# Brain Connectivity : Gender Makes a Difference

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## Abstract

It has been well known that gender plays a critical role in the anatomy and function of the human brain, as well as human behaviors. Recent neuroimaging studies have demonstrated gender effects on not only focal brain areas but also the connectivity between areas. Specifically, structural MRI and diffusion MRI data have revealed substantial gender differences in white matter–based anatomical connectivity. Structural MRI data further demonstrated gender differences in the connectivity revealed by morphometric correlation among brain areas. Functional connectivity derived from functional neuroimaging (e.g., functional MRI and PET) data is also modulated by gender. Moreover, male and female human brains display differences in the network topology that represents the organizational patterns of brain connectivity across the entire brain. In this review, the authors summarize recent findings in the multimodal brain connectivity/network research with gender, focusing on large-scale data sets derived from modern neuroimaging techniques. The literature provides convergent evidence for a substantial gender difference in brain connectivity within the human brain that possibly underlies gender-related cognitive differences. Therefore, it should be mandatory to take gender into account when designing experiments or interpreting results of brain connectivity/network in health and disease. Future studies will likely be conducted to explore the interdependence between gender-related brain connectivity/network and the gender-specific nature of brain diseases as well as to investigate gender-related characteristics of multimodal brain connectivity/network in the normal brain.

## Keywords

gender, anatomical connectivity, morphometric connectivity, functional connectivity, brain network

Brain connectivity is essential for the operations and processes of human cognition, supporting neuronal communications within the human brain (Sporns and others 2005). The disruption of brain connectivity will lead to human cognitive dysfunction. For instance, multiple sclerosis patients suffering from white matter (WM) lesions have shown multiple cognitive deficits (Calabrese and Penner 2007). Recent investigations have revealed abnormalities of the interaction/connectivity among brain regions in putative gray matter (GM) diseases such as Alzheimer disease (AD), leading to the hypothesis of them as "disconnection syndromes" (Delbeuck and others 2003). Moreover, brain connectivity has been shown to exhibit a direct interdependence with specific cognitive and behavioral performances (Johansen-Berg 2010).

A topic of enduring interest in many fields of neuroscience, gender has demonstrated a substantial influence on many areas of brain and behavior, including emotion, memory, perception, language, and other cognitive domains (Cahill 2006). For example, men perform better in mental rotation and visuospatial perception processing, whereas women have advantages in verbal memory and fluency and in the speed of articulation (Hamilton 2008). Morphologically, men have a larger brain than do women. Prior studies have suggested that focal differences of GM (e.g., cortical thickness) between males and females might account for their behavioral differences (Luders and others 2006). On the other hand, emerging studies have repeatedly reported gender effects on the structural organization of WM, indicating an important role for brain connectivity in sexual dimorphism. In particular, recent studies have revealed gender differences in the organizational patterns of brain connectivity across the entire brain by analyzing

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the topological attributes of brain networks (Gong and others 2009b; Yan and others 2010).

In this review, we summarize recent research progress in the study of gender differences in the human brain connectivity. Brain connectivity can be characterized at different scales (Sporns and other 2005): microscale (between neurons), mesoscale (between cortical columns), and macroscale (between brain voxels/regions). Specifically, we focus on the macroscale brain connectivity findings in health, which were derived from modern neuroimaging data in vivo mainly after 2000. First, we introduce basic concepts and methods for determination and quantification of the brain connectivity/network using multimodal neuroimaging techniques. Next, we review the results regarding the gender differences of a WM-based anatomical connectivity/network. A review of gender differences in the morphometric and functional connectivity/network follows. Finally, a future perspective on this topic is discussed.

## Concepts and Methods

### *Multimodal Connectivity Derived from Neuroimaging Data*

*Anatomical Connectivity.* Anatomical connectivity refers to the structural fiber/axonal pathways connecting segregated brain areas and therefore corresponds to the WM tissue of the human brain. Traditionally, the structural organization of WM was studied using invasive techniques such as dissection, histological staining, and axonal tracing (Kobbert and others 2000); therefore, early WM studies are limited to postmortem and animal brains. Modern neuroimaging techniques have allowed for investigations of the human brain noninvasively, leading to substantial enhancement of our understanding about the human brain. Several MRI techniques have been widely employed to investigate WM properties.

*Structural MRI (i.e., T1-weighted, T2-weighted, or proton density imaging).* Structural MRI provides an image intensity contrast between brain tissue types (e.g., GM, WM, and cerebrospinal fluid) that allows for classification of the WM from the entire brain in vivo. The resultant WM volume can be taken as a gross marker of the amount of anatomical connectivity in the human brain. Numerous studies have been conducted to explore gender differences in WM morphology derived from structural MRI data (Table 1).

*Diffusion MRI.* Diffusion MRI has been applied to characterize underlying water molecule diffusion in the human brain (Le Bihan 2003). The water diffusion is very informative when the voxel contains fibrous structures such as a WM axonal bundle. Water molecules diffuse more rapidly in the direction parallel to the fiber bundle and more slowly in the perpendicular direction. The water diffusivity (represented by the diffusion MRI signal) therefore differs depending on the measuring direction in the voxel. The direction with the maximum diffusivity defines the orientation of the underlying fiber bundle.

One popular form of diffusion MRI is diffusion tensor imaging (DTI) that assumes a Gaussian distribution of water diffusion in each voxel (Basser and others 1994). DTI analysis yields some scalar parameters to characterize the properties of water diffusion in a voxel. For example, mean diffusivity (MD) is the bulk mobility of water molecules, whereas fractional anisotropy (FA) or relative anisotropy (RA) represents a normalized ratio of diffusion directionality. Biologically, these parameters are believed to reflect axonal density, diameter, or degree of myelination in the WM (Beaulieu 2002) and have therefore been widely used to evaluate the WM integrity under normal and abnormal conditions (Gong and others 2008; Gong and others 2005). As expected, many studies have been dedicated to investigate gender differences in the WM diffusion properties using diffusion MRI (Table 1).

Another type of information provided by DTI is the orientation of underlying fiber bundles, which typically could be estimated by computing the eigenvector of the largest eigenvalue of the diffusion tensor. The voxel-wise orientation has been further used to reconstruct WM tracts, referred to as DTI tractography. It has demonstrated that many WM tracts derived from DTI deterministic tractography follow known WM anatomy, as shown in previous studies (Wakana and others 2004). However, DTI deterministic tractography has a limited capacity for resolving crossing fiber bundles, where the intersection of fibers with a different orientation within a voxel obfuscates any directional information for that voxel. Therefore, probabilistic diffusion MRI tractography was developed, which theoretically has the advantage of overcoming fiber crossings as well as a greater robustness against image noise (Behrens and others 2007). Taken together, diffusion MRI tractography methods are capable of providing information about how likely it is that two specific voxel/regions are anatomically connected. This information can be applied to establish the anatomical network/graph of the entire brain (Gong and others 2009a).

