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White matter tract integrity and intelligence in patients with mental retardation and healthy adults

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It is well known that brain structures correlate with intelligence but the association between the integrity of brain white matter tracts and intelligence in patients with mental retardation (MR) and healthy adults remains unknown. The aims of this study are to investigate whether the integrity of corpus callosum (CC), cingulum, uncinate fasciculus (UF), optic radiation (OR) and corticospinal tract (CST) are damaged in patients with MR, and to determine the correlations between the integrity of these tracts and full scale intelligence quotient (FSIQ) in both patients and controls. Fifteen MR patients and 79 healthy controls underwent intelligence tests and diffusion tensor imaging examinations. According to the FSIQ, all healthy controls were divided into general intelligence (GI: FSIQ < 120; n = 42) and high intelligence (HI: FSIQ ≥ 120; n = 37) groups. Intelligence was assessed by Chinese Revised Wechsler Adult Intelligence Scale, and white matter tract integrity was assessed by fractional anisotropy (FA). MR patients showed significantly lower FA than healthy controls in the CC, UF, OR and CST. However, GI subjects only demonstrated lower FA than HI subjects in the right UF. Partial correlation analysis controlling for age and sex showed that FSIQ scores were significantly correlated with the FA of the bilateral UF, genu and truncus of CC, bilateral OR and left CST. While FSIQ scores were only significantly correlated with the FA of the right UF when further controlling for group. This study indicate that MR patients show extensive damage in the integrity of the brain white matter tracts, and the right UF is an important neural basis of human intelligence.

Keywords: Diffusion tensor imaging; Tractography; Fractional anisotropy; Mental retardation; Intelligence

Introduction

Researchers have long attempted to determine the biological basis of intelligence using available neuroimaging techniques. With the use of structural imaging technique, several research teams, using different scan protocols, populations and intellectual measures, have shown positive correlations between intelligence quotient (IQ) and total brain volumes (Andreasen et al., 1993; Ivanovic et al., 2004; McDaniel 2005; Plomin and Kosslyn 2001; Reiss et al., 1996; Tisserand et al., 2001; Witelson et al., 2006). Recent studies using voxel-based morphometry have demonstrated correlations between IQ and some specific brain regions, which involve in frontal (Colom et al., 2006; Frangou et al., 2004; Gong et al., 2005; Haier et al., 2004, 2005; Thompson et al., 2001; Wilke et al., 2003), parietal (Colom et al., 2006; Haier et al., 2004, 2005), temporal (Colom et al., 2006; Haier et al., 2004) and occipital (Colom et al., 2006; Haier et al., 2004) lobes. Functional brain imaging techniques can reveal activated regions that probably support intelligent behavior. Using positron emission tomography (PET), a study has found that only lateral frontal cortex was consistently activated during three different intelligence tasks when compared with control tasks (Duncan et al., 2000). However, many other functional imaging studies have shown that good test performance recruited more brain areas (Gray et al., 2003; Haier et al., 1988; Prabhakaran et al., 1997), which suggests multiple brain regions related to intelligence. Most of the above studies support the association between brain gray matter and IQ, but the association between the integrity of brain white matter tracts and IQ in healthy adults remains largely unknown.

The brain white matter can be quantitatively assessed by the technique of diffusion tensor imaging (DTI), which measures the random motion of water molecules and provides information about the size, orientation, and geometry of brain tissue (Basser et al., 1994; Le Bihan 2003). Pathological processes, which change the microstructural environment, such as neuronal size, extracellular

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space and tissue integrity, result in altered diffusion (Anderson et al., 1996; Sevick et al., 1992; Yu et al., 2007). The integrity of white matter tracts can be assessed by fractional anisotropy (FA), an indicator of myelination and axonal thickness. With the advent of the technique of tractography, brain white matter tracts can be visualized *in vivo* and extracted from the surrounding structures (Basser et al., 2000; Jones et al., 1999), which makes the tract-based analysis of diffusion indices possible.

Using the technique of DTI, the association between white matter integrity and IQ has been investigated in many situations, such as in normal children (Schmithorst et al., 2005), adolescents with very low birth weight (Skranes et al., 2007), malignant phenylketonuria (Peng et al., 2004), fragile X syndrome (Barnea-Goraly et al., 2003), schizotypal personality disorder (Nakamura et al., 2005), and multiple sclerosis (Rovaris et al., 2002). They found that the IQ scores were correlated with the white matter integrity of different brain regions in different situations. However, the damage of the integrity of the white matter tracts in patients with mental retardation (MR) and the association between the integrity of white matter tracts and IQ in normal adults have not been investigated, especially using the DTI-based tract analysis.

