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Inferior Frontal White Matter Asymmetry Correlates with Executive Control of Attention

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Abstract: White matter (WM) asymmetries of the human brain have been well documented using diffusion tensor imaging (DTI). However, the relationship between WM asymmetry pattern and cognitive performance is poorly understood. By means of tract-based spatial statistics (TBSS) and voxel-based analyses of whole brain, this study examined the WM asymmetries and the correlations between WM integrity/asymmetries and three distinct components of attention, namely alerting, orienting, and executive control (EC), which were assessed by attention network test (ANT). We revealed a number of WM anisotropy asymmetries, including leftward asymmetry of cingulum, corticospinal tract and cerebral peduncle, rightward asymmetry of internal capsule, superior longitudinal fasciculus and posterior corona radiata, as well as heterogeneous asymmetries in anterior corpus callosum and anterior corona radiata (ACR). Moreover, specific correlation was found between asymmetric pattern of inferior frontal ACR and EC performance. Additionally, this study also proposed that there were no significant relationships of WM anisotropy asymmetries to alerting and orienting functions. Further clusters of interest analyses and probabilistic fiber tracking validated our findings. In conclusion, there are a number of differences in WM integrity between human brain hemispheres. Specially, the anisotropy asymmetry in inferior frontal ACR plays a crucial role in EC function. Our finding is supportive of the functional studies of inferior frontal regions and in keeping with the theory of the brain lateralization on human ventral attention system. *Hum Brain Mapp 34:796–813, 2013.* © 2011 Wiley Periodicals, Inc.

Key words: diffusion tensor imaging; asymmetry; attention network test; anterior corona radiata; inferior frontal lobe

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INTRODUCTION

Human brain hemispheres differ in their anatomy and function [Toga and Thompson, 2003]. The quantification of brain asymmetries may provide unique information about how homologous regions between cerebral hemispheres function in conjunction as a network or exert irrelevant effects, and therefore extend our understanding of neural structure-function relationships in health and disease. For example, Fornito et al. [2004] found that leftward asymmetry of paracingulate sulcus was associated with better performance on both verbal and spatial tasks. This may be attributed to the underlying hemispheric differences in cortical thickness [Fornito et al., 2008] and functional interactions [Yan et al., 2009] within prefrontal regions. In addition to the normal asymmetries, some neurologic diseases also showed lateralized pathologies between two hemispheres [Koziol et al., 2005; Muhlau et al., 2007]; and disturbances in structural or functional brain asymmetries have been detected in psychotic disorders, such as schizophrenia [Kawasaki et al., 2008; Narr et al., 2001; Takao et al., 2010a; Zhou et al., 2003] and bipolar disorder [Reite et al., 1999].

Voxel-based morphometry (VBM) method for structural magnetic resonance imaging (MRI) data has been extensively applied to investigate brain asymmetries on grey matter [Luders et al., 2004; Watkins et al., 2001] and white matter (WM) [Good et al., 2001; Zhou et al., 2003]. Compared with structural MRI measures of WM volume or density, diffusion tensor imaging (DTI) provides more information about WM tissue microstructure and organization, because it examines specific fiber tracts and can be used to study connectivity between neural regions of interest (ROI). The most commonly used metric of DTI is fractional anisotropy (FA), which represents the degree of constrained water diffusion along the axons and the myelin [Mori and Zhang, 2006]. Greater FA may reflect greater myelination of WM fibers, greater number of myelinated fibers, or greater longitudinal vs. oblique directional alignment of myelinated fibers in WM tracts.

Nowadays, a rising number of DTI studies concerning WM asymmetries chose the ROI-based [Huster et al., 2009] or voxel-based [Ardekani et al., 2007; Jahanshad et al., 2010; Park et al., 2004] analysis of anisotropy maps, and/or tractography-based analysis [Verhoeven et al., 2010] (for a summary, see Table I). However, there has been much debate about these methods applied for WM asymmetry studies. First, the ROI method is operator dependent and time consuming. The asymmetry results are influenced by the ROI definition and reliability of measurement. Second, in order to keep structural homology between WM structures in the left and right hemispheres, voxel-based asymmetry analysis usually needs to construct the standard symmetry template for registration. However, the gray/white matter boundary would be ambiguous in this template. Besides, spatially smoothing before voxel-wise statistics can greatly affect the final results and also increase partial volume effect [Smith et al., 2006; Van Hecke et al., 2010]. Third, the tractography technique also requires the automated or manual segmentation of ROI, and the asymmetry results would be contaminated by many parameters, such as the FA threshold and voxel numbers. In addition, the fiber pathways derived from conventional tractography usually pass through large-scale WM regions, and hence the resulting asymmetry levels may be vulnerable to the inadequate estimation of fiber orientation in brain areas of fiber crossing. Finally, the registration (linear/nonlinear) methods used in above analyses will alter the relative volumes of different brain regions. As such, differences in hemispheric integrity may reflect not just a signal difference from the same structure in both hemispheres but a lack of homology [Jahanshad et al., 2010].

Tract-based spatial statistics (TBSS), which allows voxel-wise statistical comparison between individual subjects' DTI data [Smith et al., 2006], has potential advantages for investigation of WM asymmetries. In TBSS, a skeletonized (the centers of WM tracts) FA map is created, and correspondences across subjects are based on distance, rather than by computing a correspondence field for the entire image [Smith et al., 2006]. Moreover, spatial smoothing is no necessary in the image processing, because FA tract skeleton is more Gaussian and lower variable [Takao et al., 2011a]. TBSS has been wildly used to investigate the structure-behavior correlations [Johansen-Berg et al., 2007; Kochunov et al., 2010; Rudebeck et al., 2009], and most recently one study has used TBSS to evaluate the effect of scanner on WM asymmetries in elderly people [Takao et al., 2011a]. However, the detailed WM asymmetries assessed by TBSS have not been identified yet.

Conversely, it has become a matter of concern to know whether the asymmetries of brain structures modulate cognitive specialization. Up till now, dominance of language function to the left hemisphere and of spatial attention to the right has been commonly considered a distinctive aspect of human brain organization [Iturria-Medina et al., 2011; Kinsbourne, 1978; Toga and Thompson, 2003]. As evidence of brain asymmetry for attention function accumulated from lesion [Malhotra et al., 2009; Mort et al., 2003], functional [Jansen et al., 2004; Prado et al., 2011] and anatomical [Thiebaut de Schotten et al., 2011b] findings, the concept of attention has become essential for interpreting the ubiquitous patterns of brain asymmetries, such as the right-ear advantage for verbal material [Hiscock and Kinsbourne, 2011]. Nevertheless, compared with the well-documented brain left-hemispheric asymmetry for language [Catani et al., 2007; Gannon et al., 1998; Glasser and Rilling, 2008], there is still no agreement on the neural basis of functional asymmetries for attention, partly due to the inconsistency among the various models of attention systems.