*Morphometric Connectivity.* Recently, it has been demonstrated that GM morphometric features (e.g., volume, density, and thickness) derived from structural MRI data also carry important connectivity information. For instance, Mechelli and colleagues (2005) have reported covariance of GM density between multiple bilateral homotopic regions. Also, cortical thickness has shown significant correlations among multiple cortical areas (Lerch and others 2006)—for example, between Broca's and Wernicke's areas—that are well known to be language related. In addition, Lerch and

**Table 1.** Recent studies showing gender effects on brain connectivity/network derived from neuroimaging data.

| Reference | Subjects, Male/Female | Age, y | Data Type | Method | Metric of Analysis |
|---|---|---|---|---|---|
| De Bellis and others (2001) | 61/57 | 6-17 | sMRI | Manual ROI | WM's volume, CC area |
| Sullivan and others (2001) | 51/41 | 22-71 | sMRI | Manual ROI | CC's area |
| Allen and others (2003) | 23/23 | 22-49 | sMRI | Manual ROI | WM's volume |
| Luders and others (2003) | 30/29 | ≈20-30 | sMRI | Manual ROI | CC's area |
| Szeszko and others (2003) | 9/11 | ≈20-40 | dMRI | Manual ROI | WM's FA |
| Westerhausen and others (2003) | 32/35 | 19-34 | dMRI | Manual ROI | WM's RA, MD, TD, AD |
| Westerhausen and others (2004) | 32/35 | 19-34 | sMRI, dMRI | Manual ROI | CC's area, RA, MD |
| Lemaitre and others (2005) | 331/331 | 63-75 | sMRI | Automatic segmentation | WM's volume |
| Shin and others (2005) | 15/15 | ≈20-30 | dMRI | Manual ROI | WM's FA |
| Kilpatrick and others (2006) | 36/36 | NA | PET | Seed PLS | Functional connectivity |
| Schmithorst and Holland (2006) | 157/167 | 5-18 | Task-fMRI | GLM | Functional connectivity |
| Bonekamp and others (2007) | 22/18 | 5-19 | dMRI | Manual ROI | WM's FA, MD |
| Butler and others (2007) | 12/13 | ≈20-40 | Task-fMRI | GLM | Functional connectivity |
| Eluvathingal and others (2007) | 15/16 | 6-17 | dMRI | Tractography | WM's FA, MD, TD, AD |
| Lenroot and others (2007) | 209/178 | 3-27 | sMRI | Automatic segmentation | WM's volume |
| Oh and others (2007) | 14/15 | ≈20-30 | dMRI | TGIS | CC's FA |
| Schneiderman and others (2007) | 28/20 | 14-64 | dMRI | Automatic ROI | WM's RA |
| Smith and others (2007) | 51/71 | 58-94 | sMRI | VBM | WM's volume |
| Hsu and others (2008) | 87/58 | 30-80 | dMRI | Manual ROI, VBA | WM's FA, MD |
| Leonard and others (2008) | 100/100 | ≈18-30 | sMRI | Automatic segmentation | WM's volume, CC's area |
| Schmithorst and others (2008) | 52/54 | 5-18 | dMRI | VBA | WM's FA, MD |
| Gong and others (2009b) | 47/48 | 19-85 | dMRI | Tractography | Network topology |
| Huster and others (2009) | 39/40 | 19-34 | dMRI | Manual ROI | WM's volume, FA, MD |
| Perrin and others (2009) | 204/204 | 12-18 | sMRI, MTI | Automatic segmentation | WM's volume |
| Schmithorst (2009) | 52/54 | 5-18 | dMRI | VBA | WM's FA, MD |
| Welcome and others (2009) | 100/100 | 18-34 | sMRI | Manual ROI | CC's area |
| Abe and others (2010) | 130/115 | 20-71 | sMRI, dMRI | VBA | WM's volume, FA, MD |
| Asato and others (2010) | NA | 8-28 | dMRI | TBSS | WM's FA, RD |
| Biswal and others (2010) | NA | >18 | Resting-fMRI | GLM + ICA | Functional connectivity |
| Choi and others (2010) | 22/21 | ≈20-30 | dMRI | Tractography | WM's FA, MD |
| Chou and others (2010) | 40/40 | ≈18-40 | dMRI | TBSS | WM's FA |
| Kong and others (2010) | 50/50 | 20-30 | Resting-fMRI | GLM | Functional connectivity |
| Liu and others (2010) | 11/11 | 19-31 | MWF, dMRI | Manual ROI | CC's FA, MWF |
| Lv and others (2010) | 90/94 | 18-67 | sMRI | Thickness correlation | Network topology |
| Rametti and others (2010) | 24/19 | ≈20-40 | dMRI | TBSS | WM's FA |
| Tian and others (2010) | 38/48 | 17-25 | Resting-fMRI | GLM | Network topology |
| Yan and others (2010) | 38/34 | 18-27 | dMRI | Tractography | Network topology |
| Zuo and others (2010) | 96/108 | 7-85 | Resting-fMRI | GLM | Functional connectivity |

Notably, we included only studies in health after 2000, given the limited space. sMRI = structural MRI; dMRI = diffusion MRI; WM = white matter; CC = corpus collosum; ROI = region of interest; FA = fractional anisotropy; RA = relative anisotropy; MD = mean diffusivity; TD = transverse diffusivity; AD = axial diffusivity; VBM = voxel-based morphometry; VBA = voxle-based analysis; PLS = partial least squares; TBSS = tract-based spatial statistic; GLM = general linear model; TGIS = tractography-guided statistics; MWF = myeline-water fraction; ICA = independent component analysis.

colleagues (2006) demonstrated that morphometric connectivity (i.e., thickness correlation) was correlated with intelligence quotient (IQ). Furthermore, the correlation pattern has exhibited specific alterations under various disease attacks (e.g., AD, schizophrenia, and multiple sclerosis) as compared with normal controls (Bassett and others 2008;

He and others 2008; He and others 2009). Taken together, morphometric variability across individuals is not uniquely present but shows similar patterns among various areas, suggesting a structural association/interaction of these areas. Specifically, we refer to the statistical dependences of morphometric features between distinct brain regions as morphometric connectivity. A recent study has reported a gender effect on this morphometric connectivity (i.e., cortical thickness correlation; Table 1).

*Functional Connectivity.* Functional connectivity has been specifically defined as correlations between spatially remote neurophysiological events (Friston 1994). The neurophysiological signal or neuronal activities could be indirectly measured in vivo by using functional neuroimging techniques, including electroencephalography (EEG), magnetoencephalography (MEG), blood oxygen level–dependent fMRI, PET, and so on. Among these techniques, EEG/MEG measures the changes in the electromagnetic field related to neuronal activity at a high temporal resolution (milliseconds). In contrast, fMRI/PET detects localized cerebral blood flow induced by neural activity at a relatively poor temporal resolution (seconds) but a decent spatial resolution (millimeters). Typically, functional connectivity is computationally represented by statistical dependence of a signal time series between distinct brain regions. Statistical dependence could be estimated by computing correlation or covariance, spectral coherence, or phase locking. Numerous studies have been dedicated to investigate the functional connectivity in task-invoked and task-free (i.e., resting state) conditions of health and disease (Fox and Greicius 2010). Likewise, there have been several studies demonstrating gender differences in functional connectivity (Table 1).

## Brain Network Analysis Using the Graph-Theoretical Approach

Once all possible interregional connectivities are derived from the neuroimaging data, the brain can be modeled as a complex graph/network that is composed of a collection of nodes and a collection of edges connecting pairs of nodes (Bullmore and Sporns 2009). For a macroscale brain network, each region or voxel is represented by a node, and each interregional or intervoxel connection is represented by an edge between the nodes (Achard and others 2006; Gong and others 2009a; He and others 2007). For a summarized workflow of brain network construction using neuroimaging data, see Figure 1 (Bassett and Bullmore 2009). The brain network captures the underlying connectivity pattern across the entire brain, which can be further analyzed by graph-theoretical approaches.

Graph theory is a natural framework for the mathematical representation of complex networks and provides a powerful way to quantitatively describe the topological organization of brain connectivity. Particularly in the past 5 years, graph theory has attracted considerable attention in the neuroimaging community and is being translated to investigate brain networks (He and Evans 2010). Mathematically, a graph can be undirected or directed as well as unweighted (binary) or weighted (Boccaletti and others 2006). Several key network parameters extracted from graph theory are introduced as follows.

