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Original Article

Gender Differences in the Structural Connectome of the Teenage Brain Revealed by Diffusion Tensor Imaging

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The issue of biological differences between male and female brains is a controversial one with political positions or prior expectations having a seemingly strong influence on the interpretation of scientific data. The significance of this topic pertains to the gender differences in the prevalence of several psychiatric conditions, such as autism (much more common in males), attention deficit hyperactivity disorder (ADHD, much more common in males), Tourette's syndrome (much more common in males), schizophrenia (more common in males), dyslexia (more common in males), depression (more common in females), and eating disorders (much more common in females). Understanding how gender influences vulnerability to these conditions is of importance. Therefore, we aimed to investigate the gender differences in the brain structural network of teenagers using diffusion tensor imaging (DTI). There were 59 (33 males and 26 females) age- and education-matched subjects (age range, 13 to 14 years) enrolled in this study. The structural connectome was obtained on graph theoretical and network-based statistical (NBS) analyses. Our findings showed that teenage male brains are optimized for intra-hemispheric communication, while teenage female brains are optimized for inter-hemispheric communication. Our results also suggested that the network organization of teenage male brains is more local, more highly segregated, and closer to small-world networks than that of teenage female brains. This indicated that teenage male brains are structured to facilitate connectivity between perception and coordinated action, whereas teenage female brains are designed to facilitate communication between analytical and intuitive processing modes.

Key words: gender difference, diffusion tensor imaging (DTI), structural connectome, graph theoretical analysis, network-based statistical (NBS) analysis

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Introduction

Males and females exhibit different behaviors and strengths. For example, females can better multitask, but tend to have a poorer sense of direction, whereas males can coordinate and

cooperate more easily, but are not as good at expressing emotions. That is, males have better motor ability and spatial cognition while females have superior memories and facial recognition and social skills. The issue of whether there are biological differences between male and female brains is controversial and political positions or prior expectations have a seemingly strong influence on the interpretation of scientific data[1-5].

There are gender differences in the prevalence of a number of psychiatric conditions, including autism (much more common in males), attention deficit hyperactivity disorder (ADHD, much more common in males), Tourette's syndrome (much more common in males), schizophrenia (more common in males), dyslexia (more common in males), depression (more common in females), and eating disorders (much more common in females) [6-10]. There is strong and consistent evidence that females are somewhat protected against the effects of mutations that typically cause autism in males. Females may carry such mutations with relatively little clinical effect. Conversely, females who have autistic symptoms tend to have larger or more severe mutations than affected males, suggesting that it takes a more drastic insult at the genetic level to push the female brain into a clinically autistic state. Understanding how gender influences vulnerability to these conditions is therefore very important.

Two papers related to this topic have been published in the Proceedings of the National Academy of Sciences (PNAS) in recent years. Despite fairly comparable findings, there are wide differences in interpretation[2, 4]. In both studies, differences were found between male and female brains in brain area volumes and structural connectivity, respectively[2, 4]. The authors from the University of Pennsylvania interpreted these group differences as the basis for gender differences in cognition[2], whereas the authors from Tel-Aviv University downplayed these differences and instead emphasized the inherent variability within genders, concluding that there is no such thing as a "male brain" or a "female brain" [4].

Brain differences between men and women

Researchers from the University of Pennsylvania used diffusion tensor imaging (DTI) to define the structural connectivity networks across the brains of 428 males and 521 females[2]. They subsequently analyzed these networks using a variety of statistical measures of regional and global connectivity and compared these between males and females. They found that females have greater connectivity between hemispheres than males on average, while males have greater connectivity within each hemisphere. Males also showed greater local connectivity and concomitant increase in modularity on average.

These authors extrapolated their findings to explain a variety of differences in cognition between men and women. The participants in the structural connectivity analysis were part of a larger sample for which cognitive data had already been obtained, showing gender differences in a variety of domains. Such differences have been widely documented and have ranged from very small to fairly large.

From their results, stark differences and complementarities in the architecture of the human brain provide a potential neural basis as to why men excel at certain tasks and women at others. For instance, men are often better at learning and performing a single task at hand, such as cycling or navigating, whereas women have superior memory and social cognition skills, making them better equipped for multitasking and creating solutions that work for a group.

There is no difference between male and female brains

Researchers from Tel-Aviv University analyzed the MRI scans of 169 females and 112 males and segmented them into 116 regions using a standard brain atlas[4]. By analyzing the amount of warping required to map each brain onto a reference template, it is possible to compare the relative gray matter volumes of all regions between the two genders. From this group comparison, the 10 regions showing the largest gender differences

were chosen for subsequent analyses. They found statistically significant group differences between males and females in gray matter volumes across many brain regions. A recent meta-analysis of 167 studies has confirmed group gender differences in multiple brain areas[11].

