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Gender differences in the structural connectome of the teenage brain revealed by generalized q-sampling MRI

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ABSTRACT

The question of whether there are biological differences between male and female brains is a fraught one, and political positions and prior expectations seem to have a strong influence on the interpretation of scientific data in this field. This question is relevant to issues of gender differences in the prevalence of psychiatric conditions, including autism, attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, schizophrenia, dyslexia, depression, and eating disorders. Understanding how gender influences vulnerability to these conditions is significant. Diffusion magnetic resonance imaging (dMRI) provides a non-invasive method to investigate brain microstructure and the integrity of anatomical connectivity. Generalized q-sampling imaging (GQI) has been proposed to characterize complicated fiber patterns and distinguish fiber orientations, providing an opportunity for more accurate, higher-order descriptions through the water diffusion process. Therefore, we aimed to investigate differences in the brain's structural network between teenage males and females using GQI. This study included 59 (i.e., 33 males and 26 females) age- and education-matched subjects (age range: 13 to 14 years). The structural connectome was obtained by graph theoretical and network-based statistical (NBS) analyses. Our findings show that teenage male brains exhibit better intrahemispheric communication, and teenage female brains exhibit better interhemispheric communication. Our results also suggest that the network organization of teenage male brains is more local, more segregated, and more similar to small-world networks than teenage female brains. We conclude that the use of an MRI study with a GQI-based structural connectomic approach like ours presents novel insights into network-based systems of the brain and provides a new piece of the puzzle regarding gender differences.

1. Introduction

It is commonly thought that males and females exhibit different behaviors. Common stereotypes include that females can do many things at the same time, but they have a poor sense of direction when driving, whereas males can coordinate and cooperate easily but they are not good at expressing emotions. That is, males tend to have better motor ability and spatial cognition, while females tend to have superior memories, facial recognition, and social skills (Gur et al., 2012; Halpern et al., 2007). The question of whether there are biological differences between male and female brains is a fraught one, and political positions and prior expectations seem to have a strong influence on the interpretation of scientific data in this field (Abramov et al., 2012; Fairchild et al., 2016; Ingalhalikar et al., 2014; Joel, 2011; Joel et al., 2015; Xu et al., 2015).

Gender differences in human brains is an important topic because the prevalence of psychiatric conditions varies between the genders; such differences have been observed in autism (much more common in males) (Baron-Cohen, 2009; Baron-Cohen et al., 2005), attention deficit hyperactivity disorder (ADHD, much more common in males) (Arnett et al., 2015), Tourette's syndrome (much more common in males) (Yang et al., 2016), schizophrenia and dyslexia (more common in males) (Arnett et al., 2017; McGrath et al., 2008), depression (more common in females) (Goldstein et al., 2014; Schuch et al., 2014; Shansky, 2009), and eating disorders (much more common in females) (Lipson and Sonneville, 2017). Understanding how gender influences vulnerability