*Clustering coefficient* and *characteristic path length* are two basic measurements of a complex network (Watts and Strogatz 1998). The clustering coefficient of a network is the average of the clustering coefficients over all nodes in the network, where the clustering coefficient of a node is the number of existing connections among the node's immediate neighbors divided by all of their possible connections. The characteristic path length of a network is the average minimum number of connections that link any two nodes of the network. The clustering coefficient quantifies the extent of local "cliquishness," whereas the characteristic path length quantifies the capability for parallel information propagation of a network. The two metrics can be used to distinguish different classes of network such as regular, small-world, and random networks (Watts and Strogatz 1998). A small-world network has a shorter characteristic path length than a regular network (high clustering and long path lengths) but a greater local interconnectivity than a random network (low clustering coefficient and short path lengths). The small-world concept was originally defined for unweighted networks using the clustering coefficient and characteristic path length but has been subsequently generalized to weighted networks by introducing the concept of network efficiency (Latora and Marchiori 2001). Specifically, the inverse of the average of the shortest path length between each pair of nodes within the network is defined as the *network global efficiency*. The network local efficiency is the average of the local efficiency over all nodes within the network, where the local efficiency of a node is the global efficiency of the immediate neighborhood subgraph of the node. The clustering coefficient and inverse of the characteristic path length conceptually correspond to the local and global efficiency of a network, respectively (Latora and Marchiori 2003). However, these two parameter sets are not computationally equivalent and therefore could provide different results. In terms of network efficiency, a small-world network exhibits high global and local efficiency. The small-world model for the human brain is very attractive because it supports both specialized/modularized and integrated/distributed information processing and

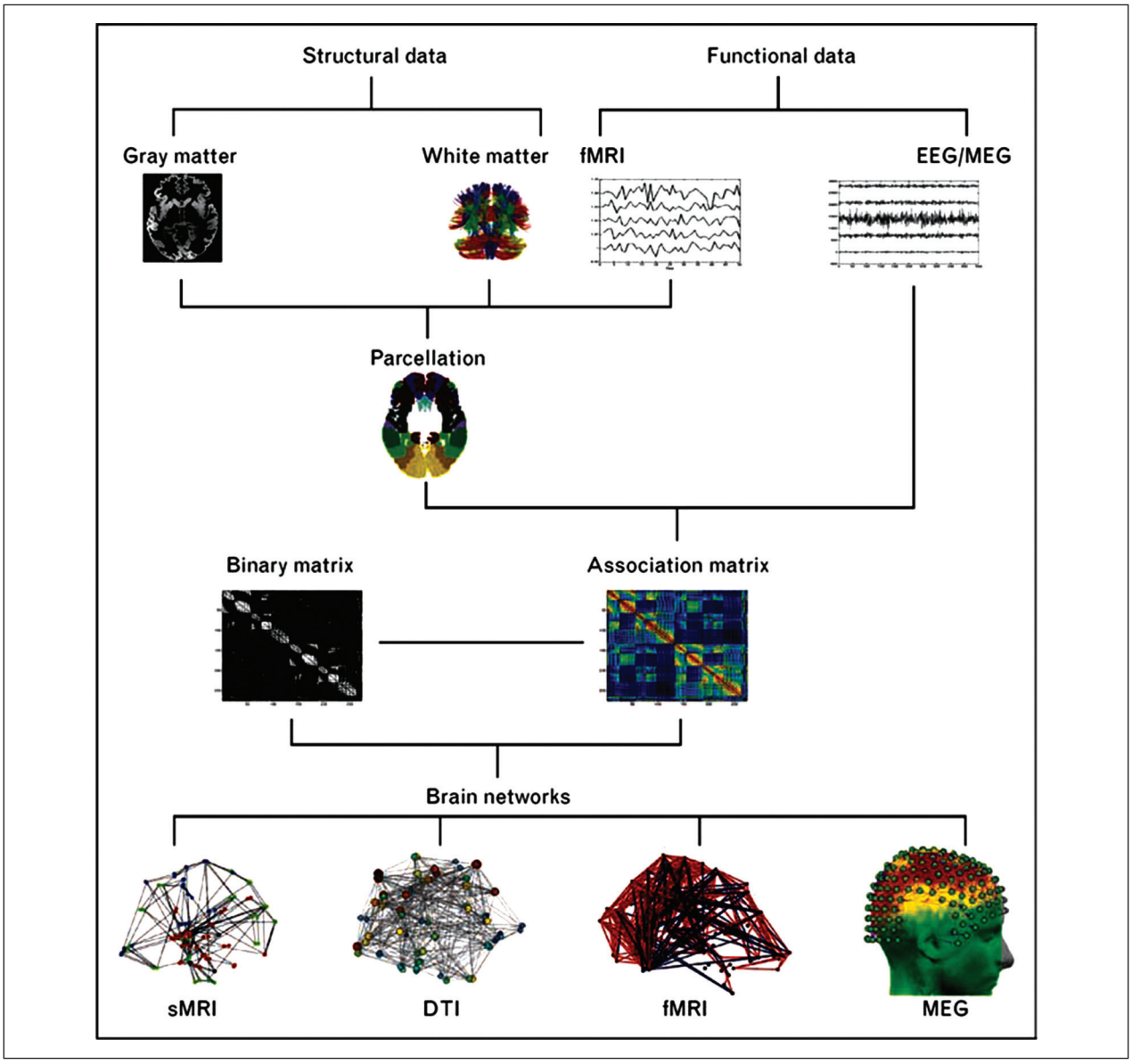


**Figure 1.** The workflow of brain network construction using multimodal neuroimaging data (Bassett and Bullmore 2009). Specifically, structural data include either gray or white matter measurements, and functional data include low-frequency fMRI data and high-frequency EEG or MEG data. Typically, the brain is parcellated into multiple (around 100) regions of interest that represent network nodes. For EEG and MEG data, each sensor already represents a node. The pairwise association between nodes is then computed and usually thresholded to create a binary matrix. A brain network is then constructed. DTI = diffusion tensor imaging; EEG = electroencephalography; MEG = magnetoencephalography; sMRI = structural MRI.

maximizes the efficiency of information transfer both globally and locally at a relatively low wiring cost (Bassett and Bullmore 2006).

In addition to the parameters for the whole network, connectivity properties for the individual nodes can be measured by several metrics such as the nodal efficiency and betweenness centrality (Boccaletti and others 2006). The nodal efficiency is the mean of the inverse of the shortest path length between the node and all other nodes in the network. The betweenness centrality of a node is the number of shortest paths between any two nodes that run through the node. These nodal metrics quantify the importance of the nodes for the information transfer within the network.

## Gender Difference in Anatomical Connectivity

### Morphology of WM Using Structural MRI

*Gender differences of WM volume in normal adults*. Taken as a marker for the total amount of anatomical connectivity, WM volume has been repeatedly applied to study gender effects on anatomical connectivity. In an early study, Filipek and colleagues (1994) reported a significantly smaller absolute volume of WM in adult women by segmenting out the WM from the structural MRI data set. Subsequent investigation from Gur and colleagues (1999) demonstrated that women also had a smaller percentage of WM but a higher percentage of GM than men, which sustained a correction for total intracranial volume. Interestingly, Gur and colleagues further showed that WM volume correlated moderately with global, verbal, and spatial performance, but the regression of cognitive performance and WM volume was significantly steeper in women. A recent study has replicated the results of smaller WM for both absolute and relative volume of women in a large sample of adults (Leonard and others 2008). In addition to the relative WM volume to the total cerebral volume, Allen and colleagues (2003) found that the gray/white (G/W) volume ratio was consistently higher across all lobes in women than in men, which is largely attributed to greater variation in WM volume. Taken together, previous results consistently suggested a smaller total volume of WM in adult women as compared with men.

*Gender effects on WM volume during normal development and aging*. Gender differences in brain neuroanatomy may vary over the life span; therefore, the gender effect has been frequently studied in normal development and aging. Using developmental data sets, multiple studies have demonstrated significant gender-by-age interactions on WM volume during adolescence, consistently showing boys with more prominent or a steeper increase of WM volume as compared with girls (De Bellis and others 2001; Giedd and others 1999; Lenroot and others 2007; Perrin and others 2009). However, studies of gender effects on WM volume in aging data sets have yielded mixed results. For example, Lemaitre and colleagues (2005) found more absolute WM together with larger WM fractions in men but no gender-by-age interaction in an elderly sample. In parallel, using a voxel-based morphometry (VBM) method, Smith and colleagues (2007) reported that men had more WM than women, but there was no significant gender difference in WM volume after controlling for brain size and no gender-by-age interaction in an elderly cohort. In contrast, a recent study observed a less absolute WM volume but a larger WM fraction in women as well as a significant gender-by-age interaction, showing a less prominent decrease of WM volume with age for women in a large life span sample aged from 20 to 71 (Abe and others 2010).