Joel et al.[4] went on to ask a more interesting question: across these 10 regions, how "male" or "female" are the structures of individual brains? This is where subjectivity comes in – there are many ways to analyze these data, and the authors chose arguably the most simplistic and extreme one, which enabled them to draw the conclusion that male and female brains are not categorically different. They reported that 35% of brains show substantial variability and only 6% of brains are internally consistent. Importantly, they classified only those subjects showing extreme male or female values for all 10 regions as internally consistent.

If we have ten different variables, each showing the same type of wide distribution with small group gender effect, and if the volumes of different brain regions vary independently within individuals after taking overall brain volume out of the equation, then we should expect some of the values to fall more toward the male end and some more toward the female end in any individual, simply due to underlying variation, which has nothing to do with gender. It would be highly unlikely for values to end up at the extreme end in all ten regions by chance, and such individuals are extremely rare.

The fact that each individual shows this type of pattern does not mean that each of us has a "mosaic brain" that is partly male and partly female, as claimed by the authors. It is exactly what is expected given that gender is only one of the factors affecting the size of each of the regions. We cannot determine what the size of each region would have been if gender was different. We can only deduce that there would be some effect based on the group average effects.

The conclusion that male and female brains are not that different is not well supported by these findings. The group differences are clear and highly significant. Even if very few of the males or females are at the extreme end of the distribution for all ten regions, the overall pattern suggests that a very good classifier can be established from the volumes of these ten regions to predict whether a given brain scan is from a male or a female. Indeed, this would have been a far more objective test of whether MRI volumetric differences between male and female brains are categorical or dimensional.

DTI and graph theoretical analysis

DTI has been increasingly applied to the study of many psychiatric disorders[12-15]. It is a non-invasive method for investigating brain microstructure and integrity of anatomical connectivity, which is not available with other imaging modalities. Fractional anisotropy (FA), the most commonly used index of DTI, provides a measure of white matter tract integrity[16, 17].

Recently, the connectome has been proposed as a conceptual framework for brain research. Tacit to this model is the observation of the structural and functional organization of the human brain into complex networks, allowing for the segregation and integration of information processing. Based on topology, graph theoretical analysis quantitatively provides novel insight into the connectome using nodes (neurons or brain regions), edges (synapses or axonal projections), and several additional topological parameters, such as clustering coefficient, characteristic path length and small-worldness[18, 19]. Available graph-theoretical studies have broadly aimed at assessing the organization of structural and functional brain networks using MRI in normal development and aging, as well as in organic and neuropsychiatric brain disorders. The results have suggested that brain networks correlate with behavioral and cognitive functions [20-23].

As the developmental trajectories of males and females separate at a young age, demonstrating wide differences during adolescence and adulthood, we focused on gender-related brain

differences during the developmental period. The aim of this study was to use DTI-based analysis to determine the differences in the teenage brain structural connectome between males and females based on graph theoretical and network-based statistical (NBS) analyses.

Materials and Methods

MRI data acquisition

A total of 59 age- and education-matched teenagers (33 males and 26 females) between 12 and 14 years of age were recruited into this study. All were right-handed. No participant had a history of psychiatric or neurological illness or substance-use disorder or was currently taking any prescription or psychotropic medications. The exclusion criteria included metallic implant or other contraindication for MRI.

All diffusion images were acquired using a 3-Tesla MRI (Skyra, Siemens, Germany) with a 20 channel head neck coil. The diffusion images were acquired using a multi-shell scheme with repetition time (TR) = 4800 ms, echo time (TE) = 97 ms, voxel size = 2 x 2 x 4 mm^3; 35 axial contiguous slices, signal average = 1, 192 non-collinear diffusion weighting gradient direction with b = 1000, 1500, 2000 s/mm^2 and 12 additional null images without diffusion weighting (b = 0 s/mm^2). The scan time was approximately 16.5 min.

DTI analysis

Following eddy current correction for diffusion image distortion, each participant's echo planar image was spatially normalized to the Montreal Neurological Institute (MNI) T2W template using parameters determined from the normalization of the diffusion null image to the T2 template on Statistical Parametric Mapping (SPM8). DSI Studio was employed for whole brain DTI tractography with FA threshold of 0.15 and max angle of 70° [24]. Then, the 90 x 90 individual structural connectivity matrix (fiber number multiplied by FA) of each participant was output followed by importation of the ROIs based on Automated Anatomical Labeling (AAL). The schematic of the pipeline for creating the structural connectivity matrix and network is shown in Figure 1.