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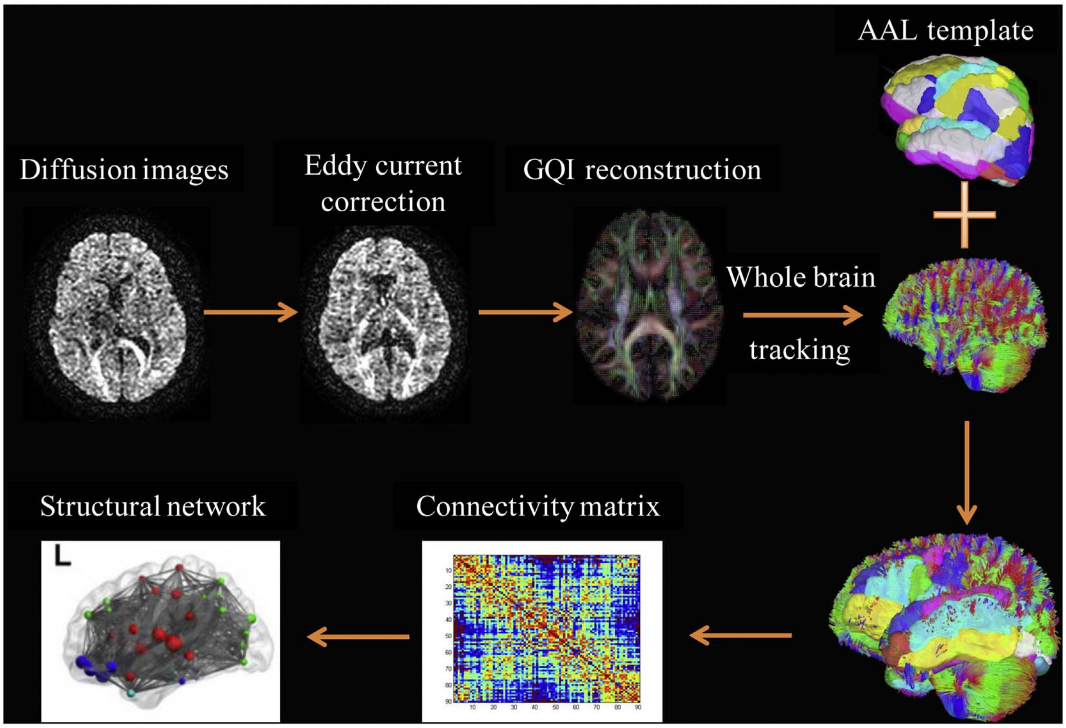

Fig. 1. Schematic of the pipeline for creating the brain structural connectivity matrix and network using GQI.

to these conditions is, therefore, a significant question.

Previous studies found strong group differences between male and female brains; despite comparable findings, the authors of these studies interpreted the results in almost polar opposite fashions (Ingalhalikar et al., 2014; Joel et al., 2015; Szalkai et al., 2015). One structural connectivity study interpreted these group differences as the basis for gender differences in cognition (Ingalhalikar et al., 2014). They defined the structural connectivity networks across the brains of 428 males and 521 females using diffusion tensor imaging (DTI). They subsequently analyzed these networks using a variety of statistical measures of regional and global connectivity and compared the results between males and females. They found that on average, females had greater connectivity between hemispheres than males, while males had greater connectivity within each hemisphere. Males also showed, on average, greater local connectivity and concomitantly increased modularity in the network.

These authors extrapolated their findings to explain a variety of group 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 range from very small to fairly large. The results revealed stark differences between the groups and suggested complementarity in the architecture of the human brain, which helps provide a potential neural basis for why men excel at certain tasks and women at others. For instance, men are usually better at learning and performing a single task at hand, such as cycling or navigating directions, whereas women have superior memory and social cognition skills, making them more equipped for multitasking and creating solutions that work for a group (Ingalhalikar et al., 2014).

A different study on the volume of brain regions downplayed these differences entirely and instead emphasized the inherent variability within genders, concluding that there was no such thing as a “male brain” or a “female brain” (Joel et al., 2015). They analyzed the MRI scans of 169 females and 112 males and segmented them into 116 regions using a standard brain atlas. By analyzing how much warping was required to map each brain onto a reference template, it was possible to compare the relative gray matter volume of all these regions across the two genders. From this group comparison, the 10 regions showing the largest gender differences were chosen for subsequent analyses. The researchers found statistically significant group differences between males and females in gray matter volume across many brain regions. A recent meta-analysis of 167 studies confirms consistent gender differences in many brain areas between men and women (Ruigrok et al., 2014).

Joel et al. (2015) went on to ask a more interesting question: across those ten regions, how “male” or “female” were 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 showed substantial variability, and only 6% of brains were internally consistent. Importantly, they chose to classify only those subjects showing extreme male or female values for all ten regions as internally consistent.

The fact that most individuals show this 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 these regions. We can only deduce from the group average effects that there would likely have been some effect. 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 of these regions, the overall pattern suggests that you could build a highly accurate classifier from the volumes of these ten regions taken together that would be successful at predicting whether a given brain scan came 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.

Another group published several studies that showed striking sex differences among human connectomes using graph theoretical parameters; they revealed clear differences and suggested the superiority of female brains (Szalkai et al., 2015). They also accounted for possible