*Gender differences in the morphology of the corpus callosum*. In addition to WM volume, a large number of studies have investigated gender differences in the morphology of the corpus callosum (CC), the major WM tract connecting the two hemispheres. Typically, the CC was extracted by outlining (manual or automatic) its border on the midsagittal slice of structural MRI data. It has been suggested that larger callosal size indicates greater interhemispheric anatomical connectivity (Aboitiz and others 1992). We will focus on relatively new findings of the gender difference in the CC (predominantly after 2000), given the limited space. For a review of early studies on this topic, see Bishop and Wahlsten (1997).

As before, recent results of a gender effect on the CC morphology are controversial. For example, Leonard and colleagues (2008) recently demonstrated a smaller absolute but a larger relative area (adjusted for brain size) for the total CC in adult women. This finding was supported by a few studies (Westerhausen and others 2004) but conflicts with others showing negative or even opposite results (Luders and others 2003; Sullivan and others 2001). According to the study by Jancke and colleagues (1997) showing that a smaller brain tends to have a larger CC/brain ratio regardless of sex, the putative gender difference in the size of CC might be more properly attributed to differences in brain size. More specifically, prior studies found that adult women have a larger or more bulbous shape in the splenium of the CC (Davatzikos and Resnick 1998). During adolescence, De Bellis and colleagues (2001) demonstrated that CC area, after adjusting for brain size, increases more prominently in boys than in girls. Intriguingly, a recent study reported that behavioral asymmetry was positively correlated with callosal area in mixed-handed females but not in other groups (Welcome and others 2009).

### Diffusion Properties of WM Using Diffusion MRI

*Gender effect on WM diffusion properties in normal adults*. As the predominant tool used for WM studies, diffusion MRI has been employed to investigate gender differences in the WM microstructural integrity. Multiple studies have been conducted to test gender effects on the diffusion properties of the CC. Specifically, Westerhausen and colleagues demonstrated that men have a higher overall RA than women on the midsagittal CC (Westerhausen and others 2004; Westerhausen and others 2003), which was replicated by others studies showing increased FA and myelin water fraction (MWF) of the CC in adult men (Liu and others 2010; Shin and others 2005). In particular,

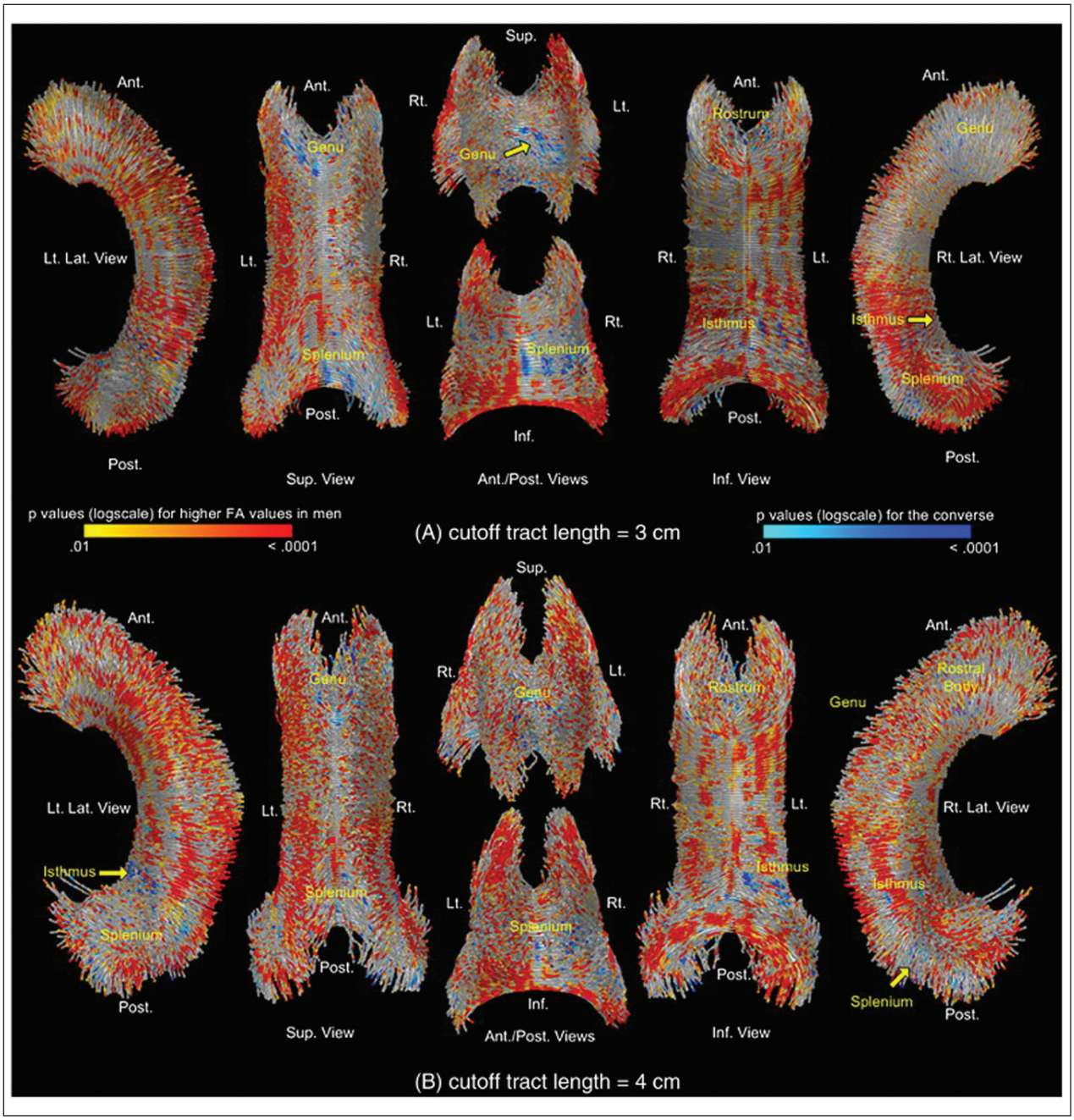


**Figure 2.** Significant gender effect on regional fractional anisotropy (FA) of the corpus callosum (CC) in 29 normal young adults (Oh and others 2007). The authors developed a tractography-guided (TGI) parameterization method that allows for statistical analysis on both midsagittal and parasagittal structure of the CC. Specifically, cutoff tract length from seed points is (*A*) 3 cm and (*B*) 4 cm, respectively. Yellow to red areas represent regions where the FA values were found to be significantly higher in men; the converse is shown as cyan to blue (see color bars). As shown, men have higher FA values for global CC structure areas in the parasagittal and midsagittal space but lower FA values in the partial areas of the rostrum, genu, and splenium.

Oh and colleagues (2007) developed a tractography-guided (TGI) parameterization method, allowing for the analysis of both midsagittal and parasagittal structures of the CC. On the basis of this method, the authors observed that men had significantly higher FA values for global CC structure areas in the parasagittal and midsagittal space but lower FA values in the partial areas of the rostrum, genu, and splenium (Fig. 2). Together, adult men consistently exhibited a higher overall FA of the CC as compared with women in recent studies.