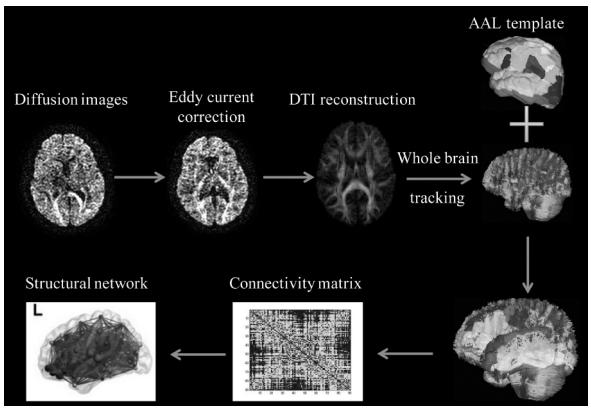

Fig. 1 Schematic of the pipeline for creating the brain structural connectivity matrix and network.

Graph theoretical and network-based statistical analyses

Graph theoretical analysis was performed on the interregional connectivity matrix using the Graph Analysis Toolbox (GAT)[19]. The topological measures of structural brain networks were calculated with different correlation thresholds (0.05 - 0.3 in 0.01 increment), including clustering coefficient (C), characteristic path length (L), local efficiency (E_{local}), global efficiency (E_{global}), small-worldness index (σ), transitivity, and modularity. C and E_{local} reflect local segregation; C quantifies the extent of local interconnectivity in the network and E_{local} indicates how well the sub-graphs exchange information with each other. High scores on these two measures correspond to highly segregated neural processing. L and E_{global} reflect global integration; L measures the capability of information transfer between brain regions and E_{global} is a measure of the overall capacity for parallel information transfer and integrated processing. Lower L score or higher E_{global} score indicates more rapid integration of specialized information from distributed brain regions. The γ and λ values were normalized relative to C and L of the 100 random networks. In addition, σ was calculated by dividing γ by λ. Transitivity is the ratio of triangles to triplets in the network and is an alternative to C. Modularity is a statistic that quantifies the degree to which the network may be

subdivided into clearly delineated groups.

On NBS analysis[25], the differences in the network topology and the regional network between groups were evaluated with two-sample t-tests and non-parametric permutation tests (1,000 repetitions). P-value < 0.05 indicated significance for both the permutation test on graph theoretical analysis and the two-sample Student's t-test on NBS analysis. BrainNet viewer was applied to visualize the significant sub-networks revealed on NBS.

Results

Significantly higher C (Fig. 2a), E_{local} (Fig. 2b), and transitivity (Fig. 2c) were observed in teenage males than in teenage females ($p < 0.05$), indicating higher local segregation of brain network in teenage males. In addition, higher σ (Fig. 2d) was found in teenage males when compared with teenage females ($p < 0.05$), which implied that the neural connections of teenage male brains are close to small-world networks. We also found slightly higher modularity in teenage males. There were no statistically significant differences in L or E_{global} between males and females. All results are expressed as means ± standard error.

From the results of NBS analysis, teenage males have better intra-hemispheric connectivity (Fig. 3a) and teenage females have better interhemispheric connectivity, primarily in the frontal regions (Fig. 3b) ($p < 0.05$).

Discussion

We examined gender differences in a group of 59 teenagers by comprehensively analyzing the DTI-based structural connectome of the brain. Our findings confirmed earlier hypotheses and provided unique insight into gender differences that were not possible with alternative modalities or forms of analysis. The myelinated axons of white matter facilitated distant signal conduction.