To investigate the correlations between IQ and the integrity of white matter tracts, we chose the corpus callosum (CC), cingulum, uncinate fasciculus (UF), optic radiation (OR) and corticospinal tract (CST) as tracts of interest because they are the main white matter tracts of the brain and are large enough to be reliably reconstructed by diffusion tensor tractography. We intend to determine the relationship between IQ and white matter tract integrity from two aspects. One is to compare the differences of the integrity of these tracts among MR patients, general intelligence (GI: FSIQ < 120) and high intelligence (HI: FSIQ ≥ 120) controls to determine which white matter tracts are damaged in MR group relative to healthy groups and in GI group relative to HI group. The other is to directly correlate IQ with the integrity of these tracts in a relatively large population controlling for sex, age and group.

Subjects and methods

Subjects

Study approval was acquired from the ethical committee of Xuanwu Hospital of Capital Medical University. Parents of the MR patients and all of the healthy controls provided written informed consent after the study had been fully explained to them. Ninety-four right-handed (Oldfield, 1971) subjects participated in the study, including 15 MR patients (10 men and 5 women; mean age 23.5 ± 3.4 years, range 18-33 years) and 79 healthy volunteers (44 men and 35 women, mean age 23.8 ± 3.9 years; range 17-33 years). The MR patients were recruited from Beijing Huiling community service for people with disabilities and Beijing Lizhi recovery center for people with disabilities. All patients were diagnosed by an experienced psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for mental retardation (American Psychiatric Association, 1994): (1) an IQ of approximately 70 or below on an individually administered IQ test; (2) at least two affected areas: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health and safety; (3) onset prior to age 18 years. Exclusion criteria included prenatal events (such as congenital infections, prolonged maternal fever in the first trimester, exposure to anticonvulsants or alcohol, and untreated maternal phenylketonuria), notable dysmorphology, near-drowning, traumatic brain injury, phenylketonuria, hypothyroidism and disorders known to be associated with MR, such as neurofibromatosis and tuberous sclerosis. Patients with visible brain lesions on conventional magnetic resonance images were also excluded from this study. In the 15 MR patients, the specifically affected areas included communication (7 patients), self-care (2 patients), home living (2 patients), social/interpersonal skills (11 patients), use of community resources (7 patients), self-direction (14 patients), functional academic skills (15 patients), work (15 patients), leisure (7 patients), health and safety (2 patients). Healthy controls were recruited by advertisement. Full scale IQ (FSIQ) score was measured by means of the Chinese Revised Wechsler Adult Intelligence Scale (WAIS-RC) (Gong, 1982). The mean ± SD FSIQ was 50.3 ± 10.5 with a range of 33-65 for MR patients and 113.2 ± 19.2 with a range of 71-145 for healthy controls. According to the FSIQ, all healthy controls were divided into GI (70 < FSIQ < 120; n = 42; 22 men and 20 women; age, 22.8 ± 4.1 years, range 17-32 years) and HI (FSIQ ≥ 120; n = 37; 22 men and 15 women; age, 24.9 ± 3.3 years, range 20-33 years) groups. Education level of each group and the educational impact on FSIQ were shown in Supplementary M1.

MRI data acquisition

All subjects were examined with a 3.0 Tesla MR scanner (Trio system; Siemens Magnetom scanner, Erlangen, Germany). The DTI scheme included the collection of 12 images with non-collinear diffusion gradients (b = 1000 s/mm^2) and one non-diffusion-weighted image (b = 0 s/mm^2), employing a single shot echo planar imaging sequence. Integrated parallel acquisition technique (iPAT) was used with an acceleration factor of 2. Acquisition time can be reduced by the iPAT method with less image distortion from susceptibility artifacts. From each participant 45 slices were collected. The field of view was 256 × 256 mm, the acquisition matrix was 128 × 128 and zero filled into 256 × 256, the number of averages was 3, and the slice thickness was 3 mm without gap, which resulted in voxel-dimensions of 1 mm × 1 mm × 3 mm. The echo time and repetition time were 87 ms and 6000 ms, respectively.

Data preprocessing

The following steps were performed to preprocess DTI data: (1) all diffusion-weighted images were visually inspected by two radiologists for apparent artifacts due to subject motion and instrument malfunction; (2) distortion induced by eddy currents and simple head motion of diffusion-weighted images were corrected by affine registration to the b = 0 images, using FMRIB's Diffusion Toolbox (free software from Oxford Centre for Functional MRI of the Brain, UK); (3) DTI data were interpolated into 1 mm × 1 mm × 1 mm of the voxel size.

The diffusion tensor of each voxel was calculated by a linear least-square fitting algorithm (Basser et al., 1994). After diagonalization of the diffusion tensor, the three diffusion tensor eigenvalues were obtained. The FA of each voxel was calculated based on the three eigenvalues and was used as a measure of the degree of diffusion anisotropy. FA varies between 0, representing isotropic diffusion, and 1, in the case of the diffusion taking place entirely in one direction.