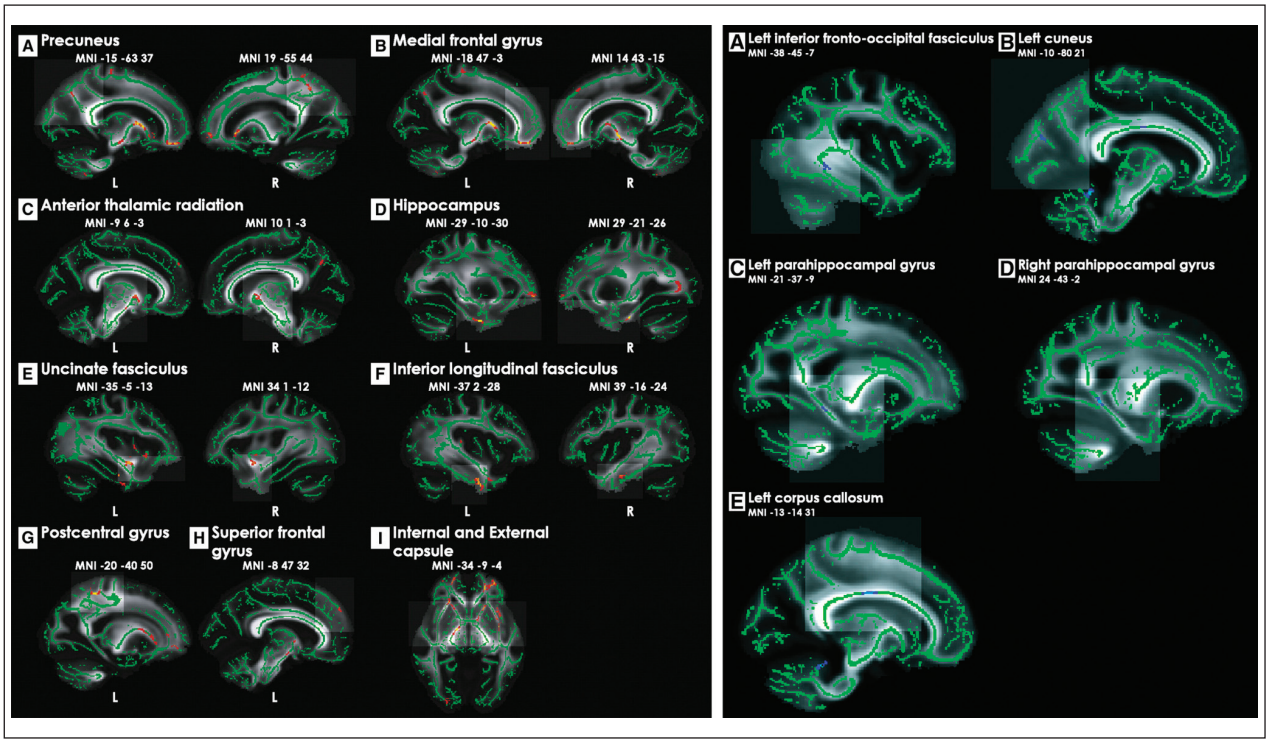


**Figure 3.** Regions with significant gender effect on fractional anisotropy (FA) in a cohort of 80 adults using the tract-based spatial statistic (TBSS) method (Chou and others 2010). Left and right figures illustrate significantly higher and lower FA in men compared with women, respectively. The mean group FA skeleton (green) was overlaid on the mean_whole_group_FA images in the axial, sagittal, and coronal views. The higher FA voxels in men versus women were highlighted on the mean FA skeleton in red to yellow, whereas the lower FA voxels in men versus women were colored in blue. As shown, there are widespread gender differences of FA across the entire brain.

In addition to the CC, gender differences in diffusion parameters have been reported in multiple other WM tracts or spatial locations. For instance, Szeszko and colleagues (2003) found that adult women had higher FA in the left frontal lobe, and only women had a leftward asymmetry of FA. In a region-of-interest (ROI) study, adult men also showed a larger volume, a higher FA, and a lower MD in bilateral midcingulum bundles, whereas a leftward asymmetry of both FA and volume was observed in both men and women (Huster and others 2009). A recent tractography study has reported gender differences in the temporal lobe WM (Choi and others 2010). Specifically, bilateral inferior longitudinal fasciculus (ILF) has a slightly higher MD in women. In particular, the asymmetry indices for FA and MD of the superior longitudinal fasciculus (SLF) were significantly correlated with the FA and MD of the CC only in women. Using the tract-based spatial statistic (TBSS) method, Rametti and colleagues (2010) found significantly lower FA values in the SLF, the forceps minor, and the corticospinal tract in normal adult women. In contrast, another recent TBSS study reported more widespread gender difference of FA. Specifically, women showed higher FA in the fronto-occipital fasciculus, body of the CC, and WM underlying the parahippocampal gyrus but lower FA values in the bilateral internal capsule, WM underlying the medial frontal gyrus, fusiform gyrus, hippocampus, insula, postcentral gyrus, and frontal and temporal lobe (Chou and others 2010; Fig. 3). Intriguingly, the authors further demonstrated that women showed a positive correlation of the systemizing quotient (SQ, a test of the capacity to analyze rules governing input-operation-output relations) with FA of WM in the inferior parietal lobule and superior temporal gyrus but a negative correlation of the empathizing quotient (EQ, a test of the capacity to infer mental states) with FA of the occipital and postcentral gyrus. However, men displayed the opposite effect.

*Gender effect on WM diffusion properties during normal development and aging*. Unsurprisingly, gender effects on WM diffusion properties have been examined in cohorts of development. A ROI study comparing adolescents to older adults have reported significant gender differences of RA, markedly in the cingulum bundle and internal capsule (Schneiderman and others 2007). Another ROI study showed significantly larger MD values in temporal lobe