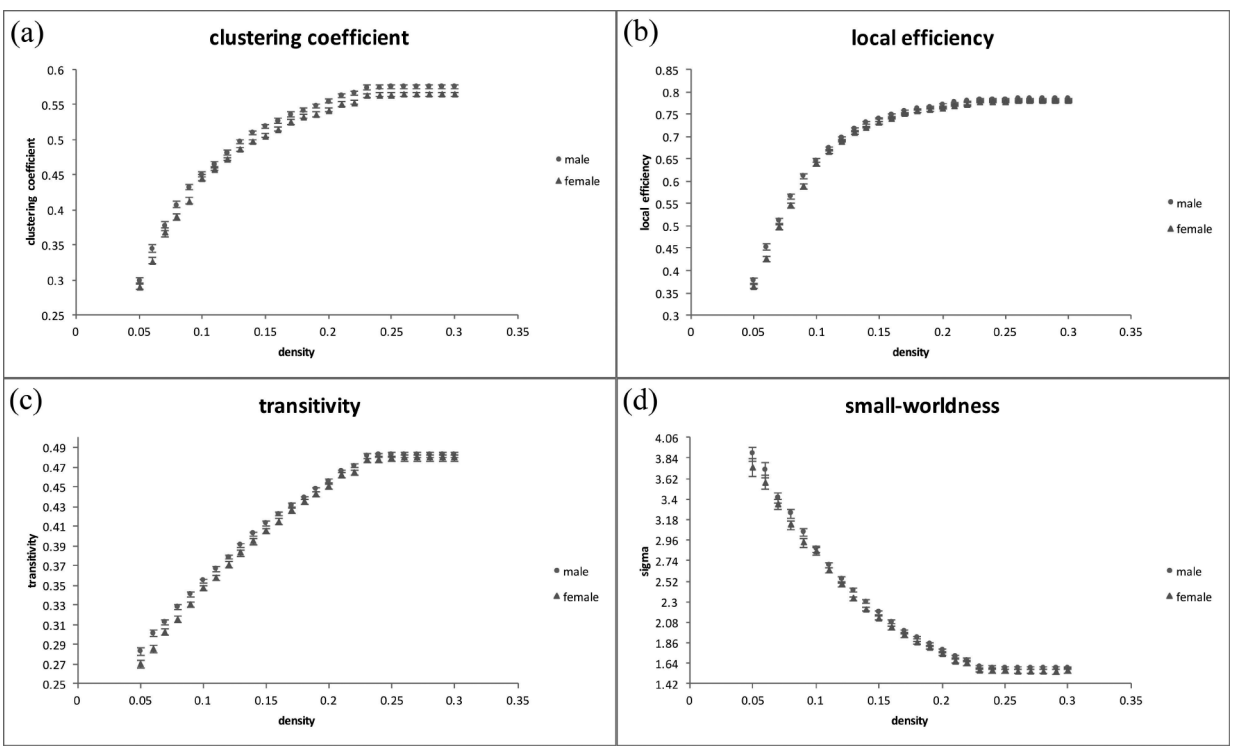

Fig. 2 Higher topological measures were found in teenage male brain networks on DTI, including (a) clustering coefficient, (b) local efficiency, (c) transitivity, and (d) small-worldness index ($p < 0.05$).

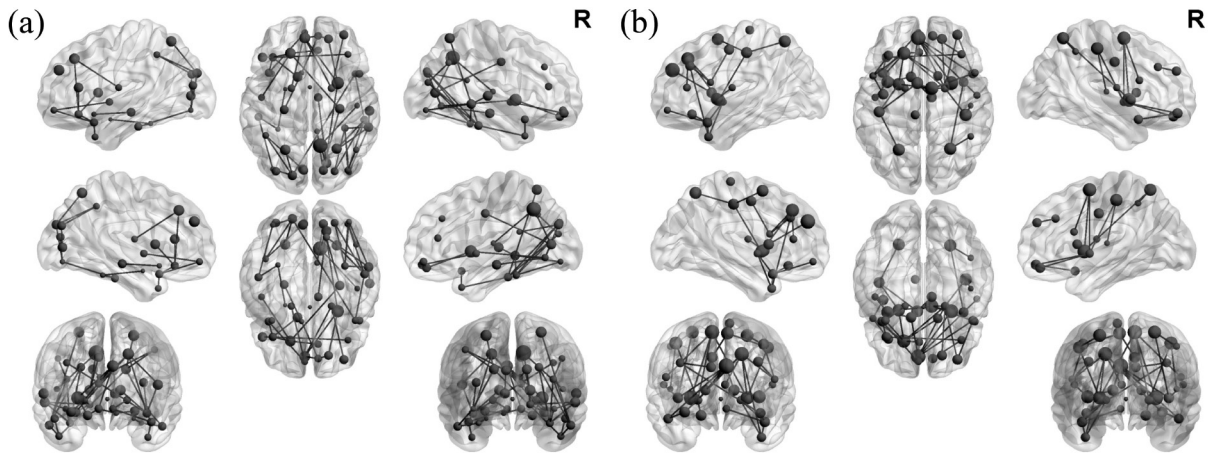

Fig. 3 From the results of network-based statistical analysis, (a) more intra-hemispheric connectivity was found in teenage males, and (b) more interhemispheric connectivity was found in teenage females ($p < 0.05$).

