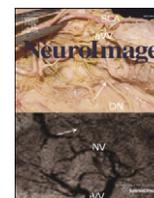


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White matter structures associated with empathizing and systemizing in young adults



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ABSTRACT

Empathizing is defined as the drive to identify the mental states of others in order to predict their behavior and respond with an appropriate emotion. Systemizing is defined as the drive to analyze a system in terms of the rules that govern it to predict its behavior. We undertook voxel-by-voxel investigations of regional white matter volume (rWMV) and fractional anisotropy (FA) of diffusion tensor imaging to discover the WM structural correlates of empathizing, systemizing, and their difference (D score: systemizing – empathizing). Whole brain analyses of covariance revealed that across both sexes, the D score was negatively correlated with rWMV in the WM area in the bilateral temporal lobe, near the right inferior frontal gyrus, near the ventral medial prefrontal cortex, and near the posterior cingulate cortex and positively correlated with FA in an area involving the superior longitudinal fasciculus. Post-hoc analyses revealed that these associations were generally formed by both the correlation between WM structures and empathizing as well as the opposite correlation between WM structures and systemizing. A significant effect of interaction between sex and the D score on rWMV, which was mainly observed because of a positive correlation between rWMV and empathizing in females and a negative correlation between rWMV and systemizing in females, was found in an area close to the right inferior parietal lobule and temporoparietal junction. Our results suggest that WM structures involving the default mode network and the mirror neuron system support empathizing, and that a WM structure relating to the external attention system supports systemizing. Further, our results revealed an overlap between positive/negative WM structural correlates of empathizing and negative/positive WM structural correlates of systemizing despite little correlation between empathizing and systemizing, which supports the previously held idea that there is a trade-off between empathizing and systemizing in the brain.

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Introduction

Empathizing is defined as the drive to identify the mental status of other individuals in order to predict their behavior and respond with an appropriate emotion (Baron-Cohen et al., 2005). Systemizing is defined as the drive to analyze a system in terms of the rules that govern the system in order to predict its behavior (Baron-Cohen et al., 2005). Empathizing and systemizing are important subjects of scientific study partly because stronger systemizing and weaker empathizing are believed to explain or underlie a wide range of characteristics associated with males and subjects with Autism Spectrum Conditions (ASCs), such as Asperger's Syndrome, compared with females and

subjects without ASCs (Baron-Cohen and Wheelwright, 2004; Baron-Cohen et al., 2003). The D score, which is the discrepancy between systemizing and empathizing (systemizing – empathizing), is a psychological variable. It is this, rather than empathizing or systemizing alone, that is suggested to describe ASCs and to differentiate typical males from typical females (Baron-Cohen, 2004). The sum of the empathizing and systemizing scores does not differ between males and females. On the basis of this evidence, it is suggested that empathizing and systemizing are competing “neurally in the brain” and that the D score provides information on the trade-off between the two (Goldenfeld et al., 2005). However, there is little correlation between empathizing and systemizing (e.g., Wakabayashi et al., 2007; Wheelwright et al., 2006), and this notion is a matter of debate (Andrew et al., 2008).

In our previous study (Takeuchi et al., submitted for publication), we proposed a hypothesis that empathizing may be associated with the function of the regions that consist of the default mode network (DMN), while systemizing may be associated with the function of

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the regions that consist of the external attention system (EAS) which consists of the lateral prefrontal cortices (LPFCs), the dorsal part of the anterior cingulate cortex (ACC), inferior parietal lobes (IPLs) and so on (Buckner et al., 2008; Corbetta and Shulman, 2002). The DMN is active at rest and usually suspended during externally-directed, attention-demanding tasks, while the network consisting from LPFCs and IPLs is the opposite (Buckner et al., 2008). Regions such as the medial prefrontal cortices (mPFCs), precuneus, posterior cingulate cortex areas and some lateral temporal cortex areas and the superior temporal sulcus (STS) belong to the DMN (Buckner et al., 2008).

The basis of our hypothesis above (more extensive discussions can be seen in Takeuchi et al., submitted for publication) is that empathizing/systemizing is supposed to underlie the wide range of inferiorities/superiorities associated with ASCs, and that these are in turn associated with the functions of DMN/EAS, respectively. In summary, on one hand, empathizing is supposed to underlie the inferiorities associated with ASCs with respect to a wide range of social, emotional, and empathetic skills or abilities, including theory of mind (TOM) (for a review, see Baron-Cohen (2004)). On the other hand, regions in DMN are also involved in cognitions related to such inferiorities. These conditions include internally focused tasks (such as self-related recognition, which includes knowing one's own emotions) and social cognition, which includes TOM and the recognition of another's perspective (Amodio and Frith, 2006; Buckner et al., 2008). On the other hand, systemizing is supposed to underlie, partly explain, or be associated with the supposed superior spatial ability, *modus tollens* reasoning ('if p, then q'), and attention to detail associated with ASCs (Baron-Cohen, 2004; Baron-Cohen et al., 2005, 2009). LPFCs and IPLs are associated with spatial tasks (Richter et al., 2000), attention (Awh and Jonides, 2001), and reasoning (Kroger et al., 2002).

Previous neuroimaging findings are generally congruent with the idea that regions in DMN are associated with empathizing, while those in EAS are associated with systemizing. These previous studies have shown that empathizing is associated with regional gray matter volume (rGMV) of (a-1) the left perisylvian areas and STS in children (Sassa et al., 2012), (a-2) mPFC and precuneus areas together with other areas in young adults (Takeuchi et al., submitted for publication), and (a-3) mPFC together with other areas (Cheng et al., 2009). On the other hand, systemizing was associated with (b-1) rGMV of the posterior parietal cortex in children (Sassa et al., 2012), (b-2) rGMV of the DLPFC area and the dorsal part of ACC together with other areas in young adults (Takeuchi et al., submitted for publication), and the dorsal part of ACC to the middle cingulate cortex in young adults (Lai et al., 2012), as well as (c) LPFC functional activity in young adults (Billington et al., 2008).

Further, although we focused on the nodes of DMN as anatomical correlates of empathizing, there are some theories that focus on the mirror neuron system as a correlate of empathy/empathizing or autistic traits (Cheng et al., 2009; Hadjikhani et al., 2006). The mirror neuron system is defined as the areas that are active during both action execution and observation in humans and involve parts of the frontal and parietal areas including regions such as the inferior frontal gyrus and areas in the posterior parietal lobule (Cattaneo and Rizzolatti, 2009). These theories state that the mirror neuron system makes it possible for one to understand the intentions of another's actions and plays an important role in empathy and empathic dysfunction in ASCs (Jacoboni and Dapretto, 2006; Rizzolatti and Craighero, 2005). Consistently, rGMV correlates of empathizing in some (though not all of) studies of empathizing seem to include the inferior frontal gyrus and/or some posterior parietal areas (Cheng et al., 2009; Sassa et al., 2012; Takeuchi et al., submitted for publication).

None of these previous neuroimaging studies of empathizing/systemizing has investigated the white matter (WM) structural correlates of empathizing/systemizing. Recently, Chou et al. (2011) used diffusion tensor imaging (DTI) to investigate WM structural integrity [fractional anisotropy (FA)] correlates of empathizing and systemizing.

This study revealed that empathizing was associated with the structural integrity of various regions such as the left superior temporal gyrus, and that systemizing was associated with the structural integrity of WM regions such as the left prefrontal lobe. Considering the involvement of these areas with DMN and EAS (Buckner et al., 2008), these findings may be at least partly congruent with our hypothesis. However, several significant areas other than these regions have shown sporadic associations. Further, in their study all of the significant results showed the effects of interaction between empathizing and sex or between systemizing and sex. These findings may thus rather suggest the importance of sexual dimorphism in the determination of correlates of empathizing/systemizing, as the authors suggested.

However, previous anatomical studies of empathizing/systemizing have not successfully revealed any regional WM volume (rWMV) correlates of empathizing/systemizing or FA/rWMV correlates of the D score, and determining these relationships thus became the purpose of our present investigation. One study of adult males with a relatively wide age range ($N = 88$, age range 18–45) investigated rWMV correlates of the D score but failed to detect any significant findings (Lai et al., 2012). Recent studies (Takeuchi et al., 2012a,b) have suggested that structural studies of cognition (especially those of WM volumetry) tend to require greater statistical power, and whether the lack of significant findings is due to a lack of statistical power remains unclear. Further, as noted above, sexual dimorphism is important in determining the structural correlates of empathizing/systemizing (Chou et al., 2011), and the sexual dimorphism of rWMV correlates of empathizing/systemizing/D score remains to be investigated. WM structural analyses enable direct determination of whether brain structural connectivity associated with DMN, mirror neuron system and EAS supports empathizing/systemizing. This is important considering the key roles of empathizing/systemizing in ASCs, as noted above. FA and rWMV were moderately to weakly related, but they were highly sensitive to the different characteristics of white matter (Fjell et al., 2008). The associations between the two seem particularly weak in deep white matter areas (Hugenschmidt et al., 2008). Distributions of the associations between FA and group/individual differences and distributions of the associations between rWMV and group/individual differences differ sometimes (Hugenschmidt et al., 2008; Jäncke et al., 2009). Thus, by utilizing both methods, we are able to investigate different neural substrates. rWMV is known to successfully correlate with cognitive functions (e.g., in the cases of our studies, see Takeuchi et al. (2011e, 2012c)). In particular, our previous studies concurrently investigating rWMV and FA correlates of cognitive functions showed more significant results for rWMV analyses in regions congruent with our hypothesis (Takeuchi et al., 2011e, 2012b). Despite there being little correlation between empathizing and systemizing, our previous study found an overlap in several areas in negative rGMV correlates of empathizing and positive rGMV correlates of systemizing (Takeuchi et al., submitted for publication), suggesting a basis for calculating the D score from a neuroimaging perspective.