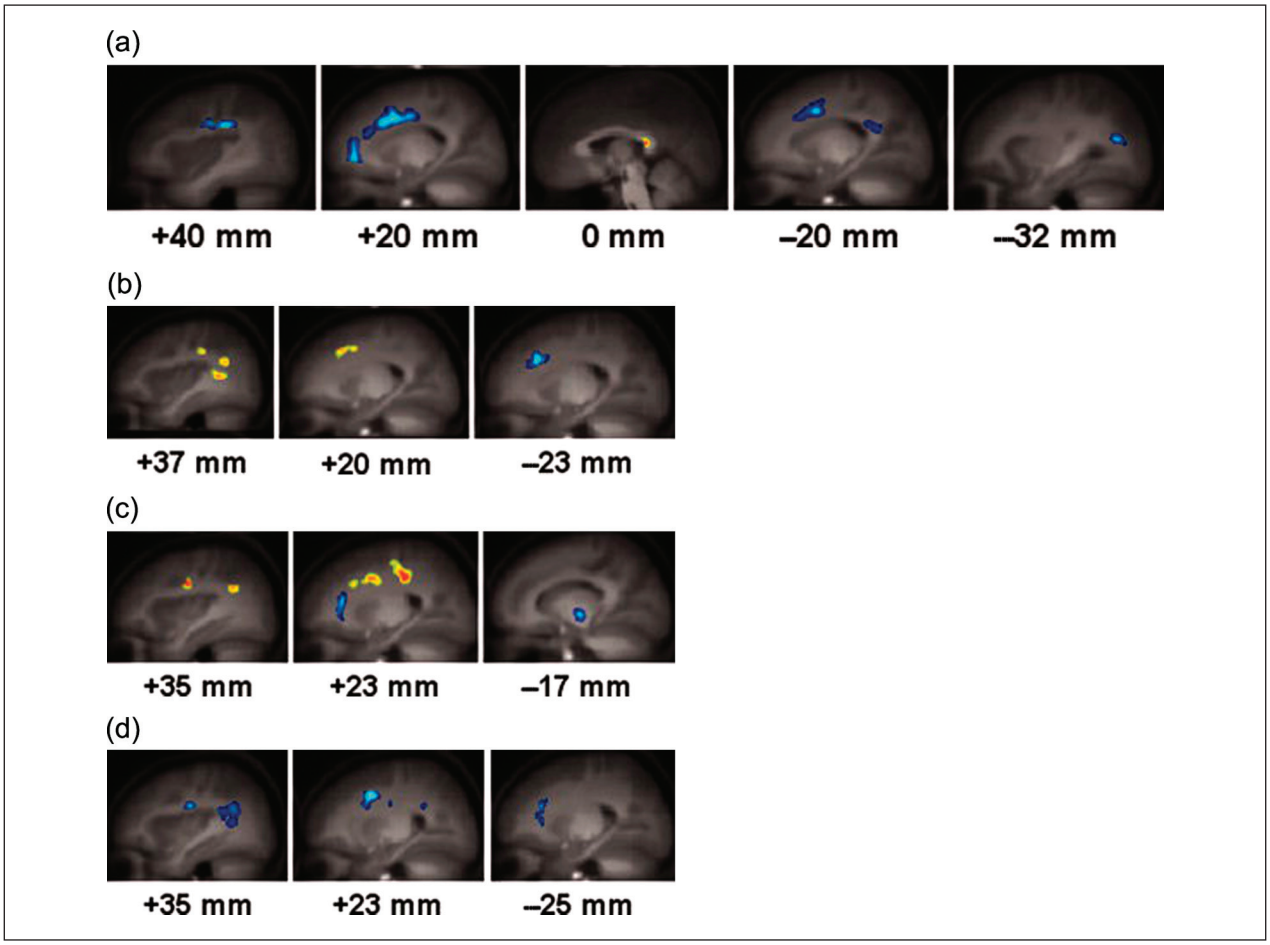


**Figure 4.** Gender effect on white matter (WM) diffusion parameters in a cohort of 105 children and adolescents aged from 5 to 18 years (Schmithorst and others 2008b). (*a*) WM areas with a significant main effect of gender on fractional anisotropy (FA) (blue = boys > girls, yellow-red = girls > boys). (*b*) WM areas with a significant gender-by-age interaction on FA (blue = boys > girls, yellow-red = girls > boys). (*c*) WM areas with a significant main effect of gender on mean diffusivity (MD) (blue = boys > girls, yellow-red = girls > boys). (*d*) WM areas with a significant gender-by-age interaction on MD (blue = boys > girls). Slice location (sagittal; Talairach coordinate system) is given at the bottom of each frame.

WM in boys but larger MD values in the cingulum in girls (Bonekamp and others 2007). A tractography study revealed that girls had lower transverse diffusivity (TD) in bilateral ILF and in the right inferior fronto-occipital fasciculus compared with boys (Eluvathingal and others 2007). In a cohort aged from 5 to 18 years, Schmithorst and colleagues (2008a) systematically investigated gender effects on the FA and MD across the entire brain by using a voxel-based analysis (Fig. 4). Specifically, the results showed higher FA in the left occipitoparietal, right frontal, left parietal, and left frontal WM and the right arcuate fasciculus for boys but higher FA in the splenium of the CC for girls. On the other hand, boys showed higher MD in the corticospinal tract and in the right frontal lobe WM; girls displayed higher MD in the right arcuate fasciculus and in the right occipitoparietal WM. There are significant gender-by-age interactions. Girls displayed a faster decline of MD in the WM of bilateral left and right frontal lobes, the right arcuate fasciculus, and right occipitoparietal WM. Surprisingly, girls showed increasing FA with age, but boys displayed decreasing FA in the right arcuate fasciculus, whereas boys showed increasing FA with age but girls displayed decreasing FA in the left frontal lobe. In a subsequent study, Schmithorst (2009) further revealed significant gender-by-IQ interactions on FA in the left frontal lobe, in frontoparietal areas bilaterally, and in the arcuate fasciculus bilaterally. Specifically, girls showed positive correlations of FA with IQ, whereas boys displayed a negative correlation. Significant gender-by-IQ-by-age interactions on FA were also observed in the left frontal lobe and in frontoparietal areas bilaterally, suggesting a developmental effect. Another recent TBSS study

also reported a significant gender-by-age interaction during adolescence, with girls showing a faster TD decrease in the majority of the WM tracts related to age (Asato and others 2010). The results of faster TD decrease or FA increase imply earlier WM maturation in girls during adolescence, which, however, seems to conflict with the prior WM volume findings indicating a slower WM volume increase in girls (De Bellis and others 2001; Giedd and others 1999; Lenroot and others 2007; Perrin and others 2009). This discrepancy might be explained by the differences of the *g* ratio between boys and girls during adolescence (Paus and Toro 2009).

There have been several studies exploring gender effects on WM diffusion parameters in aging cohorts. Using a voxel-based analysis, Hsu and colleagues (2008) found significant gender differences of FA values in precentral, cingulate, and anterior temporal WM regions, but no gender-by-age interaction was observed. Compatibly, Hasan and colleagues showed no gender-by-age interaction on the WM diffusion properties of the CC in a life span data set (Hasan and others 2008; Hasan and others 2007). However, a recent voxel-wise study reported a significant gender-by-age interaction, with men showing a steeper FA decline in the right inferior frontotemporal areas, extending to the anterior cingulate cortex, and an accelerated MD in the bilateral frontal, temporal, and parietal areas (Abe and others 2010).

### *The Topology of Brain Anatomical Networks*

As described above, diffusion MRI tractography has been widely used to infer the anatomical connectivity between brain regions. Once interregional anatomical connectivity is derived for all possible regional pairs, the brain can be characterized as a complex network in which each region represents a network node, and two nodes are determined as connected or not in terms of diffusion MRI tractography results.

For the first time, Gong and colleagues (2009b) investigated aging and gender effects on the topology of the anatomical network in 95 normal subjects aged from 19 to 85 years (Fig. 5). Specifically, the cerebral cortex was divided into 78 cortical regions, and interregional connectivity probability was estimated by diffusion probabilistic tractography. Topological parameters such as local efficiency and global efficiency were computed for the cortical anatomical network of each subject, using a graph theory approach. Statistical analysis revealed a reduction in overall cortical connectivity with age. There were also changes in the underlying network organization that resulted in decreased local efficiency and also a shift of regional efficiency from the parietal and occipital to frontal and temporal neocortex in older brains. However, no gender-by-age interaction was observed for those network indices. After controlling for age and brain size, women showed greater overall cortical connectivity and higher values in both local and global efficiency. The findings suggested the possibility that women may make more efficient use of the available WM, consistent with the stronger association between cognitive performance and WM volume in women (Gur and others 1999). Furthermore, women had a higher regional efficiency in six cortical regions, including left Heschl's gyrus, superior temporal gyrus, superior parietal gyrus, inferior parietal gyrus, insula, and right fusiform gyrus. In contrast, men showed higher regional efficiency in the right rolandic operculum and triangular inferior frontal gyrus. Notably, there was a clear hemispheric asymmetry of gender differences in regional efficiency: Women had higher efficiency in five left hemispheric regions and one right hemispheric region, but men had higher efficiency only in two right hemispheric regions. Given that the left hemisphere is generally dominant in verbal and the right in spatial processing, this asymmetry of regional efficiency may underlie a female advantage in verbal processing and a male advantage in spatial processing (Hamilton 2008).

Subsequently, Yan and colleagues (2010) have replicated the gender difference in the topology of anatomical networks in 72 young adults. The study revealed a significant brain size effect on the network local efficiency. Women also showed greater local efficiencies than men. Moreover, the authors found a significant interaction between gender and brain size, with smaller brains showing higher local efficiency in women but not in men. In addition, several regions (e.g., the precuneus, precentral gyrus, and lingual gyrus) showed significant effects of gender, brain size, and their interaction on the regional centrality. The findings further support a different organizational pattern of anatomical connectivity between men and women.

