of the diffusion tensor matrix for each voxel were computed from the DTI volumes for each subject on a voxel-by-voxel basis using established reconstruction methods (Basser and Jones, 2002). The tools are included in the FreeSurfer package (FreeSurfer version 4.2.0; http://surfer.nmr.mgh.harvard.edu/).

Fractional anisotropy and diffusivity map calculation

The primary measures acquired from the DTI data were common scalar metrics describing the white matter microstructure. We first calculated FA, which is dependent on the orientational coherence of the diffusion compartments within all voxels using the predefined standard formula (Basser and Jones, 2002). We additionally examined measures of AD (λ_1) and RD ($[\lambda_2 + \lambda_3]/2$) (Budde et al., 2007; Song et al., 2002, 2003). T2 b0 images were obtained using the exact parameters as the diffusion sensitive images except without any diffusion weighting.

Nonlinear registration and tract-based spatial statistics

Voxelwise statistical analysis of the FA data was carried out using TBSS v1.2, part of the FSL data analysis suite (FSL 4.1.2; http://www.fmrib.ox.ac.uk/fsl/). First, the T2 b0 images were processed using the brain extraction tool (BET). Those extracted brains were used to mask the brain on the FA images. All subjects' masked FA data were transformed to the FMRIB 58 brain using the nonlinear registration tool FNIRT, which uses a b-spline representation of the registration warp field, and then transformed to the MNI 152 space. Next, a mean FA image was created and thinned to create a mean FA skeleton which represents the centers of all tracts the group has in common. Each subject's aligned FA data was then projected onto this skeleton. For creating the skeleton we used the thresholds 0.2 and 0.8. Data along the skeleton were smoothed utilizing an anatomical constraint to limit the smoothing to neighboring data within adjacent voxels along the skeleton. For smoothing the neighboring voxels within a cube of 6 mm edge length were used to calculate the mean. The smoothing step was performed using matlab 7.6.0.324, R2008a (MathWorks, Inc.). All analyses were masked to only display regions with FA values of >0.2 as an additional procedure to avoid examination of regions that are likely comprised of multiple tissue types or fiber orientations. The exact transformations derived for the anisotropy maps were applied to the axial and radial diffusivity volumes for matched processing of all image volumes. Regions with altered microstructure were later defined following the Harvard-Oxford Atlas for the MNI 152 brain.

Group analysis

The resulting skeletonized images were fed into voxelwise cross-subject statistics. For the group analysis we used the tool mri-glmfit of the FreeSurfer package. The data was fit into a generalized linear model and an unpaired *t*-test was performed. The resulting data was corrected for multiple comparisons by a permutation-based approach (Nichols and Holmes, 2002). Therefore 12,000 simulations were performed under the null hypothesis; this approach was based on the AFNI null-*z* simulator (AlphaSim; http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim). Last, the data was clustered, we chose a minimum value of $p = 0.01$ for the cluster calculation. To display the results, all figures were made with exactly the same parameters, showing clusters with a significance of $p < 0.01$. The significance was given as the negative decadic logarithm of the *p*-value ($p = 10^{-x}$). A blue–lightblue color spectrum indicated clusters, where the measured value (either FA or RD or AD) was significantly decreased in male as compared to female subjects, whereas the red to yellow color indicated a significant increase of the measured value in males.

Results

Fractional anisotropy

Using whole-head DTI and an analysis without a-priori hypothesis we discovered regional microstructural white matter sex differences in the thalamus: men showing significantly higher FA values in this region ($p < 0.0001$). Additionally, FA was increased in male as compared to female subjects in parts of the corpus callosum and cingulum as well as in the capsula extrema and midbrain ($p < 0.0001$). Results are presented in Tables 1 and 2 and Fig. 1A–C.

Table 1
Brain regions showing clusters with significant differences in FA and RD values in males and females.

Region	Size (mm^3)	Maximum p (10^{-x})	Corrected overall p	X	Y	Z
Regions with significantly increased FA-values in males as compared to females						
Thalamus	3400	7.85	<0.0001	100	112	67
Midbrain (R)	418	3.98	<0.0001	79	114	65
Midbrain (L)	388	5	<0.0001	103	118	63
Capsula extrema (R)	210	4.04	<0.0001	58	118	78
Capsula extrema (L)	297	4.64	<0.0001	117	128	88
Cingulum (R)	125	4.43	<0.0001	81	124	105
Cingulum (L)	210	5.29	<0.0001	98	11	104
Corpus callosum (R)	111	3.28	<0.0001	79	123	102
Corpus callosum (L)	537	5.1	<0.0001	100	113	102
Regions with significantly decreased RD-values males as compared to females						
Thalamus	1409	5.95	<0.0001	85	112	76
Midbrain (R)	172	3.15	<0.0001	79	114	66
Midbrain (L)	330	3.71	<0.0001	104	121	64
Capsula extrema (R)	177	3.42	<0.0001	58	116	77
Capsula extrema (L)	1019	6.13	<0.0001	117	123	90
Cingulum (R)	80	3.52	<0.0001	81	124	106
Cingulum (L)	97	4.66	<0.0001	98	112	104
Corpus callosum (R)	104	2.45	<0.0001	79	123	102
Corpus callosum (L)	594	4.87	<0.0001	101	92	95