Here we used voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Good et al., 2001) to assess regional WM volume (rWMV) associated with empathizing/systemizing/D score. We also used voxel-based fractional anisotropy (FA) for diffusion tensor imaging (DTI) (Le Bihan, 2003) to assess WM structural integrity associated with empathizing/systemizing/D score. As discussed in our previous study (Takeuchi et al., 2010a), FA is interpreted as an indicator of WM pathway strength or integrity. Increased WM structural integrity as assessed by DTI is like rWMV, believed to underlie increased cognitive functions that involve WM regions (for details on the mechanism, refer to Takeuchi et al. (2010a)). We recruited 567 subjects (329 males and 238 females) with a limited age range to increase the statistical power of our study.

We hypothesized that (i) WM structures adjacent to GM structures of the mirror neuron system and those of the DMN and (ii) major WM

tracts connecting key nodes of the mirror neuron system and those of the DMN are also associated with empathizing. We also hypothesized that (iii) WM structures adjacent to GM structures of the EAS and (iv) major WM tracts connecting key nodes of the EAS are also associated with systemizing. We also hypothesized that the white matter structural correlates of the D scores are the sum of (i), (ii), (iii) and (iv).

Methods

Subjects

Healthy, right-handed university or postgraduate students ($n = 567$; 329 men and 238 women) participated in this study as part of our ongoing project investigating associations between brain imaging, cognitive function, and aging (Takeuchi et al., 2010b,c, 2011a,d,e; Taki et al., 2010, 2011a,b, in press). Data from the same 567 subjects were used in our previous study to investigate the association between empathizing/systemizing and rGMV (Takeuchi et al., submitted for publication). All subjects who participated in this study also became the subjects of our subsequent intervention studies (Takeuchi et al., 2011b,f, in press-b). Psychological tests and MRI scans that were not described in this manuscript were also gathered in this project. The data recorded before the interventions were used in this study. The mean age of the subjects was 20.8 years (standard deviation [SD], 1.9). The mean age of males and females was 20.9 years (SD, 1.9) and 20.8 years (SD, 1.8), respectively. All subjects had normal vision and none had a history of neurological or psychiatric illness. Handedness was evaluated using the Edinburgh Handedness Inventory (Oldfield, 1971). Written informed consent was obtained from each subject for the projects in which they participated. The procedures for all studies were approved by the Ethics Committee of Tohoku University.

Systemizing Quotient (SQ) and Empathy Quotient (EQ) questionnaires

Japanese versions (Wakabayashi et al., 2007) of the SQ and EQ questionnaires (Baron-Cohen and Wheelwright, 2004; Baron-Cohen et al., 2003) were administered. The EQ score was used as an index of empathizing, and the SQ score was used as an index of systemizing. These tests consist of 40 items for each quotient and 20 filler items that are not scored. The scales consist of self-descriptive statements scored on a four-point scale ranging from Strongly Disagree to Strongly Agree. Half of the items are worded to produce an “agree” response and rest to produce a “disagree” response. Items are randomized to avoid a response bias. Each strong systemizing/empathizing response is awarded 2 points, and each slightly systemizing/empathizing response is awarded 1 point (i.e., each item is scored as 2, 1, or 0), resulting in a range of total scores from 0 to 80 for each quotient.

The D score was calculated according to a previous study (Goldenfeld et al., 2005). The raw SQ and EQ scores were standardized by subtracting the population mean from the score then dividing it by the maximum possible score: $S = (\text{raw SQ score} - \text{population mean of the raw SQ score}) / 80$ and $E = (\text{raw EQ score} - \text{population mean of the raw EQ score}) / 80$. For this computation, we used the estimated population means (EQ: mean = 33.4, SQ: mean = 22.7) derived from a previous study's large sample ($N = 1250$) of Japanese university students with an almost equal number of men and women (Wakabayashi et al., 2007). The discrepancy between systemizing and empathizing was then quantified as $D = (S - E) / 2$. The greater the D score in a positive direction, the stronger one's systemizing relative to one's empathizing. D scores close to zero represent an equal drive to systemize and empathize.

Assessment of psychometric measures of general intelligence

Raven's Advanced Progressive Matrix (Raven, 1998), which is often shown to be the measure most correlated with general intelligence and

thus the best measure of general intelligence (Raven, 1998), was used to assess intelligence and adjust for the effect of general intelligence on WM structures (Schmithorst et al., 2005) for additional details on administration of Raven's Advanced Progressive Matrix, refer to Takeuchi et al. (2010b,c). The mean RAPM scores of males and females were 28.72 (SD, 3.72; range 15–36) and 28.08 (SD, 3.71; range 18–36), respectively.

Image acquisition

All MRI data acquisition was performed using a 3 T Philips Achieva scanner. A magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE) was used to collect high-resolution T1-weighted structural images (240×240 matrix, TR = 6.5 ms, TE = 3 ms, FOV = 24×24 cm, number of slices = 162, slice thickness = 1.0 mm, flip angle = 8°). Diffusion-weighted data were acquired using a spin-echo EPI sequence (TR = 10,293 ms, TE = 55 ms, big delta (Δ) = 26.3 ms, little delta (δ) = 12.2 ms, FOV = 22.4 cm, $2 \times 2 \times 2$ mm³ voxels, 60 slices, SENSE reduction factor = 2, number of acquisitions = 1). The diffusion weighting was isotropically distributed along 32 directions (b value = 1000 s/mm²). Additionally, three images with no diffusion weighting (b value = 0 s/mm²) ($b = 0$ images) and one $b = 0$ image were acquired from 440 and 127 subjects, respectively, using a spin-echo EPI sequence (TR = 10,293 ms, TE = 55 ms, FOV = 22.4 cm, $2 \times 2 \times 2$ mm³ voxels, 60 slices). From the collected images, FA maps and apparent diffusion coefficient (ADC) maps were calculated using the commercially available diffusion tensor analysis package on the MR consol. Calculations were performed by a previously proposed method (Le Bihan et al., 2001).

Preprocessing of T1-weighted structural data

The networks that underlie intellectual abilities can be identified by measuring rWMV (e.g., Haier et al., 2004; Takeuchi et al., 2011e, 2012c). rWMV and FA measures of DTI offer different information regarding WM structures. Intellectual abilities can show correlations with FA and rWMV in distinct as well as overlapped regions (Takeuchi et al., 2011e). Morphological data were preprocessed using VBM2 software (Gaser, 2007), an extension of SPM2. Default parameter settings were used (Gaser, 2007). To reduce scanner-specific bias, we used a customized GM anatomical template and prior probability maps of GM and WM images created from the T1-weighted structural images acquired using the same scanner in our previous study (Takeuchi et al., 2010b). Next, the T1-weighted structural image of each subject was segmented into GM and WM partitions using the abovementioned GM and WM prior probability maps. The resulting images included extracted GM and WM partitions in the native space. The GM partition was then normalized to the abovementioned GM probability map with linear and non-linear transformations. Normalization parameters determined from this initial step were then applied to the native T1-weighted structural image. These normalized T1-weighted structural data were then segmented into GM and WM partitions. In addition, we performed a correction for volume changes (modulation) by modulating each voxel with the Jacobian determinants derived from the spatial normalization, allowing us to also test for regional differences in the absolute amount of WM (Ashburner and Friston, 2000). Subsequently, all images were smoothed by convolving them with an isotropic Gaussian Kernel of 12-mm FWHM.

In our studies, VBM2 and not VBM5 was used for the preprocessing of morphological data. This approach was used because the T1-weighted images obtained using the MPRAGE sequence were not compatible with VBM5's preprocessing and because the use of VBM5's optimized protocol, unlike that of VBM2's optimized protocol, resulted in a large number of apparent segmentation errors. Visual

inspections of obtained images revealed that this could not be apparently attributed to the problem in obtained images. The same strategy was adopted in previous studies (Ilg et al., 2008; Takeuchi et al., 2010b, 2011d). Furthermore, direct comparisons have shown that the methods used in VBM2 produce data that are comparable with those of ROI analyses (Good et al., 2002; Testa et al., 2004).

Preprocessing of diffusion imaging data

In DTI, FA in each voxel is used as a measure of the degree of diffusion anisotropy, with FA reflecting the angle (degree of directionality) of cellular structures within fiber tracts, and thus fiber integrity (Chua et al., 2008). A pathological postmortem study showed that the FA value strongly correlates with the amount of myelin (Schmierer et al., 2007). Cognitive processing speed, which has been assumed to be associated with the structures of WM pathways (e.g., Turken et al., 2008), is positively correlated with FA in various regions (Tuch et al., 2005; Turken et al., 2008). On the other hand, FA correlates with cognitive abilities related to social and emotional competences (Takeuchi et al., 2011g). FA varies between 0, representing isotropic diffusion, and 1, in case of diffusion occurring along one plane or direction.