## Gender Differences in Morphometric Connectivity

To date, only one study has reported gender differences in morphometric connectivity (Lv and others 2010). Specifically, two regional pairs exhibited significantly higher interregional cortical thickness correlation in women. One is between the right inferior temporal gyrus and the right middle temporal gyrus, and the other is between the left middle occipital gyrus and the left lateral occipitotemporal gyrus. However, further analysis of the morphometric network across the entire cerebral cortex showed no significant gender effect for regional vulnerability (a regional metric from graph theory), a finding that suggests a degree

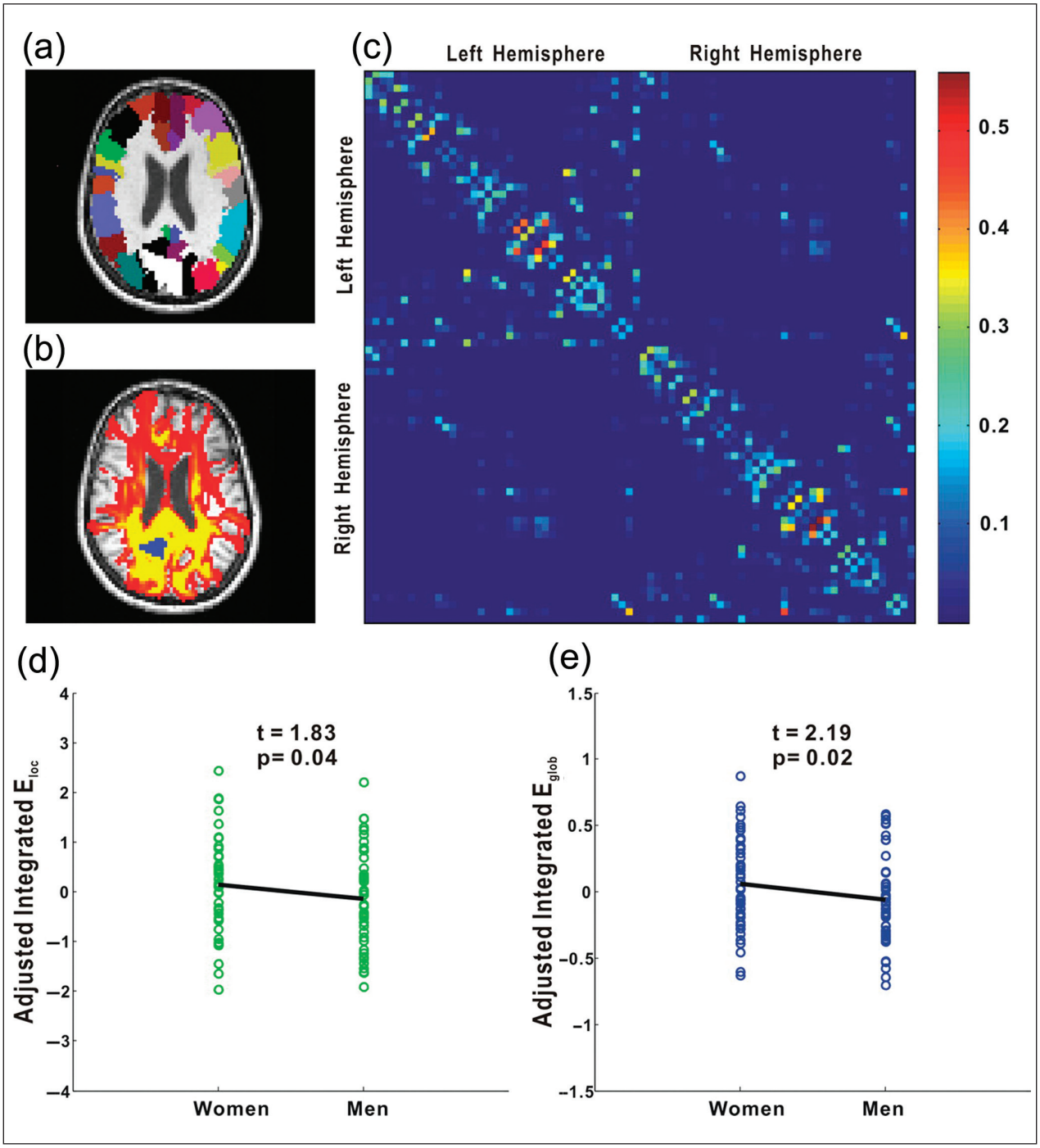


**Figure 5.** Gender differences of the topology of cortical anatomical networks in a cohort of 95 normal subjects aged from 19 to 85 years (Gong and others 2009b). (*a*) The parcellation mask for one subject, with each color representing a cortical region. (*b*) Connectivity probability using diffusion MRI tractography. The yellow-red color represents the resulting probability (yellow > red) from the left precuneus (marked as blue) to the other voxels. (*c*) The regional probability matrix from the probabilistic tractography for the same subject. Using the graph-theoretical approach, the local and global efficiency of anatomical networks were calculated for each subject. Statistical analysis demonstrated a significant gender effect on both integrated local efficiency (*d*) and global efficiency (*d*), with women showing higher efficiency. Notably, all results were obtained after adjusting for the effects of brain size and age, using a general linear model.

of consistency in the topology of a morphometric network between men and women.

## Gender Differences in Functional Connectivity

### *Functional Connectivity Derived from PET*

To our knowledge, there are few EEG/MEG studies that have observed gender differences in functional connectivity in the healthy brain. In contrast, a few PET studies have revealed such differences. In a very early study, Azari and colleagues (1992) observed gender differences in functional connectivity by using correlational analysis of normalized regional cerebral metabolic data in healthy subjects during a resting state. The results showed that females had more positive functional correlations in the left hemisphere (frontal and sensorimotor ROIs) but fewer functional correlations in the right hemisphere (sensorimotor and occipital ROIs). Recently, Kilpatrick and colleagues (2006), using seed-voxel partial least squares analysis of regional cerebral blood flow data, demonstrated gender-related differences in the functional connectivity for the amygdala in the resting brain. Specifically, the right amygdala showed a greater functional connectivity in men than in women, but the left amygdala showed the opposite trend. Interestingly, the brain regions showing stronger functional connectivity with the right amygdala in men (sensorimotor cortex, striatum, and pulvinar) significantly differed from those showing stronger functional connectivity with the left amygdala in women (subgenual cortex and hypothalamus). These gender differences shown in resting amygdala functional connectivity possibly link to gender-related differences in psychiatric disorders.

### *Functional Connectivity Derived from fMRI*

Several fMRI studies have examined gender differences in patterns of functional connectivity in task conditions. For example, Schmithorst and Holland (2006) investigated gender differences of functional connectivity during a semantic processing task, silent verb generation, in a large pediatric cohort. They observed a gender-by-IQ-by-age interaction in the functional connectivity between several brain regions in the left hemisphere (e.g., middle temporal gyrus, Broca's area, medial frontal gyrus, precuneus, and cingulate gyrus). Young girls (<13 years) exhibited no correlation of functional connectivity with intelligence, whereas older girls (>13 years) showed a positive correlation of connectivity with intelligence. In contrast, boys exhibited the opposite developmental trajectory, characterized by a positive correlation of brain connectivity with intelligence in young boys (age <9 years) to a negative correlation in older boys (age >13 years). In the same cohort, this group subsequently used Bayesian connectivity analysis to investigate gender differences in the interaction between intelligence and functional connectivity for the task of narrative comprehension (Schmithorst and Holland 2007). The results revealed a greater association in boys between intelligence and the functional connectivity among Broca's area and auditory processing areas but a greater association in girls between intelligence and the functional connectivity linking the left posterior superior temporal gyrus to Wernicke's areas bilaterally. Girls displayed a positive correlation with age in the association between intelligence and the functional connectivity linking the right posterior superior temporal gyrus to Wernicke's areas bilaterally, suggesting a developmental effect. In addition, Butler and colleagues (2007) showed that only women had anticorrelated functional connectivity between the ventral anterior cingulate cortex (vACC) and the dorsal ACC (dACC) during a visuospatial task of mental rotation (Butler and others 2007). The gender difference in the vACC-dACC connectivity might reflect gender specificity in the interaction between cognition and emotion.