As the central theme in cognitive science, attention refers to both the preparedness for and selection of certain environmental or mental aspects [Raz and Buhle, 2006]. Because of the brain's limited capacity to handle

TABLE I. A summary of WM asymmetries assessed by DTI

Studies	Subjects	Methods	Leftward asymmetry	Rightward asymmetry
Thiebaut de Schotten et al. [2011a]	40 (20 M)	TBA	CST,B-W tracts, and frontotemporal segment of AF in males	IFOF and anterior frontal-parietal connections of AF
Thiebaut de Schotten et al. [2011b]	20 (11 M)	TBA		SLF III
Takao et al. [2011a]	224 (161 M)	TBSS	AF, cingulum and CST	Present but not defined
Takao et al. [2010b]	109 (51 M)	VBA	Posterior part of IC, AF, cingulum, and CST(no difference in gender)	Frontal WM, UF, PCR, and posterior CC
Qiu et al. [2011]	75 (40 M)	TBA	AF	
Kang et al. [2011]	56 (28M)	VBA and ROI	Pericortical WM in insula, peri-Sylvian language regions, and superior parietal and motor regions	Pericortical WM in superior temporal sulcus, superior and paracentral frontal lobe
Verhoeven et al. [2010]	78 (3 L; 55 M)	TBA and ROI	FA measure: SLF, temporal part of SLF, CgH, ILF, and SCP; MD measure: temporal part of SLF	FA measure: ATR; MD measure: ATR, CgH, IFOF, UF, and SCP
Takao et al. [2010a]	48 (24 M) controls	VBA	AF, cingulum and CST	present but not defined
Schulte et al. [2010]	16 (M) controls	TBA	no asymmetry in cingulum (superior, posterior and inferior sectors)	
Putnam et al. [2010]	21 (11 M)	TBA		splenium of CC
Propper et al. [2010]	26 (7 L; 9 M)	TBA	AF	
O'Donnell et al. [2010]	26 (5 L; 9 M)	histogram	AF, cingulum and occipitofrontal connections	ATR, SLF/anterior segment of AF, UF
Lange et al. [2010]	37 (M) controls	ROI	WM FA and MD in superior temporal gyrus	
Jahanshad et al. [2010]	374 (154 M) twins	VBA	Temporal lobe	Frontal lobe
Trivedi et al. [2009]	51 (21 M)	TBA	Cingulum	
Oechslin et al. [2009] and Imfeld et al. [2009]	13 (6 M) controls	TBA		SLF, CSF
Lebel and Beaulieu [2009]	183 (97 M)	TBA	AF	
Huster et al. [2009]	79 (45 L; 39 M)	ROI	middle cinculum	
Hasan et al. [2009]	108 (47 M)	TBA	UF	
Dubois et al. [2009]	23 (12 M) infants	VBA and TBA	AF and CST	
Upadhyay et al. [2008]	4 M	DTS	AF	
Glasser and Rilling [2008]	20 M	TBA	Temporal sectors of AF	
Westerhausen et al. [2007]	60 (30 L; 30 M)	ROI	CST at the level of IC	
Wakana et al. [2007]	10 (5 M)	TBA	cingulum	CgH
Vernooij et al. [2007]	20 (13 L; 9 M)	TBA	AF, no aymmetry in CST	
Rodrigo et al. [2007a]	18 (5 M)	TBA	AF and subinsular WM (UF and IFOF)	
Rodrigo et al. [2007b]	10 (6 M) controls	TBA		UF
Lutz et al. [2007]	35 (19 M)	ROI	no asymmetry in acoustic pathway	
Catani et al. [2007]	50 (30 M)	TBA	B-W tracts	
Bonekamp et al. [2007]	40 (22 M)	ROI	FA measure: SCR, cingulum, and centrum semiovale; MD measure: frontal WM, et al	FA measure: frontal WM; MD measure: body of the CC
Barrick et al. [2007]	30 (15 M)	TBA	Pathways connecting temporal lobe to inferior parietal lobule and frontal lobe	Pathway connecting posterior temporal lobe to superior parietal lobule
Ardekani et al. [2007]	20 (11 M)	VBA, ROI	anterior limb of external capsule, posterior limb of IC, thalamus, cerebral peduncle and temporal-parietal regions	Genu, splenium and body of the CC

TABLE I. (Continued)

Studies	Subjects	Methods	Leftward asymmetry	Rightward asymmetry
Reich et al. [2006]	20 (5M)	TBA	no asymmetry in CST	
Powell et al. [2006]	10	TBA	B-W tracts along SLF	
Snook et al. [2005]	60 (5 L; 28 M)	ROI	no asymmetry in CC, IC, corana radiata, et al	
Parker et al. [2005]	11 (6 M)	TBA	B-W tracts (AF, external capsule/uncinate fasciculus)	
Nucifora et al. [2005]	27 (14 M)	TBA	AF, no aymmetry in CST	
Gong et al. [2005]	31 (20 M)	ROI	anterior cingulum	
Wang et al. [2004]	20 (M) controls	ROI	anterior cingulum	
Park et al. [2004]	32 (M) controls	VBA	Anterior part of CC, cingulum, optic radiation and SCP	Anterior limb of the IC, anterior limb's prefrontal regions, UF and SLF
Buchel et al. [2004]	43 (9 L; 25 M)	VBA	AF	
Szeszko et al. [2003]	20 (2 L; 9 M)	ROI	frontal lobe FA in women, rather than men	
Kubicki et al. [2002; 2003]	18 (M) controls	ROI	UF, cingulum	
Cao et al. [2003]	15 (10 M)	ROI	Subinsular WM	
Peled et al. [1998]	24 (8 L; 16 M)	ROI		Anterior limb of IC

The asymmetry results of normal controls in 8 DTI studies of diseases were also included. DTS, diffusion tensor spectroscopy; L, left-handed; M, males; ROI, region of interest; TBA, tractography-based analysis; VBA, voxel-based analysis; AF, arcuate fasciculus; ATR, anterior thalamic radiation; B-W tracts, tracts connecting Broca's and Wernicke's territories; CC, corpus callosum; CgH, hippocampal part of cingulum; CST, corticospinal tract; IC, internal capsule; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; PCR, posterior corona radiata; SCP, superior cerebellar peduncle; SCR, superior corona radiata; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus.

information, the appropriate selection of information for processing becomes especially critical in our daily life. Although many competing theories have proposed a number of potential components of attention, recent brain imaging studies have consistently supported the notion that there are three key distinct subsystems of attention, namely alerting, orienting, and executive control (EC) [Fan et al., 2005; Niogi et al., 2010; Posner and Petersen, 1990; Thiel et al., 2004; Thimm et al., 2010; Westlye et al., 2011]. Briefly, alerting is defined as achieving and maintaining a state of high sensitivity; orienting is the selection of sensory information; and EC is involved with the process of resolving cognitively incongruent stimuli [Posner, 2008].

In order to isolate the functional components of attention and investigate their association, Fan and colleagues [Fan et al., 2005; Fan et al., 2002] invented the attention network test (ANT). Combining the cued response time (RT) and the flanker [Eriksen and Eriksen, 1974] tasks, ANT could provide a means for exploring the behavioral reaction and the brain activity of the alerting, orienting, and EC networks in a single integrated task. Therefore, ANT has been used in numerous researches on normal populations [Fan et al., 2007a,b; Konrad et al., 2005; Niogi et al., 2010; Westlye et al., 2011] as well as patients with neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD) [Adolfsdottir et al., 2008; Konrad et al., 2006], schizophrenia [Gooding et al., 2006; Neuhaus et al., 2007; Opgen-Rhein et al., 2008; Urbanek et al., 2009], and autism [Keehn et al., 2010].