Preprocessing of the FA image was performed using Statistical Parametric Mapping software (SPM8) implemented in Matlab (Mathworks Inc., Natick, MA, USA). Using the new segmentation algorithm implemented in SPM8, FA images of each individual were segmented into six tissues (first new segmentation). In this process, default parameters and tissue probability maps were used, except that affine regularization was performed using the International Consortium for Brain Mapping (ICBM) template for East Asian brains, and the sampling distance (the approximate distance between sampled points when estimating the model parameters) was 2 mm. We next synthesized the FA image and ADC map. In this synthesized image, the area with a WM tissue probability of >0.5 in the above-mentioned new segmentation process was the FA image multiplied by -1 (hence, this synthesized image shows a very clear contrast between the WM and the other tissues), and the remaining area is the ADC map (for the reasons of this procedure, see below). This synthesized image from each individual was then segmented using the new segmentation algorithm implemented in SPM8 using the same parameters as above (second new segmentation). This two-step segmentation process was adopted because the FA image had a relatively clear contrast between GM and WM, as well as between WM and CSF, and the first new segmentation step can segment the WM tissue from the rest of the tissues. On the other hand, the ADC map had a clear contrast between GM and CSF and the second new segmentation can segment GM. Since the ADC map alone does not have a clear contrast between WM and GM, we need to use a synthesized image (and the two-step segmentation process, Supplementary Fig. 1).

We next proceeded to the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) registration process implemented in SPM8. In this process, we used the DARTEL import image of the GM tissue probability map produced in the second new segmentation process as the GM input for the DARTEL process. The WM input for the DARTEL process was created as follows. First, the raw FA image was multiplied by the WM tissue probability map from the second new segmentation process within the areas with a WM probability of >0.5 (the signals from other areas were set to 0). Then, this FA image * the WM tissue probability map was coregistered and resliced to the DARTEL import WM tissue probability image from the second segmentation. The template for the DARTEL procedures was created using imaging data from 63 subjects who participated in the experiment in our lab (Takeuchi et al., 2011c) and was included in the present study (which means that they have the same characteristics as the subjects in this study). The first reason why we created the DARTEL template from images of the portion of all the subjects (63 subjects) and not from images of all subjects is because $N = 63$ is

not a small number to create template compared with much of the previous studies and thus cannot be considered to be problematic. The second reason is the project which was introduced in subject subsection and in which subjects of this study participated, is still ongoing and, DARTEL processes, especially our processes take huge amount of time and resultant images require storage resources, and everytime we change the number of subjects we cannot reprocess images of all subjects and add newer images based on the different number of subjects to our storage. Next, using this existing template, DARTEL procedures were performed on the subjects of this study. In these DARTEL procedures, parameters were changed as follows to improve the accuracy of the procedures. The number of Gauss–Newton iterations to be performed within each outer iteration was set to 10, and in each outer iteration, we used 8-fold more timepoints to solve the partial differential equations than the default values. The number of cycles used by the full multi-grid matrix solver was set to 8. The number of relaxation iterations performed in each multi-grid cycle was also set to 8. The resultant synthesized images were spatially normalized to the MNI space. Using the parameters for these procedures, the raw FA map, the GM segmentation map [GM concentration map], and the WM segmentation map [WM concentration (WMC) map] from the above-mentioned second new segmentation process were normalized to give images with $1.5 \times 1.5 \times 1.5$ mm³ voxels. The FA image * the WM tissue probability map was used in the DARTEL procedures because this image includes different signal intensities within the WM tissues and the normalization procedure can take advantage of these intensity differences to adjust the image to the template from the perspective of not only the outer edge of the tissue but also within the WM tissues (Supplementary Fig. 2). No modulation is performed in this normalization procedure.

Next, we created an average image from the normalized WM segmentation images from the above-mentioned 63 subjects and from the created mask image consisting of voxels with a WM signal intensity >0.99 . We then applied this mask image to the normalized FA image. Finally, this masked normalized FA image was smoothed by convolving it with an isotropic Gaussian kernel of 3 mm full-width at half-maximum (FWHM). A 3-mm smoothing kernel was chosen to retain finer local information within the WM tissue because DARTEL provides more accurate registration than conventional normalization methods, and a higher smoothing value is thought to be unnecessary to compensate for suboptimal normalization (Henley et al., 2010). The resulting maps representing FA were then forwarded for group regression analysis. Through application of the mask, images that were not likely to be WM or border areas between the WM and other tissues were removed and the FA images were not affected by signals from tissues other than WM even after smoothing. This is important considering that in these areas, WM volume and FA are highly correlated (Hugenschmidt et al., 2008) and the FA map supposedly reflects the extent of WM. Further, differences in WMC compared with other tissues among different individuals can be ignored after the application of this mask since within these masks, all voxels show very high white matter probability. For validation of these preprocessing methods, see the Supplementary material.

Statistical analysis of rWMV

Statistical analyses relating to rWMV were performed using VBM5 software, an extension of SPM5, utilizing the cluster size test for VBM built into VBM5, as described below (Hayasaka et al., 2004). In the whole brain analyses, we used voxel-wise analysis of covariance (ANCOVA), with sex difference as a grouping factor (using the full factorial option of SPM). In D score analyses, age, RAPM score, total brain volume (total GM volume + total WM volume), and D score were covariates. In the analyses of the EQ and SQ scores, age, RAPM score, total brain volume (total GM volume + total WM volume), EQ score, and SQ score were covariates. In the latter analysis, we included EQ and

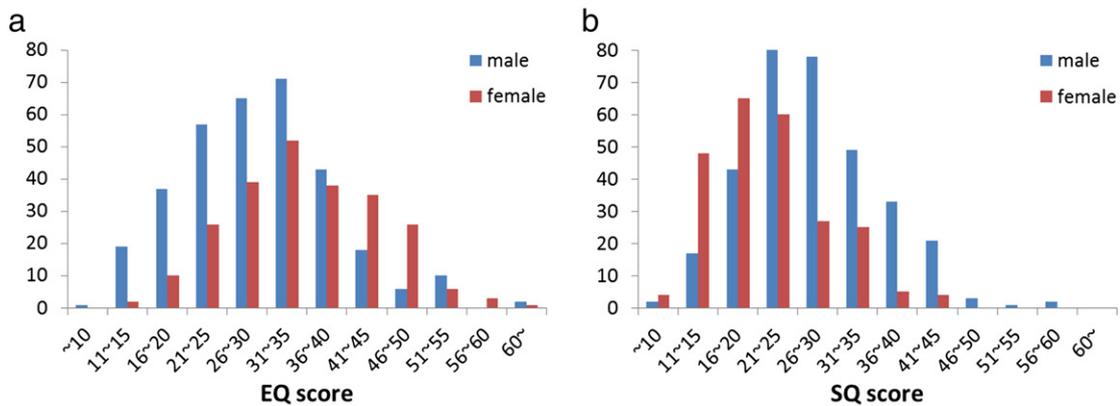


Fig. 1. Histograms showing the EQ scores (a) and SQ scores (b) for all subjects.

SQ in the same model, for the same reason that sex was included in the model, i.e., to rule out the possibility that an association between EQ (or SQ) and rGMV just reflects an association between SQ (or EQ) and rGMV as well as an association between EQ and SQ.

In rWMV analyses, age, RAPM score, and D/EQ/SQ scores were modeled so that each covariate had a unique relationship with rWMV for each sex (using the interaction option in SPM), which enabled investigation of the effects of interactions between sex and each covariate. On the other hand, total brain volume was not modeled in this manner, and a common effect of total brain volume on rWMV was assumed for both sexes. In these analyses, the centering option was used for centering the interactions. The main effects of the D/EQ/SQ score (contrasts of [the effects of the D/EQ/SQ score for males and females] were [1 1] or [−1 −1]) and the interaction between sex and the D/EQ/SQ score (contrasts of [the effect of the D/EQ/SQ score for males, the effect of the D/EQ/SQ score for females] were [−1 1] or [1 −1]) were assessed using *t*-contrasts. To calculate total brain volume (total GM volume + total WM volume), we used the total GM volume and total WM volume produced by VBM2 software. These values correspond to the sums of the signal intensity of each voxel * voxel size (mm³) of the rGMV and rWMV images, respectively.

In the analyses of rWMV, we included only voxels that returned a WM value of >0.10 to avoid possible partial volume effects around the borders between GM and WM as well as between WM and the cerebrospinal fluid.

The anatomical labels of significant clusters of major white matter fibers presented in the Results section were determined using the ICBM DTI-81 Atlas (<http://www.loni.ucla.edu/>).

Statistical analysis of FA

Statistical analyses relating to FA were performed using SPM8. In the models used in FA analyses, the total brain volume was not included as a covariate and instead the number of *b* = 0 images was

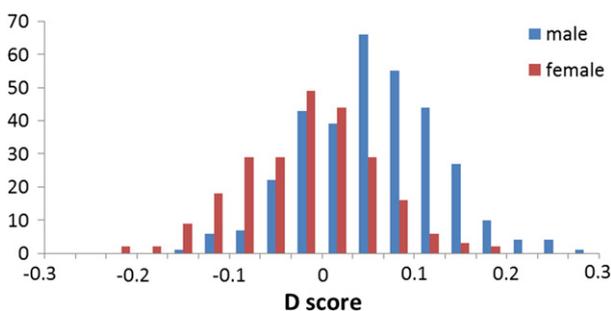


Fig. 2. Histograms showing the D scores for all subjects.

included as a covariate in each analysis. As a result, there were four whole brain ANCOVAs (one with D score on rWMV, one with EQ/SQ on rWMV, one with D score on FA, and one with EQ/SQ on FA).

The number of *b* = 0 images (1 or 3) was included in the model because the number of *b* = 0 images affects the estimation of FA values (Jones et al., 1999). A common effect of the number of *b* = 0 images on FA values was assumed for both sexes.