Tractography

The tractography for the CC, UF, cingulum, OR and CST was implemented using DTI Studio (free software from Radiology department, Johns Hopkins University, USA), in which the fiber assignment by means of continuous tracking (FACT) (Mori et al., 1999; Mori and Van Zijl, 2002) was used with a FA threshold of 0.15 and angle transition threshold of 45° during tracking. To reconstruct tracts of interest, we used a multiple–region-of-interest (ROI) approach (Catani et al., 2002; Wakana et al., 2004) based on the existing anatomic knowledge of tract trajectories. Tracking was performed from all pixels inside the brain ("brute force" approach), and results that penetrated the manually defined ROIs were assigned to the specific tracts associated with the ROIs.

The CC on the midsagittal FA image was evenly divided into 4 quadrants along its anterior-posterior axis (Shimony et al., 2006). The 4 quadrants were roughly corresponding to genu (CC1), anterior and posterior part of truncus (CC2), and splenium (CC3). Each part of the CC was traced by placing a seed ROI on the midsagittal FA image encompassing the corresponding quadrant (Fig. 1A). The seed ROI for tracing the UF was placed in the anterior part of the temporal lobe on the coronal plane. Then we used a filter ROI to exclude other fibers, which was placed in the inferior part of the frontal lobe on the coronal plane (Fig. 1B). Fibers passing through all the two ROIs were defined as the UF. Two seed ROIs in the coronal planes were used to reconstruct the cingulum, one passed through the genu-trunk junction of CC (Fig. 1C), and the second ROI was placed through the trunk-splenium junction of CC (Fig. 1D). We used three ROIs to reconstruct the OR. The first ROI was placed at the level of the trigone in the coronal plane (Fig. 1E), the second ROI was in the white matter of the occipital lobe in the parasagittal plane near to the midline, and the third ROI was set laterally to the lateral geniculate nucleus in the sagittal plane (Fig. 1F). The seed ROI for tracing the CST was placed in the cerebral peduncle (Fig. 1G). Then we used two filter ROIs to exclude non-CST fibers. They were placed in the posterior limb of the internal capsule (Fig. 1H) and the pre-and postcentral gyri (Fig. 1I), respectively.

Tract-based quantitative analysis was performed by defining all voxels penetrated by a tract as the region of the tract. Then FA values of these tracts were calculated for each participant.

Reproducibility analysis

Since the seed ROIs for tractography were manually defined by a single rater, the intra-rater reproducibility of the positioning of the seed ROIs was determined by re-defining these seed ROIs, reconstructing the tracts and re-measuring the FA of each tract in all participants on two separate occasions (separated by at least 3 months).

Statistical analysis

Data was analyzed with SPSS 11.5 for Windows (SPSS Inc, Chicago, III). They were first examined for normality to conform to the assumptions of the parametric statistics used. Between-group differences in the FA of the CC, UF, cingulum, OR and CST were calculated by means of a univariate general linear model with group (MR, GI and HI), sex (man, woman) and side (left, right) as the between-subject variables. Then a *post hoc* (Bonferroni) test was used to examine the differences between every two groups. The significance level was defined as $P<.05$, 2-tailed. When the