The p-values given are clusterwise p-values. Several connected voxels with significant changes were automatically searched and merged into one cluster. The size of each cluster is given in mm^3. X, Y and Z coordinates are presented in MNI space.

Radial and axial diffusivity

Radial diffusivity, the potential marker of myelination, was decreased in male subjects in the areas of altered FA in the thalamus, corpus callosum, cingulum, capsula extrema and midbrain ($p<0.0001$, Tables 1 and 2, Fig. 1D–F). There were no significant sex effects detected by AD, the potential measure of axonal changes.

Table 2
Mean values and standard deviation of the fractional anisotropy and radial diffusivity in regions with significant differences between males and females.

Mean values and standard deviation of the fractional anisotropy				
	Male		Female	
Region	Mean FA	SD FA	Mean FA	SD FA
Thalamus	0.44	0.04	0.40	0.02
Midbrain right	0.64	0.03	0.60	0.03
Midbrain left	0.64	0.03	0.59	0.02
Capsula extrema right	0.42	0.03	0.38	0.03
Capsula extrema left	0.40	0.02	0.37	0.03
Cingulum right	0.66	0.04	0.61	0.04
Cingulum left	0.67	0.03	0.63	0.03
CC right	0.76	0.03	0.73	0.03
CC left	0.72	0.03	0.70	0.02
Mean values and standard deviation of the radial diffusivity				
	Male		Female	
Region	Mean RD	SD RD	Mean RD	SD RD
Thalamus	0.59	0.04	0.64	0.03
Midbrain right	0.38	0.07	0.44	0.05
Midbrain left	0.44	0.05	0.49	0.05
Capsula extrema right	0.64	0.04	0.68	0.04
Capsula extrema left	0.60	0.02	0.64	0.03
Cingulum right	0.39	0.05	0.44	0.05
Cingulum left	0.39	0.04	0.42	0.03
CC right	0.38	0.05	0.42	0.04
CC left	0.39	0.04	0.42	0.03

FA: fractional anisotropy, RD: radial diffusivity in μm^2/ms, SD: standard deviation, CC: corpus callosum.

Discussion

Using a hypothesis-free whole-brain analysis (TBSS) to evaluate differences in white matter microstructure, we found increases in FA and decreases in RD in several white matter regions in men as compared to women including the thalamus bilaterally that have not been described or investigated previously. We further found differences in FA and RD in the corpus callosum and cingulum, confirming results of earlier studies (Westerhausen et al., 2003, 2004). These results suggest differences in the degree of myelination in men versus women and might be related to the higher gray/white matter ratio or less coherent cortico-cortical projections in female subjects (Allen et al., 2003; Goldstein et al., 2001; Gur et al., 1999; Peters et al., 1998; Westerhausen et al., 2003, 2004). The changes in FA were generally more widespread than the changes in RD. This finding might be explained by additional non-significant changes in AD and therefore axonal alterations (Beaulieu and Allen, 1994; Glenn et al., 2003). The observed changes are not due to differences in total brain or white matter volume as TBSS includes only voxels which are part of the white matter in all subjects (common white matter skeleton), thereby avoiding confounders such as differences in volume or total brain size. To the best of our knowledge, this is the first study investigating brain microstructural sex differences using a whole-brain analysis and the hypothesis free analysis approach TBSS.

Animal studies as well as several studies on humans point to an influence of sexual steroids on sexual dimorphism of the brain (Breedlove, 1992; Kawata, 1995), including an association of gray matter volume with hormone levels of testosterone, estrogen or progesterone (Witte et al., 2010) or acceleration of myelination caused by estrogens in the immature rat brain (Prayer et al., 1997). Estrogen and testosterone receptors can be found in the thalamus among other brain areas (Kawata, 1995; Kim et al., 1981). However, their association with sexual dimorphism remains subject to further research.