Although enormous progress has been made to identify neural correlates of attention function, the hemispheric asymmetries of related structure and function are still very controversial. For instance, some studies indicated that RT of visuospatial attention tasks was associated with functional connectivity [Prado et al., 2011] and FA values [Tuch et al., 2005] on the right attention pathways. A pathway of rightward asymmetry connecting the posterior temporal lobe to the superior parietal lobule, which is related to auditory spatial attention, has also been identified [Barrick et al., 2007]. Whereas, a number of previous fMRI studies showed that attention function tended to only activate the left dorsolateral prefrontal cortex [Botvinick et al., 1999; Fan et al., 2007b; MacDonald et al., 2000; Silton et al., 2010], which is a crucial node for EC of attention [Raz et al., 2006]. Furthermore, DTI studies have found that the WM integrity in left anterior corona radiata (ACR) [Niogi et al., 2010], or right anterior thalamic radiation (ATR) [Mamah et al., 2010], was associated with the EC function. The structure–function correlations between alerting and the anterior limb of the internal capsule (left), orienting and the splenium of the corpus callosum [Niogi et al., 2010] as well as left cingulum [Nestor et al., 2007], have also been reported.

The above studies suggest that separately cortical regions and WM tracts may correlate specifically with distinct attention domains. However, these seemingly contradictory results indicate that much remains to be learned about how morphological asymmetries, especially in WM, may underlie specific components of attention function. Therefore, the main purpose of this study was to assess the effects of DTI asymmetries on individual differences in attention performances. We used TBSS and voxel-based analyses of whole brain to investigate WM integrity asymmetries and for the first time to evaluate their relationships to distinct components of attention. We also validated the estimates through clusters of interest analyses and probabilistic fiber tracking. The results thereby could contribute to our further understanding of the integrated role of brain regions in attention network.

MATERIALS AND METRODS

Subjects

A total of 59 healthy young subjects (31 males) aged 15–19 years were included in the study. All were native speakers of Chinese with normal or corrected-to-normal vision. There were three inclusion criteria. (1) They were right-handed measured with Edinburgh Inventory [Oldfield, 1971]; (2) They had normal neurological exams, no history of psychological illness, and no abnormal findings in conventional brain MR images; (3) The accuracy of ANT performance was not less than 80% and the scores of EC were positive.

The men and women did not differ in mean age (17.3 ± 1.3 vs. 17.5 ± 1.5 years, with the precision of month) and education years (8.2 ± 1.1 vs. 8.4 ± 1.3 years). All subjects were interviewed by Chinese Version of Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) Scale [Carver and White, 1994] and no difference between genders was found. The study was approved by the Human Research Ethics Committees of the Shandong University School of Medicine. Written informed consent was obtained from all participants as well as their parents.

Behavioral Task

A version of the ANT devised by Fan and colleagues [Fan et al., 2005] was adapted as the cognitive task for this study. It could examine the efficiency of the alerting, orienting, and EC networks involved in attention in a single integrated task. Briefly speaking, subjects were instructed to press a button as quickly and accurately as possible to make a left-right determination of the target, which was a leftward or rightward arrow at the center and flanked on either side by two arrows in the same direction (congruent condition), or in the opposite direction (incongruent condition). The target and flankers were presented until the participant responded or 2000 ms elapsed. A cue (an asterisk) was presented for 200 ms before the appearance of target. There were three cue conditions: no cue (baseline), center cue (at the fixation for alerting), and spatial cue (at the target location for alerting plus orienting).

In each block, the six trial types (three cue conditions by two target conditions) were presented in a predetermined counterbalanced order. Both the durations between cue and target, and between two trials, were varied systematically. Each subject performed a total of six blocks of trials, each block lasting 5 min 42 s and consisting of 36 trials plus 2 buffer trials at the beginning. All the subjects were trained before the formal operation. Stimulus presentation and behavioral response collection were performed using E-Prime (Psychology Software Tools, Pittsburgh, PA) on the experimental control computer.

MRI Data Acquisition

MR imaging was carried out using a 3-T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI). First, the diffusion MRI was collected using spin-echo, single shot echo planar imaging sequence (TR/TE = 14,000/75.1 ms, 96 × 96 matrix, FOV = 250 mm, 2.6 mm thick slices, no gap) before the behavioral operation. The DTI scheme included 30 nonlinear diffusion gradients directions with $b = 1{,}000\ \text{s/mm}^2$ and 3 nondiffusion-weighted images ($b = 0\ \text{s/mm}^2$). Array spatial sensitivity encoding technique (ASSET) was used with an acceleration factor of 2. Acquisition time can be reduced by the ASSET method with less image distortion from susceptibility artifacts [Yu et al., 2008]. From each participant 56 axial slices were acquired and the diffusion sequence was repeated two times to increase signal-to-noise ratio.

At the end of the DTI scans, a three-dimensional volume spoiled gradient-echo (SPGR) pulse sequence with 174 slices (TR = 6.5 ms, TE = 2.0 ms, matrix of 256 × 256, FOV = 256 mm, FA = 15°, slice thickness = 1.0 mm, no gap) was used to acquire the structural images for anatomical reference.

DATA PROCESSING

Behavioral Data Analysis

Firstly the total accuracy of each subject was calculated and the subjects with poor scores (less than 80%) were excluded in this study. Then the trials with incorrect responses or with RTs longer than 1,500 ms or shorter than 200 ms were also excluded to avoid the influence of the outliers. We also removed responses following erroneous ones to avoid post-error slowing effect. Since RTs were not normally distributed, we used median RT per condition as raw scores. The accuracy for each of the six trial types was also calculated. Finally, instead of the conventional subtraction measure [Fan et al., 2007b; Fan et al., 2005], we used ratio scores of alerting, orienting, and EC to definite the effects of three attention networks. The formulas were as follows:

$$\text{Alerting effect} = (\text{RT}_{\text{no cue}} - \text{RT}_{\text{center cue}})/\text{RT}_{\text{center cue}}$$

$$\text{Orienting effect} = (\text{RT}_{\text{center cue}} - \text{RT}_{\text{spatial cue}})/\text{RT}_{\text{spatial cue}}$$

$$\text{EC effect} = (\text{RT}_{\text{incongruent}} - \text{RT}_{\text{congruent}})/\text{RT}_{\text{congruent}}$$

DTI Data Analysis

The DTI data was processed using FSL (University of Oxford, UK, http://www.fmrib.ox.ac.uk/fsl). Firstly the DTI volumes were corrected for movement and eddy current distortion using affine registration [Jenkinson and Smith, 2001]. The corrected images were masked to remove skull and nonbrain tissue using the FSL Brain Extraction Tool (BET) [Smith, 2002]. Then the FA images were calculated using the diffusion tensor analysis toolkit (FDT) [Smith et al., 2004].

We then used TBSS to test the asymmetries of fiber tracts. The main procedures were as follows: (1) All subjects' FA data were nonlinearly aligned into MNI152 space ($1 \times 1 \times 1\ \text{mm}^3$) and the mean of all aligned FA images was created. (2) The mean FA image was "skeletonized" and only the centers of tracts (maximal FA values) were spared, and voxels with FA values lower than 0.25 were suppressed. (3) The symmetrized mean FA image was generated by flipping and averaging original mean FA image. This was then "skeletonized" to generate the initial symmetric skeleton. (4) The original (asymmetric) skeleton was dilated by one voxel, and then was used to mask the initial symmetric skeleton to ensure that only skeleton structures close to being symmetric in the original data were used in this left-right analysis. (5) To make sure the final skeleton was exactly symmetric, the masked symmetric skeleton was flipped and remasked with the nonflipped version. Then each subject's aligned FA data was projected onto the final symmetry skeleton, resulting in 4D dataset. (6) To implement the interhemispheric comparison of fibers, the 4D DTI dataset was left–right flipped, and the voxel-wise difference map between the original and flipped images was created. In this new map, the left side of the image represented the difference of skeleton between the subjects' right and left hemispheres (right–left); voxels on the right had the opposite sign (left–right).