In FA analyses, we confined the areas of analyses to the areas that showed WMC values of >0.99 in the abovementioned average normalized WMC image.

Identification of the DMN

Subjects in this project also completed the fMRI paradigms of the N-back working memory task (2-back working memory condition and 0-back control condition). Details relating to these N-back fMRI paradigms can be found in our previous report (Takeuchi et al., 2011c). Details relating to preprocessing and the 1st level analysis can be found in another study (Takeuchi et al., in press-a). We used the fMRI data from the 2-back task of 248 subjects who participated in the fMRI study to show the brain regions deactivated during the 2-back working memory task in figures. A multiple comparison correction was performed using the voxel-level FWE approach at the whole-brain level using random field theory as implemented in SPM5.

The results of this analysis were added in figures to visually demonstrate that the discovered clusters substantially overlapped with (or were close WM neighbors of) the component structures of DMN.

Statistical threshold

In whole brain analyses of rWMV, the statistical significance level was set at *P* < 0.05, corrected at the non-isotropic adjusted cluster level (Hayasaka et al., 2004) with an underlying voxel level of *P* < 0.0025. Non-isotropic adjusted cluster-size tests can and should be applied when cluster size tests are applied to data known to be non-stationary (i.e., not uniformly smooth), such as voxel-based morphometry (VBM) data (Hayasaka et al., 2004). In this non-isotropic cluster-size test of random field theory, a relatively high cluster-determining threshold combined with high smoothing values of more than 6 voxels has been shown to lead to appropriate conservativeness in real data (Silver et al., 2010). In this test, under a high smoothing value, uncorrected threshold of *P* < 0.01 appears to lead to anti-conservativeness whereas uncorrected threshold of *P* < 0.001 appears to lead to slight conservativeness (Silver et al., 2010). We used a cluster-size test because of its sensitivity (Friston et al., 1996).

In whole brain analyses of FA, regions of significance were inferred using cluster-level statistics (Friston et al., 1996). Only clusters with *P* < 0.05 (corrected for multiple comparisons (controlling for family-

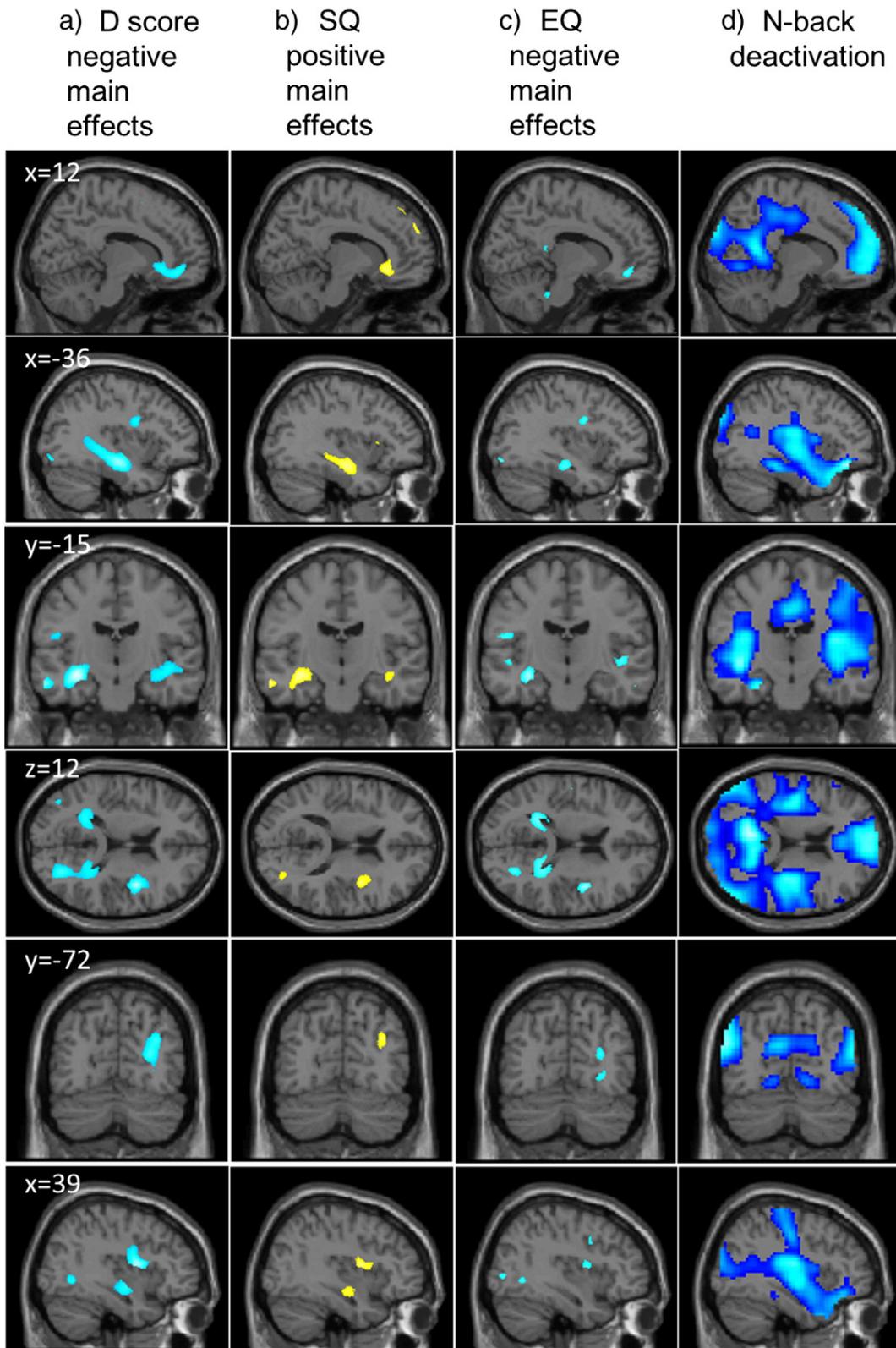


Fig. 3. The main effects (regardless of sex) of the D score/empathizing/systemizing across both sexes and areas deactivated during the externally directed attention-demanding task. (a,b,c) Results are shown with a voxel-level threshold of $P < 0.0025$, uncorrected. Regions of correlation were overlaid on “single-subject T1” SPM5 image. (a) Regions with negative main effects of the D scores on rWMV across both sexes. Regions with significant effects were observed in the WM areas of the bilateral temporal lobe, close to mPFC, PCC, right temporoparietal junction, and right inferior frontal gyrus. (b) Regions with positive main effects of the EQ score on rWMV across both sexes. Regions with significant effects were observed in the WM areas of the left temporal lobe and close to mPFC. Tendencies were observed in other areas associated with the significant negative main effects of the D score. (c) Regions with positive main effects of the SQ score on rWMV across both sexes. Regions with significant effects were observed in the WM areas of the left temporal lobe and close to the left PCC. Tendencies were observed in other areas associated with the significant negative main effects of the D score. (d) Regions that were deactivated during the 2-back task are displayed at a height threshold of 0.05, corrected for voxel-level FWE. Regions with significant effects of the D score are included in or adjacent to the areas deactivated during the 2-back task. However, note that the areas of the temporal lobe and mPFC were not included in this analysis because of susceptibility artifacts and limitations of the scan areas.

Table 1
Brain regions showing a significant negative main effect of the D score on rWMV.

Label	Nearest area		x	y	z	t score	Corrected P value	Regions with a positive main effect of EQ (%) [*]	Regions with a negative main effect of SQ (%) [*]
D-A	Temporal lobe/posterior cingulate gyrus	L	−31	−11	14	5.33	<0.001	91.5	91.4
D-B	Inferior frontal gyrus	R	41	3	13	4.95	0.006	98.3	80.7
D-C	Orbitofrontal gyrus	B	−12	21	−4	4.62	0.001	99.7	36.6
D-D	Temporal gyrus	R	33	−9	−11	4.12	0.028	96.9	86.4
D-E	Posterior cingulate gyrus/temporoparietal junction	R	27	−69	13	3.95	0.010	82.4	96.1

^{*} $P < 0.05$, corrected for FDR (SVC within each cluster) in ANCOVA with covariates of age, RAPM score, total brain volume, EQ score, and SQ score.

wise error) at cluster size, with a voxel-level cluster-determining threshold of $P < 0.0025$ uncorrected) were considered statistically significant.

Results

Behavioral data

As noted in another submitted study (Takeuchi et al., submitted for publication), the mean EQ scores of males and females were 29.69 (SD, 9.63; range 9–66) and 35.11 (SD, 9.40; range 14–63), respectively. The mean SQ scores of males and females were 27.76 (SD, 8.44; range 9–56) and 21.62 (SD, 7.11; range 8–45), respectively. The mean D scores of males and females were 0.0548 (SD, 0.0736; range −0.152 to 0.298) and −0.0174 (SD, 0.0715; range −0.221 to 0.192), respectively. For all subjects, simple regression analyses showed that the RAPM score was (a) significantly and negatively correlated with the EQ score ($P = 0.023$, $r = -0.095$); (b) significantly and positively correlated with the SQ score ($P = 0.002$, $r = 0.128$); and (c) significantly and positively correlated with the D score ($P = 1.90 \times 10^{-4}$, $r = 0.156$). For all subjects, the EQ score was not significantly correlated with the SQ score ($P = 0.780$, $r = 0.012$). For the male subjects, simple regression analyses showed that the RAPM score was (a) not significantly correlated with the EQ score ($P = 0.854$, $r = -0.010$); (b) significantly and positively correlated with the SQ score ($P = 0.032$, $r = 0.118$); and (c) positively correlated at the trend level with the D score ($P = 0.092$, $r = 0.093$). For the female subjects, the EQ score was also significantly and positively correlated with the SQ score ($P = 0.004$, $r = 0.157$). For the female subjects, simple regression analyses showed that the RAPM score was (a) significantly and negatively correlated with the EQ score ($P = 0.009$, $r = -0.168$); (b) not significantly correlated with the SQ score ($P = 0.200$, $r = 0.083$); and (c) significantly positively correlated with the D score ($P = 0.003$, $r = 0.190$). For the female subjects, the EQ score was not significantly correlated with the SQ score ($P = 0.353$, $r = 0.060$). Fig. 1 presents the data of distributions of EQ and SQ scores. Fig. 2 presents the data of distributions of D scores.