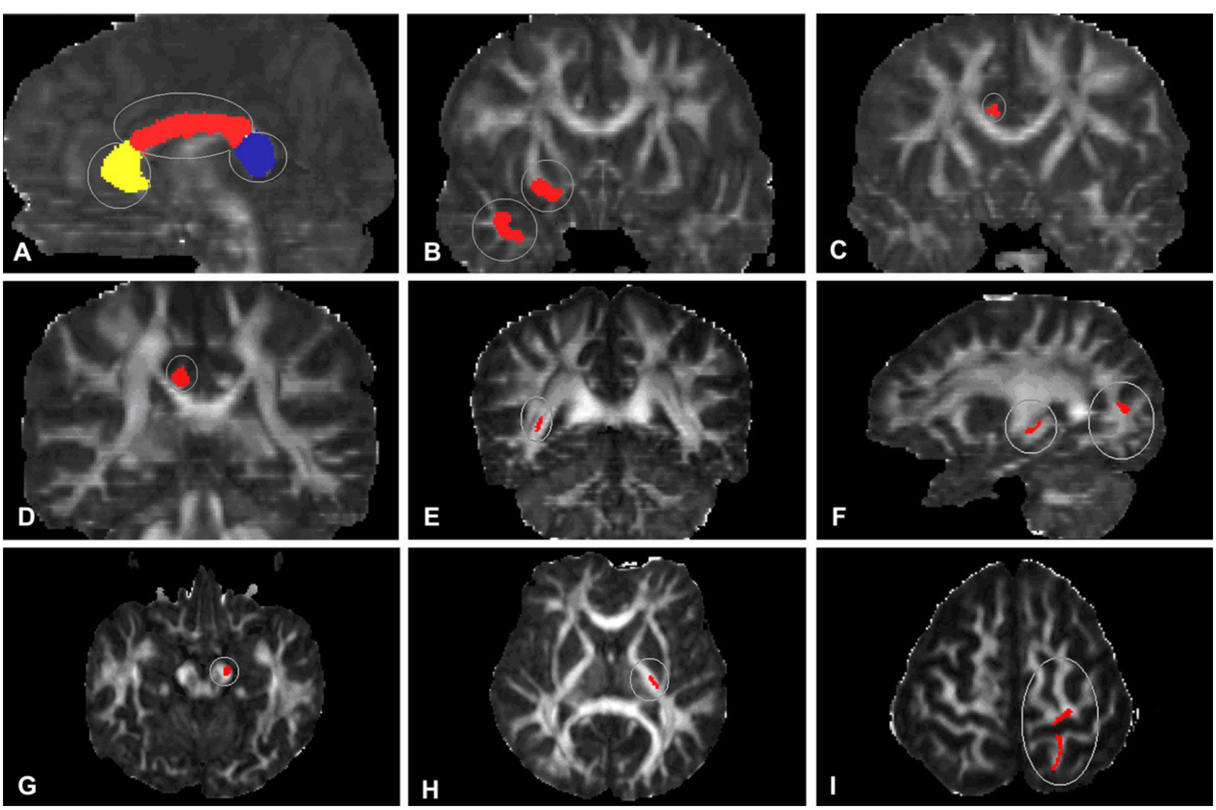

Fig. 1. Locations of the seed regions of interest for tracing the corpus callosum (A), uncinate fasciculus (B), cingulum (C and D), optic radiation (E and F) and corticospinal tract (G, H and I).

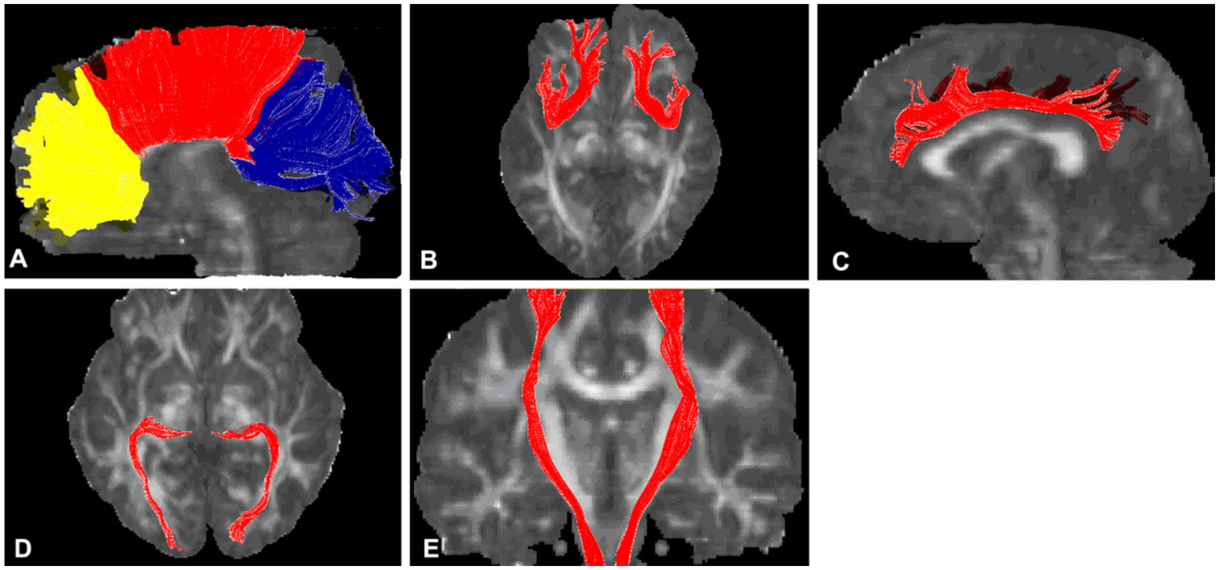

Fig. 2. Demonstration of the corpus callosum (A), uncinate fasciculus (B), cingulum (C), optic radiation (D) and corticospinal tract (E) overlaied on the fractional anisotropy images of a 24-year-old male healthy control subject.

interactions are significant, unpaired *t* test was performed to assess the detailed differences. A partial correlation analysis controlling for sex, age and group was performed to determine the correlations between the FA of these tracts and the IQ in all the 94 subjects. The intraclass correlation coefficients (ICC) calculated by one-way random effects model were used to test the intra-rater reproducibility (McGraw and Wong, 1996).