Statistical Analysis

ANOVA of 3 (no, center and spatial cues) × 2 (incongruent and congruent targets) factorial designs was used to test the effects of cues, targets and their interaction on Median RT. Partial correlation analyses between age and the ratio scores of alerting, orienting, and EC were performed, using gender as covariate. We also tested the main effects of sex on ratio scores using independent samples *t*-test. To explore the relationships between the distinct ANT components, we correlated each of the RT ratio scores after controlling for sex and age.

The nonparametric 1-sample t-test for the difference map was performed by Randomise program (http://www.fmrib.ox.ac.uk/fsl/randomise/index.html), which is based on permutation methods in the FSL, to determine the WM skeleton regions showing significant asymmetries. The output was thresholded at cluster level, which was obtained by first arbitrarily thresholding the raw *t*-statistics map on the skeleton, and then corrected for multiple comparisons using the null distribution of the max (across the image) cluster mass. Cluster mass is the sum of all statistic values within the cluster, and has been reported to be more sensitive than cluster size [Bullmore et al., 1999]. After selected a range of thresholds for the raw *t*-statistics map and compared the calculation results, we found that a strict threshold was necessary and the cutoff of $t \geq 4$ (equal to $P \leq 0.0002$) could clearly distinguish the specific skeleton asymmetries in different WM partitions, such as the corpus callosum and superior longitudinal fasciculus (SLF). Thus, we used a strict statistical threshold of $t \geq 4$ and only considered clusters of ≥ 50 mm^3 ($P \leq 0.005$ at cluster level, corrected) that survived thresholding. In order to distinguish the clusters with significant asymmetries between each other, the resulting *t*-map was firstly transferred into cluster index map. Then multiple WM atlases implemented in FSL (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html) were used for the definition of anatomical regions.

Next, the total determined clusters were binarized to generate a mask (lateralization mask), representing the skeleton regions with significant FA asymmetries. In order to investigate the relationship between fiber asymmetries and performances of attention function, the general linear models (GLMs) were implemented, with FA difference maps of all subjects as dependent variable, ratio scores of three attention networks as fixed factors, age and gender as covariates and the lateralization mask as ROI. We performed separate analyses for alerting, orienting and EC effects to explore the relations to FA asymmetries across attention function. Percent differences of FA values [2(left – right)/(left + right)] were not adopted here in order to avoid over-emphasizing differences in regions with low anisotropy [Jahanshad et al., 2010].

Probabilistic Diffusion Tractography

The clusters identified with above asymmetry analyses and GLMs were then used as seed masks to perform probabilistic diffusion tractography (PDT) [Behrens et al., 2003, 2007]. PDT could estimate a probability distribution function of fiber direction and allow modeling multiple fiber orientations at each voxel. The warpfields of nonlinear registration and the inverse versions were used for the translation between the original space and the MNI152 standard space. Tracts generated by PDT were volumes wherein values at each voxel represented the number of samples (or streamlines) that passed through that voxel. For the elimination of spurious connections, tractography in each subject was thresholded to include only voxels containing at least 100 samples (out of 5,000). These individual tracts were then binarized and summed to produce group probability map. In this map, the value in each voxel represented the number of subjects in whom the pathway passed through that voxel (see colorbars in Figs. 3 and 4).

TABLE II. The ratio scores (Mean ± SD) of attention components and their correlation coefficients (bold)

	Sample size	Alerting	Orienting	EC
Male	31	5.83 ± 3.25	10.24 ± 6.02	15.60 ± 4.22
Female	28	5.87 ± 3.79	10.11 ± 4.19	13.85 ± 4.13
t (*P*)		0.05 (0.96)	0.09 (0.92)	1.60 (0.11)
Total	59	5.85 ± 3.49	10.18 ± 5.19	14.77 ± 4.24
Alerting	59	**1**		
Orienting	59	−**0.41** (0.002*)	**1**	
EC	59	−**0.03** (0.82)	−**0.94** (0.49)	**1**

The effects of alerting, orienting and EC are expressed in percent relative to the baseline condition. The correlation analyses were adjusted for age and gender. *t*, the *t* value of independent samples *t*-test. The numbers in parentheses represent *P* values of statistical analyses. EC, executive control.

RESULTS

Behavioral Data

On average, the accuracy of ANT performance was very high (94.9%), indicating that the participants understood the instructions and were able to response reliably. There was no significant difference between genders and no correlation with age on overall accuracy. Paired samples *t*-tests between the different conditions revealed significant orienting ($t = 5.61$, $P < 0.001$) and EC ($t = 8.83$, $P < 0.001$) effects on accuracy across subjects, while the alerting effect was absent ($t = 1.67$, $P = 0.10$).

As for median RT measures, responses to incongruent stimuli were slower than to congruent, and spatial cues led to the fastest responses while no cue conditions were the slowest of the three cue conditions. Levene's test of equality of error variances was performed and RTs turned out to be equal across the six conditions. ANOVA of 3 × 2 factorial designs showed that the factors of both cue level [F (2, 348) = 50.04; $P < 0.001$] and target condition [F (1, 348) = 126.29; $P < 0.001$] were significant. Besides, the interaction between cue and target was also significant [F (2, 348) = 3.21; $P = 0.04$].

The ratio scores of alerting, orienting and EC effects as well as their correlations were summarized in Table II. One negative value for alerting and one for orienting, as well as one outlier for orienting (0.27), were excluded before the statistical analyses. Only the correlation between alerting and orienting was significant ($r = -0.41$, $P = 0.002$), after controlling for age and gender. There were no gender differences in ratio scores (Table II). We did not found age correlations with any of the ratio scores across subjects. The coefficients of determination (R^2) of linear correlation between age and alerting, orienting and EC were 0.0002 ($P = 0.97$), 0.039 ($P = 0.10$), and 0.0089 ($P = 0.95$), respectively (Fig. 1).

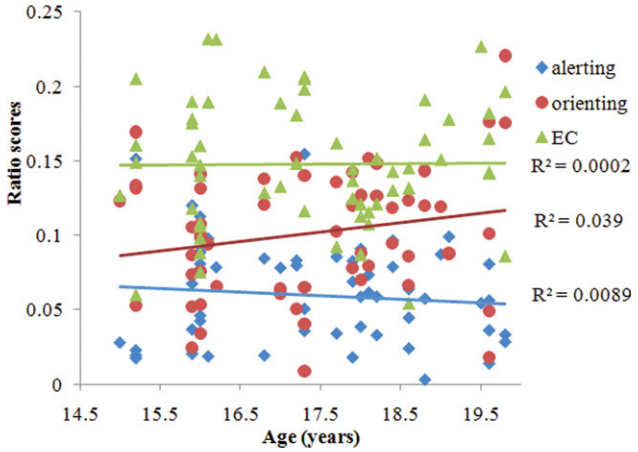

Figure 1.
Pearson's correlations between age and ratio scores of alerting, orienting and EC effects. EC, executive control.