Effects of the D score on rWMV

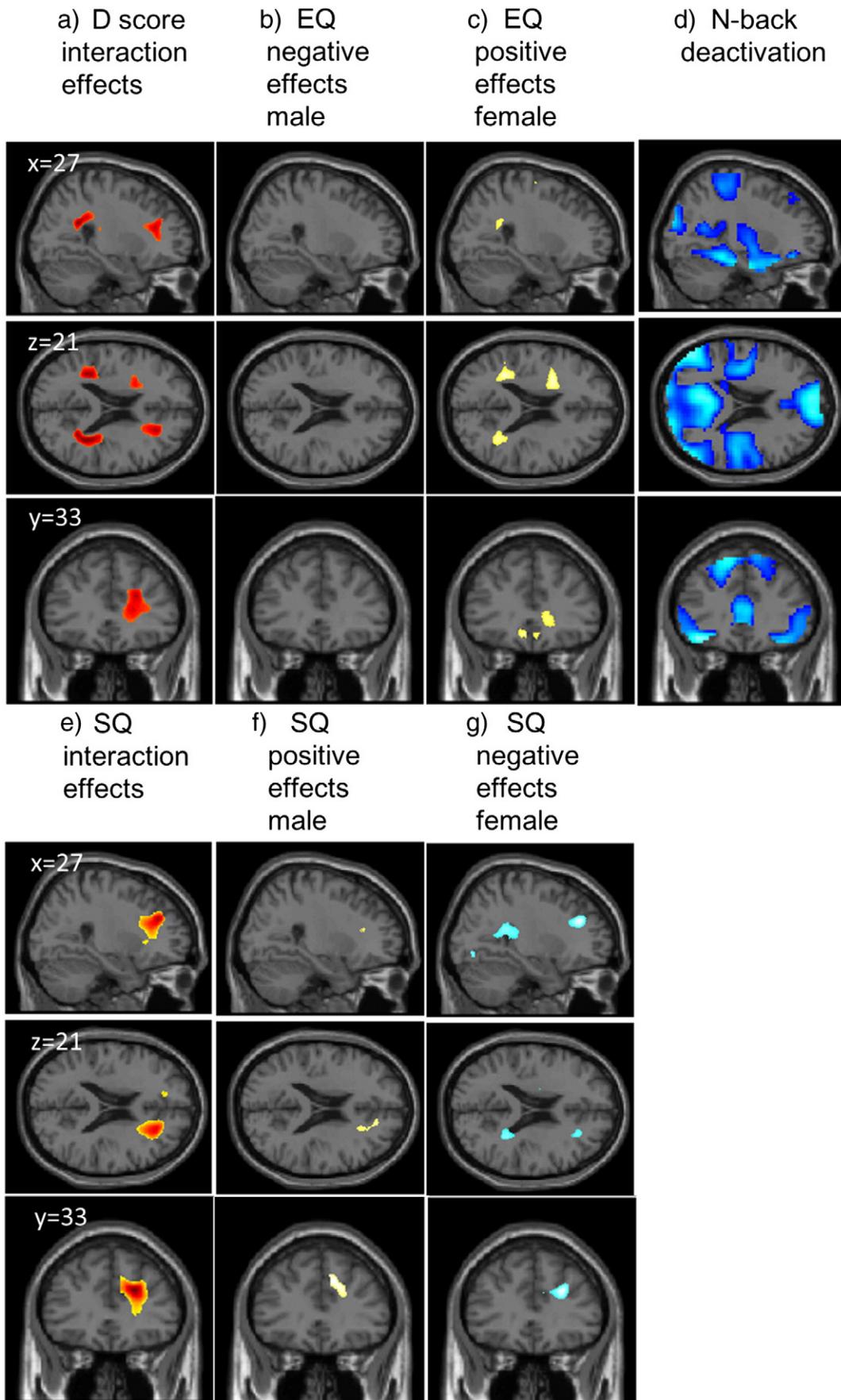
ANCOVA revealed a significant overall negative main effect (regardless of sex) of the D score on rWMV in the (D-A) anatomical cluster that spreads in the left temporal lobe along the line of STS and in a WM region around the posterior cingulate cortex. This cluster mainly includes the left part of the splenium of the corpus callosum and the

related structure (tapatum), left posterior thalamic radiation, left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, and cingulum close to the hippocampus, and fornix. Moreover, significant overall negative main effects were observed in the (D-B) anatomical cluster that is adjacent to the right inferior frontal gyrus and right anterior insula and that mainly includes the superior longitudinal fasciculus; the (D-C) anatomical cluster that is spread in the WM region around mPFC and that mainly includes part of the bilateral sides of the genu of the corpus callosum, anterior part of the inferior fronto-occipital fasciculus, and anterior corona radiata; the (D-D) WM cluster around the right middle and superior temporal gyrus (along the line with STS), medial temporal lobe and right temporal pole and that mainly includes the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus; as well as the (D-E) anatomical cluster that spreads around the WM area close to the right posterior cingulate cortex and right temporoparietal junction and that mainly includes the splenium of the corpus callosum and the related structure (tapatum), right posterior thalamic radiation, and posterior corona radiata. The tendency of the overall negative main effect of the D score was also observed in the (D-F) anatomical cluster that is adjacent to the left inferior frontal gyrus and left anterior insula and that mainly includes the left superior longitudinal fasciculus [Montreal Neurological Institute, MNI coordinates; $x, y, z = -31, 2, 26$; $t = 3.55$; $P = 0.156$ corrected for multiple comparisons at the non-isotropic (non-stationary) adjusted cluster level with a cluster-determining uncorrected threshold of $P < 0.0025$ and raw cluster size of 3447 mm^3]. These clusters are presented in Fig. 3a. Statistical values are presented in Table 1. No significant overall positive main effects (regardless of sex) of the D score were observed on rWMV.

In these significant areas, to reveal whether a relationship between rWMV and EQ and/or a relationship between SQ and rWMV contribute to a significant relationship between the D score and rWMV, we created mask images for each significant cluster of the significant relationship with the D score and rWMV and applied these images to the voxel-based ANCOVA of EQ/SQ (described above) to observe whether EQ and/or SQ scores showed any significant relationship with rWMV in these areas using a small volume correction (SVC) and a false discovery rate (FDR) ($P < 0.05$).

The results are shown in Table 1. Overall, the majority of the voxels in most areas with significant negative main effects of the D score on rWMV showed both positive main effects of the EQ score on rWMV and negative main effects of the SQ score on rWMV. In the case of the cluster near mPFC, only approximately 36% of the voxels within the cluster showed significant negative main effects of the SQ score on rWMV (Figs. 3b,c). Fig. 3d presents comparisons between these

Fig. 4. Effects of interaction between the D score and sex and between systemizing and sex on rWMV. The effects of empathizing/systemizing on rWMV in each sex and areas deactivated during the externally directed attention-demanding task. (a,b,c,d) Results are shown with a voxel-level threshold of $P < 0.0025$, uncorrected. Regions of correlation were overlaid on a "single-subject T1" SPM5 image. (a) Regions showing the effects of interaction between the D scores and sex on rWMV (positive effects in males and negative effects in females). The region with significant effects is observed in the WM areas of a region close to the right inferior parietal lobule and right temporoparietal junction together with tendencies in other areas. (b) Regions with negative effects of the EQ score in males. (c) Regions with positive effects of the EQ score in females. The effects are observed in the area with the significant interaction effect associated with the D score. (d) Regions that were deactivated during the 2-back task are displayed at a height threshold of 0.05, corrected for voxel-level FWE. (e) Regions showing the effects of interaction between the SQ scores and sex on rWMV (positive effects in males and negative effects in females). The region with significant effects is observed in the WM areas of a region close to the right DLPFC and dACC. (f) Regions with negative effects of the SQ score in males. The effects are observed in the area with the significant interaction effect associated with the SQ score. (g) Regions with negative effects of the SQ score in females. The effects are observed in the area with the significant interaction effect associated with the DQ score and in the area with the significant interaction effect associated with the SQ score.



areas and areas deactivated during the externally directed attention-demanding task.

A significant effect of interaction between sex and the D score was observed on rWMV in (D–G), the anatomical cluster that is adjacent to the right inferior parietal lobule and right temporoparietal junction, which mainly consists of the right superior longitudinal fasciculus and posterior corona radiata (Fig. 4a).