Previous structural imaging has shown a higher proportion of cortical white matter in males, except in the corpus callosum[26, 27]. A higher proportion of myelinated fibers within hemispheres in males suggests that male brains are optimized for communicating within hemispheres, whereas female brains are optimized for interhemispheric communication. Our analysis supported this hypothesis at a global to regional level and also revealed unique gender differences in the brain architecture. On NBS analysis, we established that teenage male brains are indeed structured to facilitate intra-hemispheric cortical connectivity. In contrast, teenage female brains display higher interhemispheric connectivity.

In addition to NBS analysis, we investigated a complementary network measure, transitivity, at the global level and found this to be higher in males than in females. This measure quantifies the sparsity of the connectome, that is, how easily it can be divided into subnetworks. A high lobar-level transitivity points to a region's neighbors being more strongly connected to each other within each lobe and indicates that local clustering into subnetworks is high in males, resulting in increased global modularity. However, modularity was only slightly higher in the teenage males in this study. This is also indicative of the enhanced local, short range within lobe connectivity in males when compared with females. In contrast, females develop higher long-range connectivity, which is mainly interhemispheric.

Our results revealed fundamental gender differences in the structural network of the teenage brain. During development, male brains are structured to facilitate within-lobe and within-hemisphere connectivity, with networks that are transitive, modular, and discrete, whereas female brains have greater interhemispheric connectivity and greater cross-hemispheric participation. Within-hemispheric cortical processing along the posterior-anterior dimension involves the linking of perception to action, and motor action is ipsilaterally mediated by the cerebellum. Greater within-hemispheric supratentorial connectivity combined with greater cross-hemispheric cerebellar connectivity confers an efficient system for coordinated actions in males. Greater interhemispheric connectivity in females facilitates integration of the analytical and sequential reasoning modes of the left hemisphere with the spatial, intuitive processing of information of the right hemisphere. A behavioral study in which imaging study was a subset, showed pronounced gender differences, with females outperforming males on attention, word and face memory, and social cognition tests and males outperforming females on spatial processing tests with higher motor and sensorimotor speed[28]. These differences were mainly observed in mid-adolescents (age

range, 12–14 years). Males were shown to be significantly faster in completing motor tasks, with higher accuracy on spatial memory tasks. Similar gender differences were demonstrated in another behavioral study[27].

Our results regarding structural connectivity obtained on DTI are consistent with previous data from T1 weighted imaging, showing a higher proportion of cortical white matter in males[29], except in the corpus callosum[30]. They are also consistent with activation studies using functional MRI, which have reported greater interhemispheric activation in females on language tasks[31], and greater focal intra-hemispheric activation in males on spatial tasks[32]. With respect to development, diffusion studies[33-35] have shown higher FA and lower mean diffusivity in the corpus callosum in females during mid-adolescence, which is consistent with our results. Although FA and mean diffusivity provide measures of white matter integrity, connectomic studies like ours are required to complete the picture of network-based systems. Thus, the present study provides unique insights into gender differences using structural connectivity and measures defined on the connectome. The results support the findings of previous behavioral and functional studies, as well as the notion that there is behavioral complementarity between the sexes. Developmental neural substrates can contribute to improved understanding of this complementarity.

Limitations

There are several limitations to the present study. First, the age-matched cross-sectional design did not allow us to observe developmental or aging effects in the participants. Second, DTI is limited to the crossing or branching patterns of complex regions, and reflects the weighted average of all compartments when the partial volumes of different diffusion compartments vary. To better characterize the complicated fiber patterns and distinguish fiber orientations, several novel diffusion-based methods have been proposed, providing an opportunity for more accurate, higher-order descriptions through the water diffusion process when compared with DTI[24, 36-41]. Third, on connectome analysis, the parcellation scheme we used to divide the whole brain into 90 regions was based on the AAL template. However, several studies have reported that different schemes can result in distinct topological patterns[42]. Therefore, further studies should combine more parcellation strategies to explore their effects on network topology.

Conclusions

Our results establish that teenage male brains are optimized for intra-hemispheric communication, and teenage female brains are optimized for inter-hemispheric communication. Our results also suggest that the network organization of teenage male brains is more local, segregated, and close to small-world networks than teenage female brains. This indicates that teenage male brains are structured to facilitate connectivity between perception and coordinated action, and teenage female brains are designed to facilitate communication between analytical and intuitive processing modes.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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