The present study raises questions about the origin of the observed sex differences of brain structure as well as their possible behavioral correlates that warrant future studies. In return future study results focusing on behavioral or functional changes should be interpreted in the light of possible underlying microstructural differences. In summary, the present results demonstrate the need for multimodal imaging studies analyzing the correlation between functional and structural differences.

Thalamus

The most widespread and pronounced findings of microstructural sex differences were found in the thalamus bilaterally. They were not limited to certain subdivisions or nuclei of the thalamus. Fractional anisotropy was increased in these areas in male as compared to female subjects. Also, radial diffusivity was decreased in male subjects, suggesting that the microstructural changes might be rather related to changes in myelination or glial cell morphology than to differences in axonal organization (Knake et al., 2010; Song et al., 2002, 2003, 2005; Sun et al., 2006). One earlier study investigating age and sex effects on apparent diffusion coefficient (ADC) values described increased ADC values in the thalamus of females as compared to males in the age group younger than 60 years, which the authors attributed to possible estrogen effects on myelination (Naganawa et al., 2003). Another study did not find differences in thalamic microstructure using DTI (Abe et al., 2002). However, only 6 directions as compared to the 30 directions in the present study were applied and the predefined ROI only included parts of the thalamus. Also, the statistical analysis differed and consisted of Wilcoxon signed rank tests to compare FA values in predefined ROIs as compared to the hypothesis free TBSS approach used in the present study.

The underlying cause of the thalamic sex differences as well as a possible behavioral correlate remains unclear. The thalamus is known as a relay station for information from the periphery and subcortical

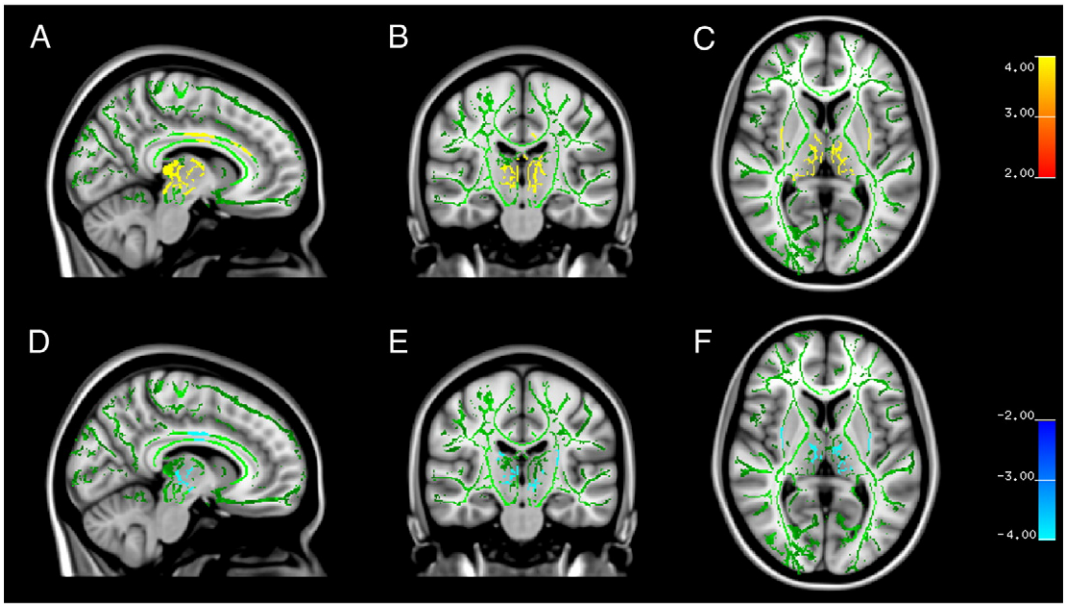

Fig. 1. Sagittal, coronal and axial view of the MNI 152 image with the overlaid common white matter skeleton (green), showing areas of significantly ($p<0.0001$) increased fractional anisotropy (yellow, A–C) and areas of significantly ($p<0.0001$) decreased radial diffusivity (blue, D–F) in the thalamus, corpus callosum and cingulum in males as compared to females.

areas to the cerebral cortex. Intralaminar and midline nuclei of the thalamus are involved in the regulation of arousal, awareness and consciousness (Schiff, 2008; Van der Werf et al., 2002). As far as sex differences are concerned, there are studies describing differences in the basic glucose metabolism in the thalamus of subjects between the ages of 20 and 40 (Fujimoto et al., 2008) and a stronger thalamic activation during pain perception in female subjects, suggesting sex differences in the neural mechanisms that mediate pain perception, pain tolerance or perceived pain (Casey, 1999; Paulson et al., 1998). Additionally, earlier fMRI studies found sex differences in thalamic activation during the processing of emotional stimuli or unpleasant linguistic information concerning interpersonal difficulties (Lee et al., 2005; Shirao et al., 2005). The microstructural changes observed in the present study might be related to differences in thalamocortical projections and to sexual differences in awareness, in the neural processing of emotional stimuli and interpersonal conflicts or in the processing and perceived intensity of pain.