In this significant area, to reveal whether the relationship between rWMV and EQ in males/females and/or the relationship between SQ and rWMV in males/females contribute to the significant relationship between the D score and rWMV, we created mask images for each significant cluster of the significant relationship with the D score and rWMV and applied these images to the voxel-based ANCOVA of EQ/SQ (described above) and determined whether the EQ and/or SQ scores showed any significant relationship with rWMV in either sex using SVC and FDR ($P < 0.05$). These results are shown in Table 2. This significant interaction seems to be formed by the positive effect of EQ on rWMV in females and the weaker and less widespread negative effect of SQ in females, although a suprathreshold tendency of a negative effect of EQ on rWMV in males was also observed (4375 mm^3 , voxel level $P < 0.05$, uncorrected). Fig. 4d presents comparisons between these areas and areas deactivated during the externally directed attention-demanding task. Figs. 4b,c,f,g present all these results. There was tendency of the effect of interaction between sex and the D score on rWMV in (D–H), the left homolog area of this significant cluster, as well as in (D–I), the WM area close to the right DLPFC (Fig. 4a both raw cluster size of $>4500 \text{ mm}^3$ with a cluster-determining uncorrected threshold of $P < 0.0025$).

Effects of the EQ/SQ score on rWMV

ANCOVA revealed a significant overall positive main effect (regardless of sex) of the EQ score on rWMV in (E–A), the anatomical cluster that spreads in the left temporal lobe along with STS and that mainly includes the left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, and fornix (Fig. 3b, MNI coordinates; $x, y, z = -30, -9, -11$; $t = 4.39$; $P = 0.032$ corrected at the non-isotropic adjusted cluster level with a cluster-determining uncorrected threshold of $P < 0.0025$). The location of this cluster corresponded to that of cluster (D–A). However, in this analysis, the cluster did not spread into the posterior cingulate cortex at this cluster-determining threshold. ANCOVA also revealed a significant overall positive main effect (regardless of sex) of the EQ score on rWMV in (E–C), the anatomical cluster that is spread in the WM region around mPFC, and that mainly includes part of the bilateral sides of the genu of the corpus callosum and anterior corona radiata (Fig. 3b, MNI coordinates; $x, y, z = -12, 25, -7$; $t = 3.88$; $P = 0.016$ corrected at the non-isotropic adjusted cluster level with a cluster-determining uncorrected threshold of $P < 0.0025$). A trend-level significant overall positive main effect of the EQ score on rWMV was also observed in an area that corresponded to the location of clusters (D–B), (D–D), and (D–E) (Fig. 3b, all raw cluster size of $>800 \text{ mm}^3$ with a cluster-determining uncorrected threshold of $P < 0.0025$).

ANCOVA revealed a significant overall negative main effect (regardless of sex) of the SQ score on rWMV in the (S–A) anatomical cluster that spreads through the left temporal lobe and in a WM region around the posterior cingulate cortex. This cluster mainly includes the left of the splenium of the corpus callosum and the related structure (tapatum), left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, and fornix (Fig. 3c, MNI coordinates; $x, y, z = -30, -14, -13$; $t = 3.92$; $P = 0.018$ corrected at the non-isotropic adjusted cluster level with a cluster-determining uncorrected threshold of $P < 0.0025$). The location of this cluster corresponds to that of cluster (D–A). A non-significant tendency of the overall negative main effect of the EQ score on rWMV was also observed in an area that corresponded to the location of clusters (D–B),

(D–C), and (D–E) (Fig. 3c, all raw cluster size of $>500 \text{ mm}^3$ with a cluster-determining uncorrected threshold of $P < 0.0025$).

No significant effects of interaction between sex and the EQ score were observed on rWMV in any of the regions. Non-significant tendencies of the effects (negative effect in males and positive effect in females) of interaction between the EQ score and rWMV were observed in areas that corresponded to the locations of clusters (D–G) and (D–H) (Figs. 4b,c, bilateral areas close to the inferior parietal lobule and the temporoparietal junction; both raw cluster sizes of $>4500 \text{ mm}^3$ with a cluster-determining uncorrected threshold of $P < 0.0025$).

A significant effect of interaction between sex and the SQ score was observed on rWMV in (S–I), the WM cluster adjacent to the right DLPFC that also includes the anterior corona radiata and the right side of the genu and the body of the corpus callosum (Fig. 4e). The location of this cluster corresponded to the that of cluster (D–I).

In this significant area, to reveal whether the relationship between rWMV and SQ in males/females contributes to the significant interaction, we created mask images for each significant cluster of the significant effect of interaction between the SQ score and sex on rWMV and applied these images to the voxel-based ANCOVA of EQ/SQ (described above) to observe whether there was a significant positive effect of SQ on rWMV in males and/or a significant negative effect of SQ on rWMV in females using SVC and FDR ($P < 0.05$). The results are shown in Table 3. This significant interaction seems to be observed because of both the positive effect of the SQ score on rWMV in males and the negative effect of the SQ score on rWMV in females (Figs. 4f,g).

Effects of the D score on FA

ANCOVA revealed a significant overall positive main effect (regardless of sex) of the D score on FA in (DFA–K), the WM cluster that not only includes mainly SLF but also the superior and posterior corona radiata (Fig. 5a). As was the case with rWMV analyses, we next investigated whether this significant relationship was formed by the overall positive main effect of SQ on FA and/or by the overall negative main effect of EQ on FA. The results are shown in Table 4. The significant overall positive effect of the D score in this area seemed to be observed because of both the overall positive main effect of SQ on FA and the overall negative main effect of EQ on FA (Figs. 5b,c).

Effects of the EQ/SQ score on FA

ANCOVA revealed no significant overall main effects of the EQ or SQ scores on FA. A non-significant tendency of an overall positive main effect of the SQ score on FA was observed in an area that corresponded to the location of the cluster (DFA–K) (Fig. 5b, MNI coordinates; $x, y, z = 33, -35, 6$; $t = 3.96$; $P = 0.109$ corrected for multiple comparisons at the cluster level with a cluster-determining uncorrected threshold of $P < 0.0025$).

ANCOVA also revealed no significant effects of interaction between sex and the EQ score and between sex and the SQ score on FA.

Discussion

To the best of our knowledge, this is the first study to successfully reveal rWMV correlates of empathizing/systemizing, FA/rWMV correlates of the D score, as well as sexual dimorphisms of rWMV correlates of the D score/systemizing. Our results showed that across both sexes the D score [(systemizing – empathizing) / 2] is negatively correlated with (a) rWMV of an anatomical cluster primarily located in the WM region of the bilateral temporal lobes, mPFC, PCC, and the right inferior frontal gyrus. Post-hoc analyses revealed both a mostly positive correlation between empathizing and rWMV and a negative correlation between systemizing and rWMV in these areas and that both contribute to the formation of this relationship. Our results also showed that there was a significant interaction effect between the D

Table 2

Brain regions showing significant effects of interaction between sex and the D score on rWMV (positive effect in males and negative effect in females).

Label	Nearest area	x	y	z	t score	Corrected P value	Regions with a negative effect of EQ in males (%) [*]	Regions with a positive effect of EQ in females (%) [*]	Regions with a positive effect of SQ in males (%) [*]	Regions with a negative effect of SQ in females (%) [*]	
S-G	Temporoparietal junction/inferior parietal lobule	R	34	−43	23	3.76	0.025	0	94.7	0	31.7

* $P < 0.05$, corrected for FDR (SVC within the cluster) in ANCOVA with covariates of age, RAPM score, total brain volume, EQ score, and SQ score.

score and sex on rWMV in WM regions located near right IPL, TPJ, and PCC. Post-hoc analyses revealed that this interaction was observed because of the positive correlation between empathizing and rWMV in females and the negative correlation between systemizing and rWMV in females. Among these regions, mPFC, various areas of the temporal lobes, PCC, and right TPJ are part of DMN (Buckner et al., 2008), while the inferior frontal gyrus and IPL are typical parts of the mirror neuron system (Cattaneo and Rizzolatti, 2009). Moreover, a significant effect of interaction between systemizing and sex was observed on rWMV in WM regions close to the right DLPFC and right dACC, which form the typical nodes of EAS (Buckner et al., 2008; Corbetta and Shulman, 2002). The post-hoc analysis revealed that this interaction was observed because of the positive correlation between systemizing and rWMV in males and the negative correlation between systemizing and rWMV in females. Furthermore, the D score was positively correlated with WM integrity in the left SLF, which connects nodes of EAS (Petrides and Pandya, 2002) across both sexes. The post-hoc analysis revealed that both the negative correlation between empathizing and WM integrity and the positive correlation between systemizing and WM integrity led to this relationship. These results are at least partly consistent with our hypothesis, and our findings support the idea that regions linked to EAS support systemizing and regions in DMN support empathizing. However, despite the slight correlation between empathizing and systemizing, substantial overlaps were observed between positive/negative WM structural correlates of empathizing and negative/positive WM structural correlates of systemizing, providing evidence of the previous suggestion that there is a trade-off or competition (Baron-Cohen, 2004; Goldenfeld et al., 2005) between empathizing and systemizing in the brain.