Skeleton Asymmetries

The skeleton FA differences between hemispheres were shown in Table III. In general, there was no noteworthy difference in mean FA values of symmetry skeleton between the left and right hemispheres (0.497 ± 0.015 vs. 0.493 ± 0.015) across subjects. However, more voxels in right hemisphere showed prominent asymmetry than in the left (5156 vs. 3240 voxels, the clusters with less than 50 voxels were excluded), after corrected for multiple comparisons of asymmetry analysis.

As a result, we found most WM structures, such as internal capsule, external capsule, posterior corona radiata, SLF, and temporoparietal WM showed rightward asymmetry. On the contrary, cingulum as well as some fibers in brain stem displayed left-greater-than-right anisotropy asymmetry (Fig. 2, Table III). Besides, both the leftward and rightward asymmetries within some other WM structures, such as corpus callosum (Fig. 2) and ACR (Fig. 3), were revealed in current study. For better visualization of these regions, we discarded the irrelevant clusters in Figures 2 and 3.

Relationships between Skeleton Asymmetries and Attention Function

Using asymmetric information in the difference map, statistics of GLMs were performed to correlate the FA differences across the hemispheres with ANT performance. We found that there was a significantly positive correlation of EC ratio scores with the levels of leftward asymmetry in the inferior part of ACR (Fig. 4A,B). The peak coordinate of correlated region is −24, 24, and 3 (*x*, *y*, *z*, in mm) and the voxel number is 14 ($P < 0.05$, FDR

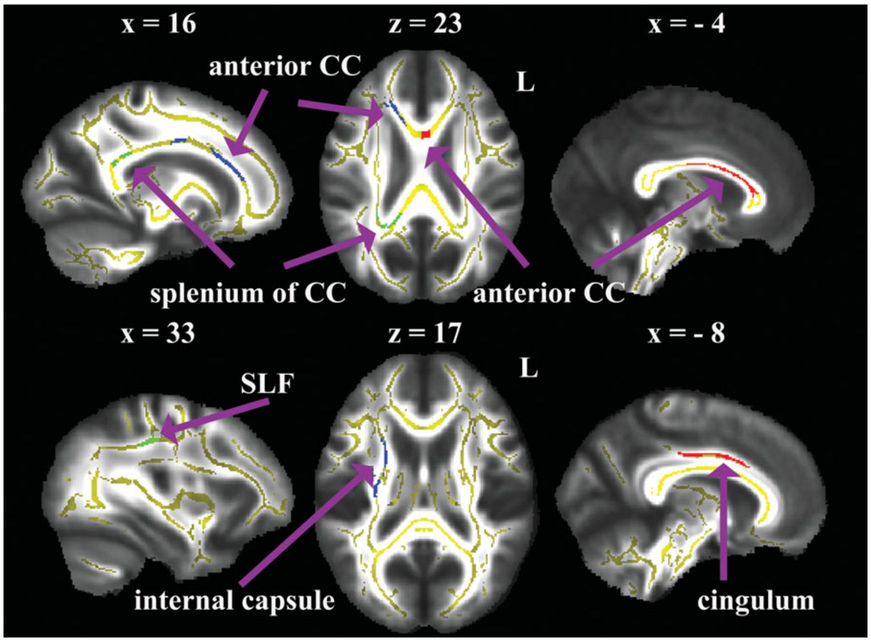

Figure 2.
Regions that show skeleton asymmetries. The white matter tracts with leftward asymmetry were shown in red, while those with rightward asymmetry were represented in green and blue. The symmetry skeleton, which is overlaid on the symmetry mean FA image of all subjects, is displayed in yellow. The numbers are the axial and sagittal coordinates in mm. CC, corpus callosum; L, left hemisphere; SLF, superior longitudinal fasciculus.

TABLE III. FA skeleton regions showing significantly hemispheric asymmetries

Clusters	Regions	MNI Peak Coordinates			Voxels
		x	y	z	
Rightward asymmetry (Right > Left)					
1	Anterior limb of internal capsule extending to posterior limb and external capsule	16	12	5	1062
2	**Superior part of ACR**, Genu and body of Corpus callosum	21	36	1	875
3	Posterior corona radiata, Splenium of corpus callosum	33	−63	7	829
4	Medial lemniscus	4	−40	−40	178
5	Posterior part of SLF	35	−34	32	176
6	WM in superior temporal gyrus	46	−24	2	142
7	WM in middle temporal gyrus	51	−41	−5	138
8	WM in precentral gyrus	52	3	20	135
9	WM in supramarginal gyrus	47	−34	9	133
10	**Middle part of ACR**	28	35	5	133
11	Anterior part of SLF	40	−12	28	110
12	External capsule	31	0	14	109
13	Superior corona radiata	26	−17	28	103
14	Fornix	32	−17	−10	103
Leftward asymmetry (Left > Right)					
15	Medial lemniscus, CST, superior cerebellar peduncle	−2	−37	−45	548
16	Cerebral peduncle	−12	−26	−19	429
17	Genu and body of Corpus callosum	−4	27	6	318
18	Middle cerebellar peduncle	−10	−30	−41	236
19	Forceps minor	−17	53	0	159
20	Thalamus	−16	−18	11	158
21	WM in precuneous gyrus	−8	−59	19	147
22	**Inferior part of ACR**	−19	22	−6	128
23	Cingulum (anterior part)	−9	21	25	127

ACR, anterior corona radiata; CST, corticospinal tract; SLF, superior longitudinal fasciculus. Minimum cluster size: 100 voxels (100 mm^3). $P \leq 0.005$ at cluster level, corrected for multiple comparisons. The ACR asymmetries are emphasized in bold font.

corrected). The statistical results also revealed that there were no significant relationships of alerting and orienting to WM asymmetries.

To verify that it is the asymmetric effect, rather than unilateral influence of WM on the individual variations of attention function, we performed multiple correlation analyses between the ANT ratio scores and bilateral mean FA values as well as their asymmetry indexes in eight clusters of interest. These clusters had been reported to be related with attention function (see Discussion) and showed significant asymmetries during the aforementioned skeleton comparison. The regions included the superior and middle parts of ACR, anterior, and posterior parts of SLF, post limb of internal capsule and splenium of corpus callosum, all of which showed significant rightward asymmetry, and inferior part of ACR as well as cingulum, in which leftward asymmetry was detected (Table IV). To restrict the regions, we respectively isolated post limb of internal capsule, superior part of ACR, and splenium of corpus callosum from cluster 1, 2, and 3 in Table III by means of corresponding structural templates in ICBM-DTI-81 White-Matter Labels Atlas [Mori et al., 2005]. The mean FA values in each of the clusters of interest were extracted from individual symmetric skeleton maps as well as the flipped ones. We then performed correlation analyses between unilateral fiber FA values and behavioral performances using SPSS (IBM Company, US).

Again, only the leftward asymmetry (left–right) in the inferior part of ACR showed modest but significant correlation ($r = 0.40$, $P = 0.003$) with EC effect (Fig. 4D). The correlation still exited ($r = 0.38$, $P = 0.007$) even we used another asymmetry index [2(left − right)/(left + right)]. No any other significant correlations ($P > 0.05$, uncorrected) was detected between WM asymmetries and alerting as well as orienting functions. Note that age and gender were included as covariates in all analyses.