As well as task-based investigations, gender differences in functional connectivity have been studied by using resting-state fMRI (R-fMRI) where subjects do not perform specific cognitive tasks. R-fMRI has recently attracted a great deal of interest because it is able to detect intrinsic or spontaneous brain activity in health and disease (Fox and Raichle 2007). A recent R-fMRI asymmetry study reports that both men and women have strong functional asymmetry in the vision, attention, language, and the default mode network (DMN) systems with a small but significant group difference in the laterality degree distribution of left lateralized brain regions, with women showing more symmetric functional organization than men (Liu and others 2009). Recently, Kong and colleagues showed gender differences in resting-state functional connectivity of the periaqueductal gray (PAG), a region known to play a crucial role in pain modulation (Kong and others 2010). Specifically, women exhibited greater connectivity from PAG to dACC and weaker connectivity from PAG to the left medial orbital prefrontal cortex, right insula/operculum, and prefrontal cortex. In a very large R-fMRI cohort of 1414 volunteers collected independently at 35 international centers, Biswal and colleagues (2010) examined gender effects on resting functional connectivity. Both independent component analysis (ICA) and seed-based functional connectivity analysis revealed that women exhibited significantly greater connectivity in the posterior cingulate cortex, medial prefrontal cortex, and inferior parietal lobe

but weaker connectivity in the dACC, insula, superior temporal gyrus, superior marginal gyrus, and occipital regions (Fig. 6). Zuo and colleagues (2010) recently revealed gender effects on the life span developmental trajectory of functional homotopy (i.e., homotopic resting functional connectivity). Specifically, functional homotopy showed an age-related increasing pattern for males in the dorsolateral prefrontal cortex (Broca's areas [BA] 9 and 46) but a decreasing pattern for females. In contrast, males exhibited an age-related decreasing pattern in functional homotopy in the amygdala, with females showing the opposite.

Notwithstanding the observations of gender differences in functional connectivity reported above, there have been other studies that report no effect of gender on functional connectivity. For instance, Weissman-Fogel and colleagues (2010) reported no such effect in three resting-state functional networks (executive control network, salience network, and DMN), implying a similar resting-state connectivity pattern between the genders.

### *The Topology of Brain Functional Networks*

Very recently, Tian and colleagues (2010) have employed R-fMRI to examine hemisphere- and gender-related differences in the topological organization of functional networks in the entire human brain. Specifically, brain functional networks were constructed by measuring interregional temporal correlations of R-fMRI data within each hemisphere in 86 young, healthy, and right-handed adults, followed by a graph-theoretical analysis. The hemispheric networks exhibited small-world attributes (i.e., high clustering and short characteristic paths). The authors further found that men had a higher normalized clustering coefficient in the right hemispheric network but a lower clustering coefficient in the left hemispheric network, suggesting a gender-by-hemisphere interaction.

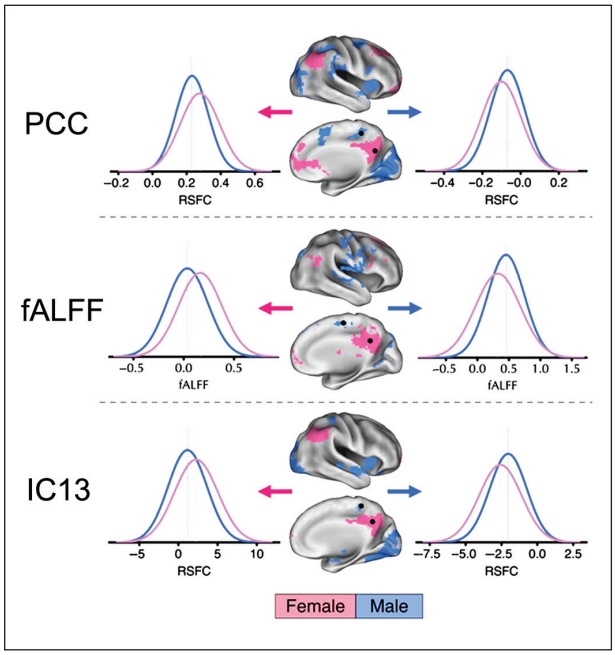


**Figure 6.** Illustrative areas showing significant gender effect on the resting-state fMRI properties in a large cohort of 1441 subjects from 35 international centers (Biswal and others 2010). Specifically, seed-based functional connectivity from the posterior cingulated cortex (PCC; first row), fractional amplitude of low-frequency fluctuation (fALFF) analysis (second row), and independent component analysis (ICA; third row) were applied to the data set. Group-level maps were derived from one-way analysis of variance across 1093 participants from 24 centers (factor: center; covariates: age and sex). All group-level maps depicted were corrected for multiple comparisons at the cluster level using Gaussian random-field theory ($Z > 2.3$; $P < .05$, corrected). "Male" (blue) refers to significantly greater connectivity (or amplitude) in males. Similarly, "female" (pink) refers to significantly greater connectivity (or amplitude) in females. Gender-related differences are represented as histograms depicting the distributions of resting-state functional connectivity (RSFC) values for males (blue) and females (pink) separately. Vertical lines indicate peak values. Corresponding topographical brain areas are indicated with black dots.

## Future Perspective

In this review, we concentrated only on recent literature involving gender difference of brain connectivity in the healthy human brain. There have been a few studies of brain connectivity in diseases that included a gender component (Labus and others 2008; Sachdev and others 2009; Slewa-Younan and others 2004). An intriguing future direction will be to reveal the association between gender-specific brain connectivity patterns and gender-related differences of various brain diseases. Many brain disorders show gender-specific incidence and/or clinical features. For example, autistic spectrum disorder has shown a higher prevalence in males (Yeargin-Allsopp and others 2003). In schizophrenia, male and female patients on average show different symptoms, age of onset, and the time course of the illness. It is possible that the differences in underlying brain connectivity may account for the gender-specific vulnerability and nature of these disorders.

Although group differences have been reported in numerous studies, only a few studies have considered behaviors and cognitive performance when examining brain connectivity between genders (Chou and others 2010; Schmithorst 2009; Welcome and others 2009). Whether differences of brain connectivity directly underlie specific cognitive differences between men and women remains unclear. To address this, more studies regarding the gender

effect on brain connectivity and/or networks should be conducted by combining with evaluation of gender-related cognitive performances.

It has been demonstrated that gender differences in brain connectivity vary over the life span. Moreover, gender has been shown to influence the development and aging of brain connectivity. It should be noted that previous results of a gender-by-age interaction on brain connectivity have been mixed, which may be attributed to sampling or other technical differences across studies. On the other hand, it remains largely unknown how the topological change of large-scale brain anatomical/morphometric/functional networks is modulated by gender during different stages of the human life span.

Finally, a recent challenge is to evaluate the relationship between anatomical, morphometric, and functional connectivity/network derived from different neuroimaging data (Rykhlevskaia and others 2008). Preliminary studies have suggested a degree of convergence between anatomical and functional networks (Honey and others 2007; Honey and others 2009). So far, the majority of gender-related studies have been confined to unimodal brain connectivity by using structural MRI, diffusion MRI, or fMRI data. It would be intriguing to perform a comprehensive analysis of gender effects on multimodal brain connectivity/network in the same population and further explore how the gender difference of each connectivity modality interacts with each other.

## Conclusion

In summary, recent neuroimaging studies have accumulated substantial evidences, supporting the notion that gender makes a difference in brain connectivity. This strongly suggests that gender has a significant influence on the patterns of neuronal communication within the human brain, possibly underlying cognitive and behavioral differences between genders. In reality, however, the gender dimension has been largely neglected in studies of brain connectivity, probably due to traditional misconceptions about this factor (Cahill 2006), and apparently conflicting findings might be attributed to the ignorance of gender effects. It should be mandatory to take gender into account when designing experiments or interpreting results of brain connectivity/network in health and disease. Future work on this topic will explore the interdependence of gender-related brain connectivity and the gender-specific nature of some brain disorders, as well as investigate the interactions between gender-related multimodal brain connectivity.

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