Results

Reproducibility analysis

The CC, UF, cingulum, OR and CST were well reconstructed in all subjects (Fig. 2), in a manner consistent with the description of known anatomy, which indicates the reliability of the tractography method used. The ICC of the FA was 98.53% for the CC, 96.87% for the CC1, 97.36% for the CC2, 97.19% for the CC3, 97.85% for the left UF, 97.47% for the right UF, 98.32% for the left cingulum, 97.89% for the right cingulum, 96.49% for the left OR, 96.73% for the right OR, 97.88% for the left CST and 97.54% for the left CST. These findings indicated an acceptable reproducibility in defining seed ROIs.

Analysis of variance

Table 1 shows the differences between MR, GI and HI groups in the FA of the white matter tracts. There was a significant group effect on the FA of the CC, CC1, CC2, CC3, UF, OR and CST, but not on the FA of the cingulum. A significant sex effect was found in the FA of the CC, CC1, CC2 and UF. We also found a significant side effect on the FA of the cingulum and CST. Moreover, we did not find any significant group × sex, group × side, sex × side, and group×sex×side interactions except for the sex × side interaction in the FA of the cingulum.

The FA values of the white matter tracts in each group are shown in Table 2. When *post hoc* comparisons (Bonferroni) were performed, we found significant differences between MR and GI groups in the FA values of the CC, CC1, CC2, CC3, left OR, right

Table 1
Differences among mental retardation, general and high intelligence groups in FA of white matter tracts

Effects	CC (df=1, 88)		CC1 (df=1, 88)		CC2 (df=1, 88)		CC3 (df=1, 88)		UF (df=1, 176)		cingulum (df=1, 176)		OR (df=1, 176)		CST (df=1, 176)	
	F	*P* *	*F*	*P* *	*F*	*P* *	*F*	*P* *	*F*	*P* *	*F*	*P* *	*F*	*P* *	*F*	*P* *
Group	8.296	.001‡	14.380	<.001‡	7.489	.001‡	5.257	.007‡	14.853	<.001‡	2.723	.068	9.654	<.001‡	6.878	.001‡
Sex	7.277	.008‡	9.421	.003‡	7.790	.006‡	2.579	.112	5.524	.020†	0.010	.919	0.001	.981	2.103	.149
Side	NA	NA	NA	NA	NA	NA	NA	NA	1.784	.183	14.011	<.001‡	1.531	.218	6.756	.010†
Group and sex	2.926	.059	2.010	.140	1.774	.176	2.258	.111	1.207	.302	0.041	.959	1.213	.300	0.022	.978
Group and side	NA	NA	NA	NA	NA	NA	NA	NA	0.726	.485	0.019	.981	0.166	.847	1.406	.248
Sex and side	NA	NA	NA	NA	NA	NA	NA	NA	0.048	.826	3.915	.049†	2.125	.147	1.549	.215
Group, sex and side	NA	NA	NA	NA	NA	NA	NA	NA	0.068	.934	1.159	.316	0.798	.452	0.000	1.000

FA, fractional anisotropy; CC: corpus callosum; CC1, genu of corpus callosum; CC2, truncus of corpus callosum; CC3, splenium of corpus callosum; UF, uncinate fasciculus; OR, optic radiation; CST, corticospinal tract; NA: not applicable.
*Univariate general linear model, with group, sex and side as the between-subject variables.
†$P<.05$; ‡$P<.01$.

Table 2
FA of white matter tracts in MR and control subjects

White matter tracts	FA, group mean (SD)			*P* value (*post hoc* comparisons)		
	MR (n=15)	GI (n=42)	HI (n=37)	MR *vs.* GI (df=55)	MR *vs.* HI (df=50)	GI *vs.* HI (df=77)
CC	0.476(0.031)	0.495(0.019)	0.498(0.020)	.014†	.003‡	1.000
CC1	0.461(0.039)	0.488(0.022)	0.497(0.020)	.001‡	<.001‡	.363
CC2	0.461(0.038)	0.483(0.025)	0.488(0.024)	.023†	.004‡	1.000
CC3	0.495(0.028)	0.512(0.021)	0.513(0.023)	.049†	.037†	1.000
Left UF	0.356(0.032)	0.367(0.024)	0.381(0.025)	.439	.007‡	.070
Right UF	0.352(0.028)	0.376(0.025)	0.391(0.024)	.005‡	<.001‡	.025†
Left cingulum	0.388(0.038)	0.392(0.032)	0.403(0.031)	1.000	.405	.438
Right cingulum	0.361(0.038)	0.374(0.032)	0.382(0.028)	.458	.079	.769
Left OR	0.421(0.036)	0.454(0.030)	0.454(0.029)	.001‡	.002‡	1.000
Right OR	0.415(0.041)	0.444(0.029)	0.445(0.032)	.011†	.009‡	1.000
Left CST	0.508(0.037)	0.522(0.027)	0.536(0.026)	.328	.005‡	.089
Right CST	0.495(0.033)	0.516(0.028)	0.514(0.027)	.042†	.087	1.000

Abbreviations: FA, fractional anisotropy; MR, mental retardation; GI, general intelligence; HI, high intelligence; CC: corpus callosum; CC1, genu of corpus callosum; CC2, truncus of corpus callosum; CC3, splenium of corpus callosum;UF, uncinate fasciculus; OR, optic radiation; CST, corticospinal tract.
†$P<.05$.
‡$P<.01$.