To further explore the presumable relationships between attention function and unilateral fiber integrity across subjects, we employed other GLMs, using original (asymmetric) skeletons of all subjects as dependent variable, and age as well as gender as covariates. However, after FDR corrected of multiple comparisons, no correlations was detected across the entire group.

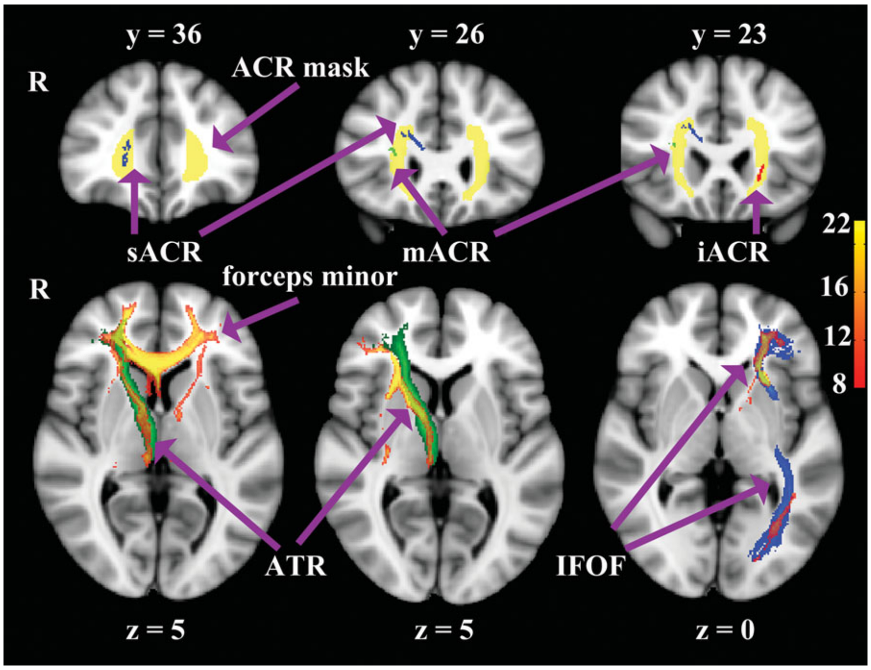

Figure 3.

Upper low: Coronal slices (in mm) of the asymmetric regions in ACR overlaid on the standard MNI152 T1 image. The red, green and blue clusters represent the inferior, middle and superior ACR (iACR, mACR, and sACR) regions showing skeleton asymmetries, respectively. The right clusters indicate rightward asymmetry, vice versa. The bilateral ACR templates are displayed in yellow and derived from the ICBM-DTI-81 White-Matter Labels Atlas [Mori et al., 2005]. Lower row: Axial sections of the group probability maps (Red-Yellow, *N* = 22) generated from the iACR (right), mACR (middle), and masked sACR (left), respectively. The underlying tracts illustrate the templates of IFOF (inferior fronto-occipital fasciculus) in blue and ATR (anterior thalamic radiation) in green. R, right hemisphere.

Probabilistic Tractography

Our main interest here was to assess the fiber pathways arising from behavior-related region (Fig. 4A) and three asymmetric clusters in ACR (Table IV), so we only tracked the fibers in the prominent side. Differing from the PDT of behavior-related region, we only chose 22 subjects (11

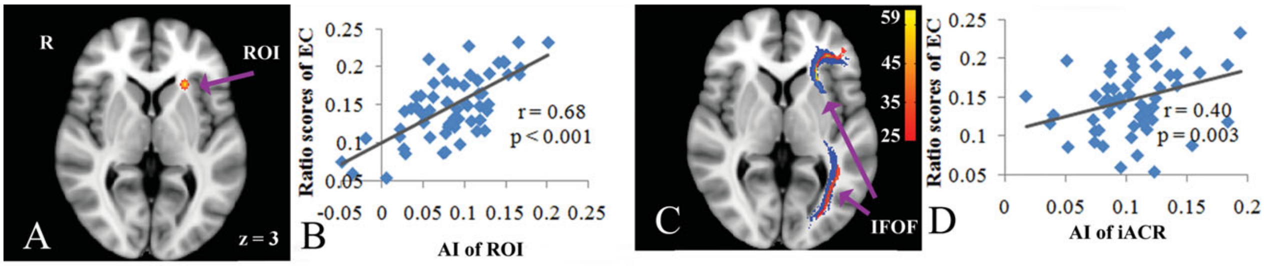

Figure 4.

Local correlation between FA asymmetry in inferior part of ACR (iACR) and attention function, and probabilistic tractography from behavior-related region (*N* = 59). A: ROI illustrates the correlated region (Red-Yellow), which is dilated by one voxel for visualization. C: Group probability map (Red-Yellow, *N* = 59) generated from PDT of behavior-related region (14 voxels). The underlying blue tract represents the left thresholded IFOF (inferior fronto-occipital fasciculus) template. B and D: Scatterplots showing correlations of EC ratio scores with FA asymmetry indexes (AI, Left–Right) derived from ROI (14 voxels) and inferior part of ACR with leftward asymmetry (128 voxels), after controlling for age and gender. r, partial correlation coefficient.

TABLE IV. Mean FA values and asymmetry indexes (mean ± SD) across subjects in clusters of interest showing significant asymmetries ($N = 59$)

			Mean FA value		Asymmetry index	
Regions	Clusters	Voxels	L	R	L − R	2(L − R)/(L + R)
Superior part of ACR	2	367	0.45 ± 0.04	0.54 ± 0.04	−0.09 ± 0.03	−0.18 ± 0.06
Middle part of ACR	10	133	0.40 ± 0.03	0.48 ± 0.04	−0.08 ± 0.04	−0.18 ± 0.09
Inferior part of ACR	22	128	0.49 ± 0.03	0.38 ± 0.04	0.10 ± 0.03	0.25 ± 0.09
Cingulum	23	127	0.60 ± 0.04	0.51 ± 0.05	0.09 ± 0.03	0.17 ± 0.06
Post limb of internal capsule	1	336	0.70 ± 0.02	0.74 ± 0.02	−0.04 ± 0.02	−0.06 ± 0.02
Anterior part of SLF	11	110	0.46 ± 0.04	0.53 ± 0.05	−0.06 ± 0.03	−0.13 ± 0.07
Posterior part of SLF	5	176	0.44 ± 0.04	0.51 ± 0.04	−0.06 ± 0.04	−0.14 ± 0.08
Splenium of corpus callosum	3	333	0.68 ± 0.02	0.74 ± 0.02	−0.06 ± 0.02	−0.09 ± 0.02

The cluster numbers correspond with those in Table III. ACR, anterior corona radiata; SLF, superior longitudinal fasciculus; L, left; R, right.

males, age-matched between genders) to perform multi-fiber tracking from the three ACR clusters. As the three clusters showing anisotropy asymmetries were much broader than behavior-related region, we thresholded the tracking map in each subject using 1,000, rather than 100 samples. Then The JHU White-Matter Tractography Atlas, which was thresholded to include at least 15% of probability, was chosen as the template to identify the determined tracts.