Overall, regions with significant results in the rWMV and FA (structural integrity) analyses did not overlap, suggesting the different physiological bases of these correlates. This is congruent with previous studies that showed differences in the distribution of associations between FA and group/individual differences and the distribution of associations between rWMV and group/individual differences (Hugenschmidt et al., 2008; Jäncke et al., 2009). As described in the Introduction section, this is not surprising considering that FA and rWMV are moderately to weakly related (Fjell et al., 2008), and the associations between the two seem particularly weak in deep WM areas (Hugenschmidt et al., 2008). In addition, our FA analyses focused on WM areas that are very likely to be WM. FA and rWMV are believed to be highly sensitive to the different characteristics of WM (Fjell et al., 2008). As discussed in our previous study (Takeuchi et al., 2011e), myelination and myelin or membrane thickness and increases in the diameter of axons can lead to an increase in FA, rWMV, and cognitive ability. The size and number of glial cells (forming a major portion of WM), number of axon collateral spines, or a pure increase in WM

volume (or an increase in all of the physiological components of WM, while the composites remain the same) may selectively affect rWMV and leave diffusion anisotropy relatively unchanged. These mechanisms may underlie the positive associations between rWMV and empathizing (or the lower D score). On the other hand, how fibers run in one direction (Tuch et al., 1999) or how fiber tracts are integrated may more selectively affect FA leaving rWMV unchanged because crossing fibers can appear as a voxel of low anisotropy (Tuch et al., 1999). These mechanisms may underlie the positive associations between FA and systemizing (or the D score). In DTI, where large WM tracts cross, increases in myelination (or increases in structural integrity) do not necessarily increase FA. Further, our DTI analyses focused on areas that are very likely to be WM. Despite this focus, DARTEL-based normalization procedures retain much of the WM areas in the analyses. However, the small ramification areas of WM and border areas between WM and other tissues, where FA and rWMV show relatively strong correlations, were removed from the processed images. These areas were blindspots of the DTI analyses performed in this study, and discrepancies between rWMV findings and FA findings may be partly explained by these mechanisms.

Consistent positive/negative correlates of empathizing and negative/positive correlates of systemizing may suggest possible underlying mechanisms and provide evidence for the prior suggestion that there is a trade-off or competition (Baron-Cohen, 2004; Goldenfeld et al., 2005) between empathizing and systemizing in the brain. In this study, more significant findings were obtained in the analyses of the D score than in the analyses of empathizing and systemizing. Post-hoc analyses showed generally significant correlations between WM structures and the D score, which were observed because of both the positive/negative correlation between empathizing and WM structures and the negative/positive correlation between systemizing and WM structures. This appears to be the reason why the analyses of the D score, which is the difference between systemizing and empathizing, resulted in more significant results in the whole brain analyses. This was observed despite there being little correlation between empathizing and systemizing (see Behavioral data in Results section) and despite the fact that the items relating to empathizing and those relating to systemizing had different areas of focus. Our results are congruent with some GM findings, which have shown similar overlaps in some of these regions (Takeuchi et al., submitted for publication). As described in the Introduction section, while there is little correlation between empathizing and systemizing, the sum of the empathizing and systemizing scores does not differ between males and females. This was the basis for the suggestion that empathizing and systemizing are competing “neurally in the brain” and that the D score provides information about the trade-off between the two (Goldenfeld et al., 2005). However, this has been criticized as lacking sufficient evidence (Andrew et al., 2008). Our results could at least partly provide evidence supporting

Table 3

Brain regions showing significant interaction effects between sex and the S score on rWMV (positive effect in males and negative effect in females).

Label	Nearest area	x	y	z	t score	Corrected P value	Regions with a positive effect of SQ in males (%) [*]	Regions with a negative effect of SQ in females (%) [*]	
S-I	DLPFC	R	23	34	25	4.63	0.008	92.4	87.7

* $P < 0.05$, corrected for FDR (SVC within the cluster) in ANCOVA with covariates of age, RAPM score, total brain volume, EQ score, and SQ score.

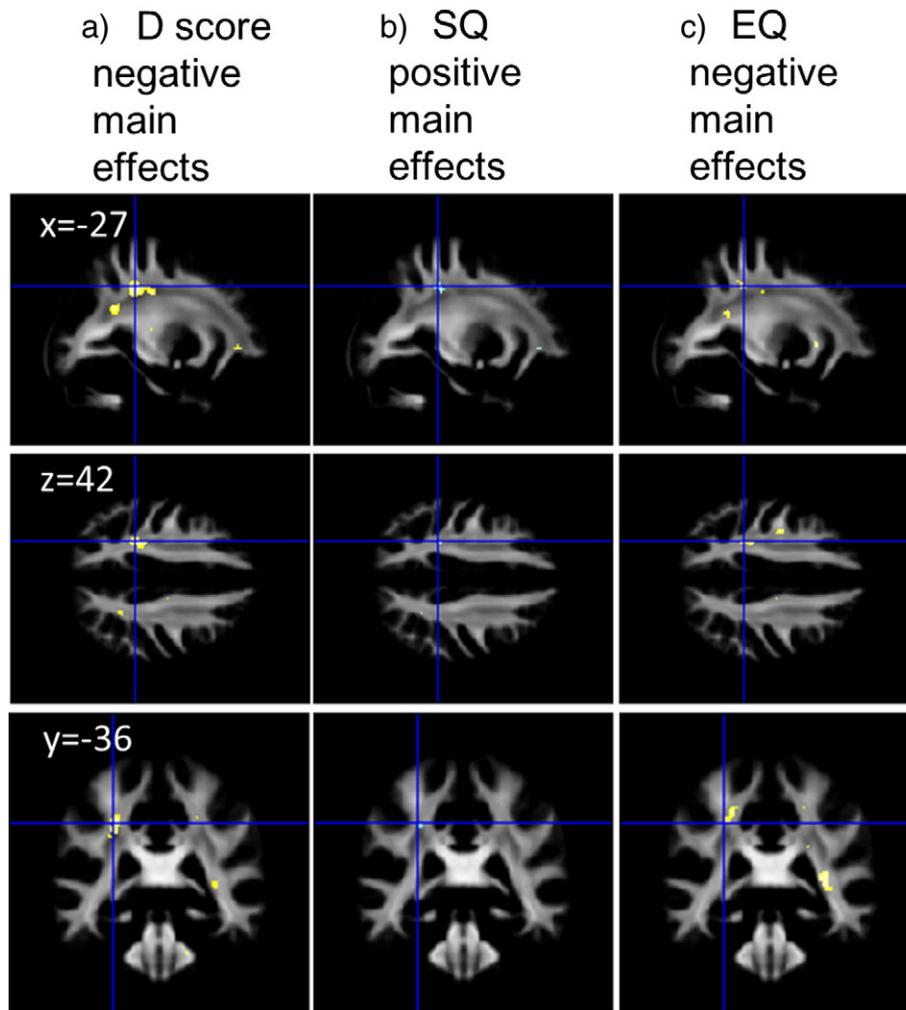


Fig. 5. The main effects (regardless of sex) of the D score/empathizing/systemizing across both sexes on FA. (a,b,c) Results are shown with a voxel-level threshold of $P < 0.0025$, uncorrected. Regions of correlation were overlaid on mean preprocessed, but not smoothed, FA images of a subset of participants. (a) Regions with the positive main effects of D scores on FA across both sexes. The region with the significant effect is observed in the WM area of SLF. (b) Regions with the negative main effects of EQ scores on FA across both sexes. Tendencies were observed in the area associated with the significant effects of the D score. (c) Regions with the positive main effects of SQ scores on FA across both sexes. Tendencies were observed in the area associated with the significant effects of the D score.

this claim from a brain imaging perspective. This is because our results indicate that when WMV or WM integrity is increased in certain networks, it is associated with an increase in empathizing/systemizing and a decrease in systemizing/empathizing. The reason why this was observed is not clear from this study's design and we can just speculate. One possibility is as (1) ASCs, (2) males and (3) students in science show higher systemizing and lower empathizing, some biological and/or developmental mechanisms may commonly affect white matter structures in certain regions, empathizing and systemizing, and that may be why these are seen in the same groups. Another possibility is that it may be difficult to achieve a good balance between high empathizing and high systemizing cognitively (Baron-Cohen, 2004). For example, empathizing too much with others may make it difficult to analyze a system effectively. The slight correlation between empathizing and systemizing despite the widespread overlap in their anatomical

correlates might suggest that there are factors that cause higher empathizing and lower systemizing and factors that lead to lower empathizing and higher systemizing, but these were not clear from the WM structural analyses performed in this study.

rWMV in WM areas adjacent to the key nodes of DMN, as well as those of the mirror neuron system, was negatively correlated with the D score and positively correlated with empathizing, while rWMV of the WM areas adjacent to the key nodes of EAS was associated with systemizing, suggesting the involvement of nodes of these networks in empathizing and systemizing.

As for the findings related to DMN, mPFC and PCC are the key nodes of DMN (Buckner et al., 2008). mPFC is believed to be involved in assessing the psychological attributes of a person, regardless of self (for a review, see Amodio and Frith, 2006; Christoff and Gabrieli, 2000) or non-self (Amodio and Frith, 2006). A number of studies

Table 4
Brain regions showing a significant main effect of the D score on FA.