UF, right CST and right OR. We also found significant differences between MR and HI groups in the FA values of the CC, CC1, CC2, CC3, left and right UF, left and right OR and left CST. However, we only found significant differences between GI and HI groups in the FA value of the right UF. A scatter plot of FA values against tracts for different groups can be seen in Supplementary Fig. 1.

When independent samples *t* test was separately performed in the MR (n=15), GI (n=42) and HI (n=37) groups, sex difference was only significant in the FA of the left (man>woman, $t=2.140$, $P=.039$) and right (man>woman, $t=2.454$, $P=.019$) UF in HI group. Independent samples *t* test showed side differences in the FA of the cingulum (left>right, $t=2.545$, $P=0.013$) in GI group and in the FA of the cingulum (left>right, $t=3.015$, $P=0.004$) and CST (left>right, $t=3.508$, $P=.001$) in HI group.

We also divided groups based on the performance and verbal IQ scores, respectively. The same mehtod for group comparisons were performed. We got similar results (See Supplementary M2).

Table 3
Correlations between FA of white matter tracts and FSIQ, verbal IQ and performance IQ in total subjects

White matter tracts	FSIQ (n=94)		Verbal IQ		Performance IQ	
	PCC	*P* Value*	PCC	*P* Value*	PCC	*P* Value*
Corpus callosum	0.2740	.008‡	0.2797	0.007‡	0.2525	0.015†
Genu of corpus callosum	0.4396	<.001‡	0.4414	<.001‡	0.4252	<.001‡
Truncus of corpus callosum	0.2876	.005‡	0.3074	.003‡	0.2529	.019†
Splenium of corpus callosum	0.2026	.053	0.2023	.053	0.1939	.064
Left uncinate fasciculus	0.2983	.004‡	0.2977	.004‡	0.2856	.006‡
Right uncinate fasciculus	0.4855	<.001‡	0.4893	<.001‡	0.4546	<.001‡
Left cingulum	0.1234	.241	0.0986	.350	0.1495	.155
Right cingulum	0.1353	.198	0.1431	.173	0.1251	.235
Left optic radiation	0.2529	.015†	0.2715	.009‡	0.2178	.037†
Right optic radiation	0.2548	.014†	0.2549	.014†	0.2481	.017†
Left pyramidal tract	0.3334	.001‡	0.3258	.002‡	0.3292	.001‡
Right pyramidal tract	0.1556	.139	0.1312	.212	0.1743	.097

Abbreviations: FA, fractional anisotropy; FSIQ, full scale intelligence quotient; PCC, partial correlation coefficiecent.
**Partial correlation analysis*, controlling for age and sex.
†$P<.05$.
‡$P<.01$.

Correlation analysis

Considering the possible influence of sex and age to the correlation analysis between white matter tract FA and IQ, we performed partial

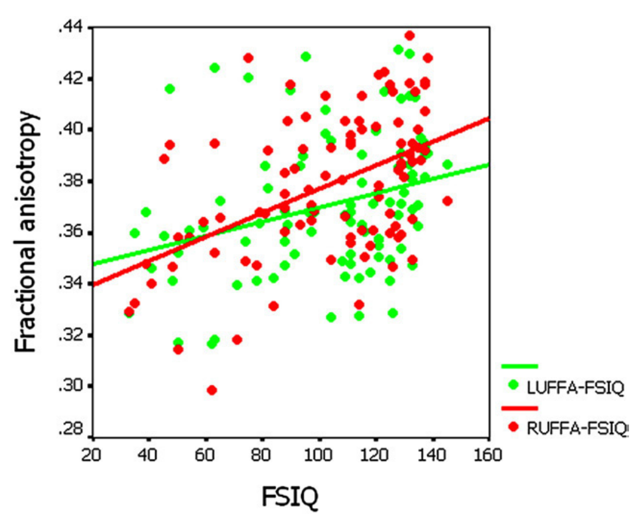

Fig. 3. Associations between full scale intelligence quotient (FSIQ) and the fractional anisotropy (FA) of the uncinate fasciculus (UF) in total 94 subjects. The individual values represent the FA values of the left (LUFFA, green dot) and right UF (RUFFA, red dot). Partial correlation analysis adjusted for sex and age shows that the FA of the right UF is markedly correlated with FSIQ (partial r=0.486, $P<0.001$, green line), while the FA of the left UF only shows a mild correlation (partial r=0.298, $P=0.004$, red line).