The behavior-related region in the left inferior frontal ACR generated sagittal paths connecting inferior frontal region with temporal–occipital cortex (Fig. 4C). Meanwhile, the whole ACR cluster of leftward asymmetry showed the same connecting trajectories (Fig. 3), which exactly overlapped with inferior fronto-occipital fasciculus (IFOF). In contrast, connections with the two ACR clusters of rightward asymmetry traveled mainly within anterior brain regions (Fig. 3). Here we identified these connections as forceps minor and ATR. Tracking from the middle ACR cluster also generated some fibers that could be considered as IFOF (not shown in the figures).

DISCUSSION

It is often assumed that the attention system comprises three separable functional networks of alerting, orienting, and EC [Fan et al., 2005; Raz and Buhle, 2006]. However, whether such networks evaluated by behavioral performances are independent remains a matter of debate. Our results revealed the interaction between cue and flanker effects, and the negative correlation between alerting and orienting, which could be explained by the incremental effect of spatial as compared with alerting cue [Mahoney et al., 2010]. Such correlation was in line with some previous studies [Callejas et al., 2004; Mahoney et al., 2010; Westlye et al., 2011] but inconsistent with others [Fan et al., 2007a; Fan et al., 2002; Matchock and Toby Mordkoff, 2009; Niogi et al., 2010]. It is speculated that methodological and group differences across studies might account for the controversial results. For instance, one experiment using ANT with various stimulus onset asynchrony (SOA) values has clarified that the cuing effects as well as the interaction between alerting and orienting effect could be influenced by the cue–target time intervals [Fuentes and Campoy, 2008]. Age-related differences in ANT, especially in alerting effect, have also been reported in previous literatures [Gamboz et al., 2010; Jennings et al., 2007].

Conversely, this study support the independence of EC function [Fan et al., 2002], indicating that ANT could fractionate the distinct components of attention. Robust evidences suggest that selective EC alteration has become an important neuropsychological endophenotype in ADHD [Konrad et al., 2006; Makris et al., 2008] and schizophrenia [Gooding et al., 2006; Neuhaus et al., 2007; Opgen-Rhein et al., 2008; Urbanek et al., 2009]. We also argued that ratio scores, which had been used to explore the structure–behavior correlations [Westlye et al., 2011], heritability [Fan et al., 2003] and impairment of attention function in diseases [Nestor et al., 2007; Urbanek et al., 2009; Wang et al., 2005], would be more appropriate than RT scores in ANT studies, because the former could isolate the attention system from the overall RT. Recent studies have pointed out that RT in behavioral tasks would be interfered by the effect of speed-accuracy tradeoff, which modulated the competing demands of response speed and response accuracy [Bogacz et al., 2010].

The voxel-wise analysis of skeleton difference images revealed a number of regions with a significant FA difference between hemispheres. In contrast to previous tractography-based asymmetry results [Verhoeven et al., 2010], more observed WM asymmetries showed rightward predominance. Further comparisons showed that most of FA asymmetry indexes (division measurement) in determined clusters obviously exceeded the values in the tractography-based study [Verhoeven et al., 2010], indicating that VBA and cluster-mass correction was more appropriate to detect asymmetry effect. Consistent with prior literatures, the current study demonstrated the leftward asymmetry in anterior cingulum [Bonekamp et al., 2007; Gong et al., 2005;

Huster et al., 2009; Takao et al., 2011b], cerebral peduncle [Ardekani et al., 2007], and corticospinal tract [Dubois et al., 2009; Takao et al., 2011a; Thiebaut de Schotten et al., 2011a]; and rightward asymmetry in anterior limb of internal capsule [Park et al., 2004], splenium of corpus callosum [Ardekani et al., 2007; Putnam et al., 2010; Takao et al., 2011b], SLF [O'Donnell et al., 2010; Oechslin et al., 2009; Park et al., 2004], and posterior corona radiata [Takao et al., 2011b]. In addition, The leftward FA asymmetry in medial region, and the inverse asymmetry in lateral region of genu and body of corpus callosum revealed in this study might mediated the disputes in previous DTI studies [Ardekani et al., 2007; Bonekamp et al., 2007; Park et al., 2004; Snook et al., 2005], and extend the understanding of rightward thickness asymmetry in anterior body and anterior third of the corpus callosum [Luders et al., 2006].

Interestingly, we also found the heterogeneous asymmetries in ACR, which continues caudally as the internal capsule and consists of a mixture of projection, association, and callosal fibers [Mori et al., 2005; Wakana et al., 2004]. Probabilistic fiber tracking demonstrated that the clusters with rightward asymmetry were occupied by ATR, forceps minor, and IFOF, while the cluster showing leftward predominance contained fibers connecting inferior frontal cortex to lower edge of insular lobe and temporal-occipital regions. Here we also defined the left bundle as IFOF. However, it needs to be declared that IFOF and inferior longitudinal fasciculus share most of the projections at the posterior temporal and occipital lobes, while the uncinate fasciculus and IFOF share the projections at the frontal lobe [Wakana et al., 2004]. Asymmetries in ATR and IFOF are highly genetically influenced [Jahanshad et al., 2010]. ATR carried nerve fibers between thalamus and prefrontal cortex. The rightward asymmetry of ATR integrity was in congruence with previous studies [O'Donnell et al., 2010; Verhoeven et al., 2010]. The incongruent asymmetries in local regions of IFOF also support the dorsal-ventral anatomic segmentation of IFOF [Martino et al., 2010], although further studies are needed to clarify the exact segmentation in DT images. Finally, since leftward asymmetry in forceps minor is also existent, we propose that bidirectional connectivity between hemispheres [Bitan et al., 2010] coincides with current findings.

In addition to the examination of asymmetries in WM integrity, we also investigated the relationship between WM asymmetries and distinct components of attention—alerting, orienting, and EC. With the combination of voxel-based analyses and ROIs approach, we found that left-greater-than-right FA asymmetry in inferior frontal ACR, was positively correlated with EC ratio scores. Because larger EC scores were indicative of worse performance as a result of longer RTs required for conflict resolution [Fan et al., 2003], our finding implicated that greater fiber integrity difference across bilateral inferior frontal ACR provided an disadvantageous influence on EC performance. Further tractography from correlated regions generated sagittal fiber paths connecting inferior frontal lobe to temporal–occipital regions. Group probalility map verified that these tracts corresponded to IFOF.

The finding of inferior frontal–temporal–occipital tracts associated with EC function is strongly supported by previous studies. EC of attention refers to the higher order processes involved in the self-regulation of behavior [Garavan et al., 2002], cognition [Marklund et al., 2007; Smith and Jonides, 1999; Tomita et al., 1999], and emotion [Pessoa, 2009]. It is construed as the monitoring and resolution of conflict between computations (such as decision making, error detection or regulation of thoughts and feelings) in different neural areas [Raz and Buhle, 2006]. Accordingly, temporoparietal cortex and inferior frontal cortex together constitute the ventral attention system, which is specialized for the detection of behaviorally relevant stimuli, particularly when they are salient or unexpected [Corbetta and Shulman, 2002]. Meanwhile, IFOF provided the main anatomical connections for ventral attention system [Umarova et al., 2010], and reductions of WM integrity in IFOF are associated with deficits of executive function in patients with first-episode psychosis [Perez-Iglesias et al., 2010] or chronic trauma [Kraus et al., 2007].