Label	Main WM tracts	x	y	z	t score	Corrected P value	Regions with a negative main effect of EQ (%) [*]	Regions with a positive main effect of SQ (%) [*]	
DFA-K	SLF	L	-27	-36	42	4.37	0.011	95.6	96.0

^{*} $P < 0.05$, corrected for FDR (SVC within the cluster) in ANCOVA with covariates of age, RAPM score, number of b = 0 images, EQ score, and SQ score.

have shown that PCC is involved in perspective taking (for review, see [Cavanna and Trimble \(2006\)](#)), which plays a key role in empathy ([Baron-Cohen and Wheelwright, 2004](#)). The GM and WM structures in and adjacent to the temporal lobe include a number of structures involving DMN [as observed in this study ([Figs. 3d, 4d](#)) and in previous studies ([Buckner et al., 2008](#))] and/or social cognition such as TPJ, TP, STS, and amygdala. The principle function of STS is suggested to be analyzing changing sequences of inputs in the auditory or visual domain and interpreting the communicative significance of such inputs ([Milligan et al., 2007](#)). By utilizing this function, STS plays a key role in perception related to social signals, language, and speech (for review, see [Milligan et al. \(2007\)](#)). It has been suggested that the function of TP is to link high-level sensory representations with emotional responses and social memory ([Olson et al., 2006](#)), and the right TP may be involved in both empathy and TOM through these functions ([Völlm et al., 2006](#)); it may also be involved in other tasks that require subjects to think about another individual's thoughts and emotions ([Olson et al., 2006](#)). TPJ is involved in various aspects of self cognition and in distinguishing self and others ([Decety and Lamm, 2007](#)), and this area may be involved in empathy through these functions (for review, see [Decety and Lamm \(2007\)](#)); it may also be involved in perspective taking and TOM (for review, see [Decety and Lamm \(2007\)](#)), both of which are important for empathy ([Baron-Cohen and Wheelwright, 2004](#)). The amygdala also plays an important role in social cognition because it serves as a protective “brake” in social situations through fear ([Amaral, 2002](#)). The inferior longitudinal fasciculus originates in the occipital lobe and fusiform gyrus and terminates in the lateral and medial temporal areas ([Catani et al., 2003](#)); it is thought to contribute to facial, emotional, and paralinguistic information processing ([Takeuchi et al., 2011g](#)), which appear to be important in social situations. The inferior fronto-occipital fasciculus directly connects the frontal lobe (mainly the ventromedial PFC and other prefrontal regions) with the posterolateral temporal and occipital lobes ([Catani et al., 2003](#); [Fernández-Miranda et al., 2008](#); [Martino et al., 2010](#)), and the role of this bundle seems to include functions related to the ventromedial PFC, which is critically involved in empathy ([Rankin et al., 2006](#); [Shamay-Tsoory et al., 2006, 2009](#)).

Regarding the findings relating to the mirror neuron system, the inferior frontal gyrus and IPL are typical nodes of this system. In particular, these structures in the right hemisphere are believed to play an important role in ascribing intentions to others. Since these structures are part of EAS and are believed to have other functional roles ([Corbetta and Shulman, 2002](#)), we cannot be sure of how exactly these structures contribute to empathizing. However, the involvement of these areas in empathizing is consistent with a widely held view that the mirror neuron system facilitates the understanding of the intentions of others and plays important roles in empathy and in the empathic dysfunction characteristic of ASCs ([Iacoboni and Dapretto, 2006](#); [Rizzolatti and Craighero, 2005](#)).

Finally, regarding the findings related to EAS, the right DLPFC and dACC are robust parts of EAS ([Fox et al., 2005](#)). DLPFC is involved with the manipulation or mental operation of objects retained in the mind of an individual (for a meta-analysis, see [Owen \(2000\)](#)). dACC is involved in the prediction, monitoring, and detection of errors ([Egner, 2011](#)). These regions may contribute to systemizing via these functions.

Associations between empathizing and rWMV of the WM regions adjacent to the right TPJ and right IPL were limited to females. Although the exact cause of this is unknown, there are a number of possible reasons for this observation. For example, because females have a larger social network ([Stileman, 2007](#)), they may require stronger recruitment of certain nodes than males. On the other hand, differences in the ways in which parents educate males and females regarding empathy ([Baron-Cohen, 2004](#)) may lead to enhanced recruitment of certain nodes in females. On the other hand, positive correlations between systemizing and rWMV in the right DLPFC in males and negative correlations between systemizing and rWMV in the right DLPFC in females may have

something to do with how males with a higher aptitude for systemizing and females with a higher aptitude for systemizing have been treated. Related to this point, it has been shown that girl's interest in math will decrease with the strength of their father's adoption of the gender stereotype that math and science are more important for boys than for girls, whereas boy's interest in math will increase with the strength of their father's adoption of these gender stereotypes ([Jacobs et al., 2005](#)). However, these are only speculations and future studies are required to investigate the cause of this phenomenon.

The WM region in which structural integrity (FA) was positively correlated with the D score (because of the positive correlation between structural integrity and systemizing) corresponds to SLF II ([Makris et al., 2005](#)), and this structure may support systemizing through cognitive functions related to spatial cognition and manipulation of mental information. SLF II is believed to connect the prefrontal regions (anterior and posterior parts of the dorsolateral PFC) with the posterior parts of the inferior parietal regions ([Makris et al., 2005](#)). The posterior parts of the inferior parietal regions play a key role in spatial attention and spatial functions ([Makris et al., 2005](#)), and the posterior parietal cortex is a key neural locus of mental representation of the visual world ([Todd and Marois, 2004](#)). The dorsolateral PFC regions are involved in the manipulation, or mental operation, of objects retained in one's mind (for a review, see [Owen \(2000\)](#)). Because SLF II provides a way to connect these parietal and prefrontal regions, SLF II may provide a means by which PFC can regulate the focusing of attention in different parts of the space ([Makris et al., 2005](#)) and dissociate, manipulate, and analyze visuospatial systems. In this manner, the integrated SLF II may support systemizing and associated spatial functions ([Baron-Cohen, 2004](#)).

No regions showed significant positive correlations between empathizing and FA. Although we cannot read much into the negative findings of the whole imaging analyses, there are a number of possible reasons for these findings. First, while empathizing is associated with rGMV ([Takeuchi et al., submitted for publication](#)), empathizing may not be associated with WM structural integrity. Increased myelination, which may underlie increased FA in DTI, leads to faster conduction velocity of action potential (for detail of this discussion, see [Takeuchi et al. \(2010a\)](#)). Faster conduction velocity can facilitate information flow not only by speeding it up, but also by allowing for precise temporal coding of high-frequency bursts of neuronal activity ([McDonald and Sears, 1970](#); [Shrager, 1993](#); [Swadlow, 1985](#)). Increased empathizing may not require this type of information processing. Second, crossing of two or more fibers may prevent significant findings relating to empathizing. In DTI, regions where two or more neuronal fibers cross can appear as a voxel of low FA ([Tuch et al., 1999](#)). In this case, theoretically, increased myelination of two crossed neuronal fibers would not lead to higher FA. Empathizing may be associated with the WM structural integrity of regions with crossing fibers.

Moreover, we failed to replicate the findings relating to WM structural integrity correlates of empathizing/systemizing in a previous study by [Chou et al. \(2011\)](#), which used tract-based spatial statistics (TBSS) ([Smith et al., 2006](#)), which we described in the [Introduction](#) section. There are differences in the methodologies used by these studies. Cultural differences might also have a role in explaining the different outcomes. Another possibility is that there are differences in the sensitivity of the two analyses. We did not and could not utilize TBSS in this study. This is because we favored the SPM-based analyses and believed that our new DTI's preprocessing methods substantially alleviate the problems associated with voxel-based DTI analyses noted by [Smith et al. \(2006\)](#). In addition, TBSS-based analyses require the use of permutations (which cannot be applied to this study because of the increased computation time required) for the non-parametric inference. Further, random field theory (RFT)-based correction for multiple comparisons cannot be applied to images in TBSS because of apparent violation of the preconditions of RFT ([Friston et al., 1996](#)). Our preliminary analyses using TBSS indicated that when the threshold used in the study by [Chou et al. \(2011\)](#) ($t > 3$ and 10 mm^3) was applied

to TBSS-based analyses of our DTI data, the contrast of the target showed various results [e.g., the positive main effects of the D score on FA showed 12 results that surpassed this threshold (i.e., there was no negative main effect of the D score on FA surpassing the threshold)]. Similarly, 1 suprathreshold result showed a positive main effect of the EQ score on FA, 6 suprathreshold results showed negative main effects of the EQ score on FA, and 12 suprathreshold results showed positive main effects of the SQ score on FA. The smoothness of the raw images differed between the two studies, and we cannot say anything conclusively based on these results. Perhaps, the TBSS-based analyses may have more sensitivity.

There were at least few limitations to this study, and they were identical to that of our previous studies as well as of other studies that use college cohorts (Jung et al., 2010; Song et al., 2008; Takeuchi et al., 2010b,c, 2011c). We used young healthy subjects with a high educational background. Limited sampling of the full range of intellectual abilities is a common hazard when sampling from college cohorts (Jung et al., 2010). Whether the findings from college cohorts would also hold across the full range of population samples and a normal distribution must be determined with larger and more representative samples. The narrow age range is another limitation of this study. Although, focusing on the narrow range is important for two reasons. One is increasing sensitivity for analyses by removing variances. The second is in the analyses of rGMV/rWMV, focusing on narrow age range is also important because, rGMV/rWMV shows non-linear age-related changes and these age-related changing patterns differ among different regions (Pagani et al., 2008; Sowell et al., 2003; Taki et al., in press) and focusing on wide age range in cross-sectional studies may significantly complicate the structure–function relationships and may result in potential loss of significant results. However, on the other hand, focusing on the narrow range certainly limits the generalizability of the results. Furthermore, while we analyzed FA/rWMV in relation to empathizing/systemizing/D score and investigated main effects, and interaction effects, we did not perform any corrections for multiple comparisons across different analyses. This is the gold standard approach used in almost all studies of this type, particularly in this type of structural correlation study, since a large sample size is generally required in whole brain structural analyses and applying stringent corrections for multiple comparisons extinguishes both true- and false-positive results. However, the possibility of a false positive being applicable to some of the marginally significant results should still be taken into consideration.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2013.04.004>.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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