correlation analysis adjusted for sex and age to assess these correlations (Table 3). The FA of the right UF showed the highest correlation with FSIQ (partial r=0.486, P<0.001, Fig. 3), while the FA of the left UF only showed a mild correlation (partial r=0.298, P=0.004, Fig. 3). The FA of the CC demonstrated a mild correlation with FSIQ (partial r=0.274, P=0.008). After further analysis, we found FSIQ was significantly correlated with the average FA of the CC1 (partial r=0.440, *P*<0.001) and CC2 (partial r=0.288, *P*=0.005), but not correlated with the FA of the CC3. We also found correlations between the FSIQ and the FA of the left CST (partial r=0.333, *P*=0.001), OR (partial r=0.253, *P*=0.015), and the right OR (partial r=0.255, *P*=0.014). The patterns of the correlations between white matter tract FA and verbal or performance IQ scores were similar with those between white matter tract FA and FSIQ scores (Table 3). However, when we further controlled for group, we only found significant correlation between the FA of the right UF and FSIQ (partial r=0.259, *P*=0.013), verbal IQ (partial r=0.265, *P*=0.011) and performance IQ (partial r=0.22, *P*=0.036). We also performed partial correlation analysis adjusted for sex and age to assess these correlations in MR and control groups. No significant correlations were found in MR patients, however, the FA of the right UF was found to correlate with FSIQ (partial r=0.274, *P*=0.016), verbal IQ (partial r=0.267, *P*=0.019) and performance IQ (partial r=0.258, *P*=0.023) in healthy adults (n=79).

Discussion

In this study, we investigated the association between intelligence and the integrity of brain white matter tracts using DTI-based tract analysis. We found that healthy controls showed superior integrity than MR patients in the CC, UF, OR and CST, however, HI subjects only showed superior integrity than GI subjects in the right UF. We also found significant correlations between FSIQ scores and the average FA of the right and left UF, genu and truncus of CC, bilateral OR and left CST in the total population, but FSIQ scores were only significantly correlated with the average FA of the right UF in healthy adults. These findings indicate that MR patients have extensive damage in the integrity of the brain white matter tracts, and the right UF is an important white matter tract for supporting human intelligence.

Mental retardation is a common condition with low IQ scores and limitations in adaptive skills, but its neural basis is poorly understood. Some studies tried to identify the structural abnormalities on conventional magnetic resonance images in MR patients (Deb, 1991; Gabrielli et al., 1998; Schaefer et al., 1991; Schaefer and Bodensteiner 1999; Soto-Ares et al., 2003; Spencer et al., 2005). With the use of the voxelwise analysis of DTI data, some earlier studies have investigated the relationship between white matter integrity and IQ in different populations. Schmithorst et al. (2005) found positive correlations of IQ scores with FA values in frontal and occipito-parietal white matter areas in a normal pediatric population; Skranes et al. (2007) showed that low IQ adolescents born with very low birth weight had low FA values in the external capsule and inferior and middle superior fasciculus; Barnea-Goraly et al. (2003) found that females with fragile X exhibited lower FA values in white matter in fronto-striatal pathways and in parietal sensory-motor tracts. Using region of interest analysis of DTI data, Peng et al. (2004) found that the FA of the parieto-occipital central white matter was positively correlated with verbal IQ in patients with malignant phenylketonuria; Nakamura et al. (2005) found that the FA of the left UF area was correlated with cognitive function in unmedicated subjects with schizotypal personality disorder. Using histogram analysis of DTI data, Rovaris et al. (2002) found the FA of normal-appearing white and gray matter were correlated with cognitive functions. Although both our study and the above mentioned studies investigated the relationship between white matter integrity and intelligence, the studied populations (MR patients and normal adult subjects in our study) and analysis method (DTI-based tract analysis in our study) were different. With the use of the DTI-based tract analysis, our study has identified extensive damage in the integrity of the brain white matter tracts in MR patients, which suggests that impaired cortical connectivity may have a role in the pathogenesis of mental retardation.