Corpus callosum

Microstructural changes in the corpus callosum have been described in earlier DTI studies. Some studies described higher anisotropy in the corpus callosum of men than in those of women (Oh et al., 2007; Shin et al., 2005; Westerhausen et al., 2003, 2004), however these changes could not be attributed to axonal or glial differences as axial and radial diffusivity were not investigated and the analysis was based on measures in preselected ROIs. Other DTI studies could not replicate this finding (Abe et al., 2002; Sullivan et al., 2001), possibly due to methodological and technical differences including ROI placement, analysis and number of subjects.

The present whole-brain analysis found several areas of increased fractional anisotropy in the male corpus callosum using a hypothesis free whole brain analysis, thereby confirming microstructural sexual dimorphism (Oh et al., 2007; Shin et al., 2005; Westerhausen et al., 2003, 2004). The observed increases in FA that were accompanied by decreased radial diffusivity in male as compared to female subjects support the hypothesis that differences in myelination account for those changes (Song et al., 2002, 2003, 2005; Westerhausen et al., 2003).

The morphology of the corpus callosum was associated with interhemispheric transfer time (Schulte et al., 2004) as well as higher cognitive functions like language lateralization, intelligence and verbal fluency (Hines et al., 1992; Strauss et al., 1994). A study evaluating transcallosal inhibition using transcranial magnetic stimulation revealed sex differences in time and amount of transcallosal inhibition pointing to differences in interhemispheric connectivity that may be reflected by our imaging results (De Gennaro et al., 2004). As far as possible behavioral or cognitive gender differences are concerned, earlier studies could show a reduced degree of hemispheric lateralization in female as compared to male subjects during verbal as well as spatial orientation tasks (Hattemer et al., 2009; Kulynych et al., 1994; Vikingstad et al., 2000), which might be related to the microstructural organizational differences of the corpus callosum. However, study results concerning sex differences in hemispheric lateralization are controversial (Haut and Barch, 2006). The differences between male and female Corpora callosi in the present study might be a microstructural correlate of the possible sex differences in hemispheric lateralization.

Cingulum

The cingulum is structurally and functionally complex and heterogeneous: it is part of the limbic system and is involved in emotion, nociception, motor function as well as higher-level cognitive processes like attention, conflict or error monitoring, visuospatial and memory functions (Devinsky et al., 1995). Our study revealed sex differences in microstructure of the cingulum, confirming earlier evidence that men have an altered microstructure (higher FA values) compared to women in the midcingulum bundle (Huster et al., 2009).

As the cingulum receives projections from more thalamic regions than any other cortical region (Devinsky et al., 1995), microstructural changes in the cingulum might be secondary to the observed extensive microstructural differences in the thalamus discovered in the present study. The functional significance of the sexual dimorphism in the cingulum remains unclear and should be subject of further studies.

Critical considerations and open questions

The present study raises questions about possible behavioral as well as clinical correlates that warrant future studies. The described differences may contribute to our understanding of sex-specific

epidemiology of different neurological and psychiatric diseases: depression, for example, appears to be twice as common in women as in men (Pitychoutis and Papadopoulou-Daifoti, 2010) and juvenile myoclonic epilepsy, a disease known to be associated with alterations of the thalamocortical network (Deppe et al., 2008) is also more common in females (McHugh and Delanty, 2008). It also remains unclear why the observed sex differences are limited to certain brain regions, namely the thalamus, corpus callosum and cingulum, and if possibly related behavioral and clinical sex differences are limited to functions of these brain regions or affect connected brain regions as well.

Conclusion

Using DTI and TBSS we found extensive microstructural sex differences in the thalamus bilaterally as well as in the cingulum and in the corpus callosum. The changes are mainly due to changes in radial diffusivity, suggesting differences in the myelination or in glial cell morphology. These results fortify the need to account for sex while selecting control groups for DTI studies. The sex differences in microstructure of the described areas provide a sound basis for further studies on behavioral and possible clinical correlates of the sexual dimorphism.

Acknowledgment

We thank Dr. Thomas Benner, AA Martinos Center, Massachusetts General Hospital, Boston for technical support and for providing the DTI sequence.

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