Specially, the significant correlation between ACR integrity asymmetry and EC function indicated that EC of attention was underpinned by both hemispheres. As in the classic Stroop [MacLeod, 1991] task and Simon task [Simon and Berbaum, 1990], EC in ANT is assessed by subtracting RTs to congruent or neutral stimuli from those to incongruent ones. Previous functional imaging studies showed that EC function as measured by the ANT was associated with the blood-oxygenation-level dependent (BOLD) [Fan et al., 2005] as well as oscillatory [Fan et al., 2007a] activity in bilateral inferior frontal cortex among healthy controls. Using Stroop task, one study also found the activation in bilateral inferior frontal cortex, which showed functional connectivity with superior frontal area and anterior cingulate gyrus [Kemmotsu et al., 2005]. Additionally, attention function was also linked to WM anisotropy in bilateral pericallosal frontal regions [Madden et al., 2007]. Niogi et al [2008; 2010] found that correlation between EC scores of ANT and FA values within a ROI in the ACR was significant in the left hemisphere, and appeared a nonsignificant trend in the right. It was speculated that both the left and right ACR regions played a role in EC and the right contributions might be apparent in studies with great power [Niogi et al., 2010]. Furthermore, damage in either side of ACR due to mild [Niogi et al., 2008] or severe [Kraus et al., 2007] trauma could induce deficit in the attention domain.

To our knowledge, such a significant relationship between brain WM asymmetry and EC performance has never previously been described. The negative effect of leftward asymmetry on EC function also suggests that fibers connecting inferior frontal and posterior temporal–occipital regions in the right hemisphere confer an advantage for EC function. This finding is supported by theory of rightward asymmetry for human sustained attention [Pardo et al., 1991]. Moreover, many of the paradigms involving response inhibition have focused on ventrolateral regions (primarily within BA 47 and 45) within the right inferior frontal gyrus [Aron et al., 2004]. It is thought that inhibitory control processes during EC or response selection could enhance the cognitive efficiency by inhibiting the irrelevant stimulus dimension and emphasizing the required response. Consistently, behavioral performance of Simon task showed strong correlation with both fMRI and DTI characteristics of the right inferior frontal region [Forstmann et al., 2008]. In addition, attention tasks that activate the brain central–executive network (including the dorsolateral prefrontal cortex and posterior parietal cortex) have been consistently shown to evoke decreased activation in the default-mode network (including the ventromedial prefrontal cortex and posterior cingulated cortex), and the right ventrolateral prefrontal cortex and anterior insula (IFOF travels in the WM between insular cortex and putamen) play a major role in switching between these two networks [Sridharan et al., 2008].

For deeper explanation, asymmetrical brains, for example, have a corpus callosum with a reduced midsagittal area relative to more symmetrical ones [Witelson, 1985]. This might reflect fewer and/or thinner fibers connecting the two hemispheres [Galaburda et al., 1990]. The theory was confirmed by one recently fMRI-DTI study, which revealed that atypical language lateralization (nonleftward dominance) was associated with high anisotropic diffusion through the corpus callosum [Haberling et al., 2011]. Another insight to these phenomena emerges from the split-brain researches. Using patients with surgical disconnection of the cerebral hemispheres, previous studies confirmed that the two hemispheres relied on a common orienting system to maintain a single focus of attention, and the process of discriminating stimulus and making choice by one hemisphere will delay the other hemisphere in making a similar choice [Gazzaniga, 2000]. Therefore, we could speculate that the increased leftward asymmetry of inferior frontal ACR might diminish EC function by competitively suppressing the activity of right attention system or by decreasing the interactions between two hemispheres. Analogous to our speculation, one pioneering DTI study about language lateralization demonstrated that symmetry in direct connections between remote cortical territories, not extreme lateralization, might ultimately be advantageous for specific cognitive functions [Catani et al., 2007]. However, this study cannot expose the exact mechanisms for the resulting structure–behavior relationship. The combined fMRI-DTI studies in the future are necessary to solve the conundrum.

The fact that there were no other significant correlations between WM integrity/asymmetries and attention subcomponents is surprising. Instead, Niogi et al. [2010] found the structure–function correlations between alerting and the anterior limb of the internal capsule. Besides, the splenium of the corpus callosum [Niogi et al., 2010], right SLF (II, III, and arcuate fascicle) [Umarova et al., 2010] and left cingulum [Nestor et al., 2007] have been reported to be linked with orienting function. Furthermore, adults with ADHD, which is characterized primarily by behavioral symptoms of inattention and impulsivity, showed significant FA abnormalities in the right cingulum and SLF II [Makris et al., 2008]. However, our voxel-based and clusters of interest analyses did not found any significant relationships of alerting and orienting to the unilateral integrity or bilateral FA asymmetry indexes in these WM regions. It is conceivable that strong FDR correction in current voxel-based analyses and differences in pre-defined ROI regions could explain the incongruence with these previous findings. Taking together, we could discreetly suppose that alerting and orienting are irrelevant to the asymmetries of WM integrity.

Although these findings are robust, some limitations of the present study need to be addressed. First, given the relatively smaller sample size, we did not take account of sex and age effects on WM asymmetries. Pioneering VBA studies in large populations have showed that there were no significant relationships of sex [Jahanshad et al., 2010; Takao et al., 2011b] and age [Takao et al., 2010b] to WM FA lateralization. Secondly, we chose the FA skeleton, instead of the entire FA map, to test the relationships between WM asymmetries and attention function. In that case, our results will tend to be conservative because some WM regions would be omitted after being skeletonised. Meanwhile, the relatively smaller positive regions after statistical analyses would mismatch with actually large-scale fiber tracts. Regardless of these drawbacks, our methods avoid the contaminations of standard registration algorithms and spatial smoothing in conventionally quantified DTI studies.

Besides, voxel-based statistics are still difficult to estimate the FA changes at crossings or junctions. For instance, an apparent reduction in regional FA value might in fact be due to an increase in other tracts feeding into the junction [Smith et al., 2006]. In this case, the interpretations of FA asymmetries at crossings or junctions can be quietly complicated. Hence, a combination of different diffusion parameters (such as mean diffusivity, as well as axial and radial anisotropies) might be an alternative approach. At last, this study does not allow us to evaluate the direction of causality between WM structure and attention function. Although it is speculated that innate variations in brain structure influence subsequent cognition or behavioral levels, some studies also indicated that short-term meditation training could improve EC performance on the ANT [Tang et al., 2007] and induce WM FA changes [Tang et al., 2010]. Furthermore, strong improvement of EC function after attention training was also shown in children [Rueda et al., 2005]. Future longitudinal studies using DTI should test whether alterations in attention load or training result in observable changes in WM integrity as well as asymmetries.

CONCLUSION

This study demonstrates that TBSS is a powerful unbiased technique for evaluating human brain WM asymmetries. Our data replicate many well established DTI findings of WM asymmetries, while expanding on the regional details, which are attractive for further studies. Specially, we identified, for the first time, the significant correlation between WM asymmetry in inferior frontal ACR and the independent EC function of attention. Our findings suggest that the WM asymmetries in ACR are heterogeneous and less asymmetry degree in inferior frontal ACR in the normal population might be advantageous for EC of attention. We speculate that WM anisotropy symmetry might be crucial for specific cognitive functions, especially the implement of which employs both hemispheres. Future studies with larger population sample and multi-modal methods should be applied to further investigate the underlying explanations for the association between brain WM asymmetries and attention function.

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