The UF is the major fiber tract that connects the orbital gyrus in the frontal lobe and the anterior part of the temporal lobe (Ebeling and Von Cramon, 1992) and contains cholinergic fibers from the basal nucleus of Meynert that innervate cortical regions (Selden et al., 1998). The function of this tract is considered to be related to memory (Gaffan et al., 2002; Levine et al., 1998). Our study showed that the integrity of the UF was damaged in MR patients which is consistent with the deficit of memory function in these patients (Dobson and Rust, 1994; Ellis et al., 1989; Gutowski and Chechile, 1987). In our study, converging evidence shows that the right UF is the only tract whose integrity are correlated with intelligence. We can not exactly explain why only the integrity of the right UF relates to IQ, but we think a previous autopsy study may help for understanding our finding. In that study, the UF was found to be asymmetrical, being 27% larger and containing 33% more fiber in the right than the left hemisphere (Highley et al., 2002). The authors considered their findings might contribute to the anatomical basis of the relative specialization of the right hemisphere for integrative and global processing. Since the integrative processing of memory imformation is important in intelligence tests, we speculate the right UF is an important neural basis of intelligence.

The CC is the major white matter tract connecting the right and left cerebral hemispheres of the brain and is the most important structure for the communication of sensory, motor and higher-order information between the hemispheres. The CC allocates each kind of processing to the brain area which is programmed for the job, controls arousal and the distribution of attention over the two hemispheres and enables sustained attention during complex cognitive tasks (Gladstone and Best, 1983). Our study identified the damage of the integrity of the CC in MR patients, which is consistent with some previous studies that reported thinning or reduced size of the CC in MR patients (Njiokiktjien et al., 1994; Spencer et al., 2005). In our study, we also found that such damage was prominent in anterior part of the CC connecting right and left frontal lobe and the integrity of this part of the CC had a higher correlation coeficient with FSIQ than the other part of the CC. These findings support the notion that the frontal lobe is one of the central areas underlying the intelligence drawing from earlier studies (Colom et al., 2006; Duncan et al., 2000; Frangou et al., 2004; Gong et al., 2005; Haier et al., 2004, 2005; Thompson et al., 2001; Wilke et al., 2003). Thus, we suggest that the damage of the integrity of the CC may partially account for the low IQ scores and limitations in adaptive skills in MR patients.

The CST is a major pathway of the central nervous system, originating in the sensorimotor areas of the cerebral cortex and generally descending through the brain stem to the spinal cord (Davidoff, 1990; Toyoshima and Sakai, 1982; Van Crevel and Verhaart, 1963). The CST plays a special role in the control of the fingers for discrete fine movements (Davidoff, 1990; Martin, 2005; Wiesendanger, 1984). Our study demonstrated the damage of the integrity of the CST in MR patients, which agrees with some previous studies in which a poor motor performance was noted in MR patients (Kokubun, 1999; Mandelbaum et al., 2006; Shinkfield et al., 1997). Our finding indicates that the damage of the integrity of the CST is at least a possible neural basis for the impaired motor function in MR patients. Our study also showed the left-greater-than-right asymmetry in the cortical spinal tract in healthy controls, which may reflect experience-dependent plasticity in right-handed subjects.

The OR (also known as the geniculo-calcarine tract) is a collection of axons from relay neurons in the lateral geniculate nucleus of the thalamus carrying visual information to the visual cortex along the calcarine fissure. The function of the OR is known to transmit visual imformation. Many studies have reported an alarming prevalence of visual impairments in MR patients (Atkinson et al., 2001; Warburg, 2001a,b), which leads to sensory vision problems, such as strabismus, visual acuity loss, amblyopia, reduced stereopsis, and low visual discrimination (Atkinson et al., 2001; Shinkfield et al., 1997). These reports may be helpful for understanding our finding of the damage of the integrity of the OR in MR patients.

The cingulum is a bundle of white matter fibers projecting from the cingulate gyrus to the entorhinal cortex in the brain, allowing for communication between components of the limbic system. This tract is related with the executive function of the human brain. Although we did not find any significant differences between MR and healthy controls in the FA of the cingulum and any significant correlation between the FA of the cingulum and intelligence, we found a significant left-greater-than-right asymmetry pattern in the FA of the cingulum, which is consistent with some earlier studies (Gong et al., 2005; Park et al., 2004).

Our study also has some limitations. Firstly, echo-planar acquisition used in DTI introduces distortion in the images due to magnetic field inhomogeneity, especially at borders between tissue and air. Although we used iPAT technique and affine registration with the b=0 images to reduce distortion, we can not absolutely exclude it. Secondly, we only analyzed five relatively large white matter tracts. Consequently, we can not exclude the possibility of other tracts with significant differences or correlations. Finally, we carried out multiple statistical comparisons and thereby increased the risk of a type I error (false-positive outcomes). However, we believe this is unlikely to fully explain our results since significant effects exist in both comparative analysis and correlation analysis.

In conclusion, our results showed extensive damage in the integrity of the brain white matter tracts in MR patients, which may be one of the possible neural basis of deficits in multiple functional systems. Converging evidence from univariate general linear model and partial correlation analyses indicate that the right UF is an important white matter tract underlying intelligence. Future studies with a larger sample size and other available methods should be done to replicate our findings.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2008.01.063.

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