COMT Val158Met Modulates Association Between Brain White Matter Architecture and IQ

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The intelligence quotient (IQ) is typically associated with the architecture of gray and white matter in specific brain regions, and this association appears to be genetically based. However, specific sources of genetic variation for the association have not been studied extensively. Using diffusion tensor imaging in 15 mental retardation patients and 80 healthy volunteers, we studied the association between white matter architecture and IQ and also investigated the effects of COMT val158met on this association. The results showed that fractional anisotropy (FA) values in the prefrontal lobe and the hippocampus formation were associated with IQ and that val158met may affect this association. Subjects who were val homozygous showed steeper slopes for regression of the FA value on IQ than met carriers. Our findings suggest that COMT val158met may contribute to intelligence by affecting the association between IQ and the white matter architecture in the prefrontal lobe and the hippocampal formation. © 2008 Wiley-Liss, Inc.

Key words: catechol-o-methyltransferase; dopamine; intelligence; diffusion tensor imaging; white matter

INTRODUCTION

General intelligence, an important aspect of one’s overall well being, refers to a person’s capability to acquire and apply knowledge. General intelligence can be measured by an intelligence quotient (IQ) derived from standardized tests, of which the most commonly used are the Wechsler intelligence scales for both adults (WAIS) and children (WISC). IQ is typically associated with the properties of both gray and white matter in specific brain regions, and this association appears to be genetically based [Posthuma et al., 2002].

Brain structure and activity are two of the most important factors in the etiology of IQ. Neuroimaging studies using magnetic resonance imaging (MRI) have assessed the correlation between IQ and brain properties. At least seven structural MRI studies have explored the correlations between IQ and gray matter volumes within specific brain regions. Five of these studies found positive results in the frontal lobe [Frangou et al., 2004; Haier et al., 2004; Gong et al., 2005; Colom et al., 2006; Shaw et al., 2006], four in the parietal lobe [Frangou et al., 2004; Haier et al., 2004; Colom et al., 2006; Shaw et al., 2006] and three in the temporal and occipital lobes [Haier et al., 2004; Colom et al., 2006; Shaw et al., 2006]. Using functional MRI, many studies investigated brain activity under reasoning tasks and found that the frontal lobe was very important [Christoff et al., 2001; Kroger et al., 2002; Geake and Hansen, 2005]. Our recent resting functional MRI study found that functional connectivity within the frontal lobe and between the frontal and posterior brain regions were both important predictive factors for IQ [Song et al., 2008]. Diffusion tensor imaging (DTI) is a relatively new MRI technique, which uses fractional anisotropy (FA) as a measure of the degree of water diffusion anisotropy to reflect the integrity of myelinated white matter fiber tracts. A high FA value may be associated with increased nerve conduction or information transmission, which has been proposed as contributing to intelligence [Miller, 1994; Neisser et al., 1996]. Using this technique, several published studies have assessed the correlations between IQ and white matter properties. For example, Schmithorst et al. [2005] studied 47 healthy children and found significant correlations...
between the WISC IQ and the FA value within the bilateral frontal lobe and the temporoparietal lobe. A previous study using essentially the same samples as this present study, that is, 94 subjects with IQs ranging from 33 to 145, found a strong correlation between IQ and the right uncinate fasciculus [Yu et al., 2008]. Moreover, several studies found a positive correlation between IQ and FA value in various diseases including 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] among others.

In addition to brain properties, genetic factors are also important for IQ. Twin studies have indicated a strong genetic basis for both intelligence and brain structural properties. For example, Posthumma et al. [2002] found that the heritability for whole brain gray matter, whole brain white matter and WAIS IQ were 0.82, 0.87 and 0.86, respectively. Using 24 monozygotic twin pairs, 31 dizygotic twin pairs and 25 additional siblings, this study further indicated that the association between IQ and brain volume, including both gray matter and white matter volume, was entirely decided by genetic factors. However, specific sources of the genetic variation for these associations have not been studied to our knowledge. Many biochemical factors may contribute to intelligence, including neurotransmitters, neurotrophin factors, neurogrowth factors and so on. All of the genes encoding these factors may be candidates for studies on the genetic basis of intelligence. Among these factors, catechol-o-methyltransferase (COMT) may be of special importance. The human COMT gene is located on chromosome 22, band q11.2 and contains a common functional polymorphism leading to a valine (val) to methionine (met) substitution at codon 158 (val158met) [Mannisto and Kaakkola, 1999], resulting in threelfold to fourfold lower enzymatic activity [Lotta et al., 1995]. In the 22q11.2 deletion syndrome (this syndrome results from a deletion in the chromosome region where the COMT gene is located; thus affected individuals are hemizygous for this gene), the high activity val allele showed a lower full scale IQ (FSIQ) and verbal IQ [Shashi et al., 2006] than the low activity met allele. Moreover, the val allele showed a greater decline in verbal IQ from childhood to adulthood than the met allele [Gothelf et al., 2005]. A recent meta-analysis pooling 16 studies (9115 subjects in total) showed evidence for the association between val158met and IQ, and this association did not differ significantly by ancestry, sex, average sample age, or patient status (d = 0.06) [Barnett et al., in press].

Based on the above evidence, the current study simultaneously combined neuroimaging, genetics and assessment of IQ in order to: (1) investigate the correlation between IQ and white matter microstructural properties; (2) investigate the effects of val158met on such a correlation.

**MATERIALS AND METHODS**

**Subjects**

Ninety-five subjects, including 15 mentally retarded (MR) patients and 80 healthy volunteers were included in this study. The MR patients were recruited from the Beijing Huling Community Service for People with Disabilities and the Beijing Lizhi Recovery Center for People with Disabilities. All the patients (10 males and 5 females; mean age = 23.5, SD = 3.4, range = 17.8–33.0) were diagnosed by experienced clinicians according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria and the Chinese Classification and Diagnostic Criteria of Mental Disorders (CCMD-3) for MR. Other neurological and psychological diseases were excluded. Additional 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, Down syndrome 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. Healthy subjects (45 males and 35 females; mean age = 23.8, SD = 3.9, range = 16.6–33.0) were recruited by advertisement. Both MR patients and healthy volunteers were screened using the Chinese Revised Wechsler Adult Intelligence Scale (WAIS-RC), the FSIQ of which has been reported to be one of the best indexes of general intelligence [Jensen, 1998]. For the MR patients, the mean FSIQ was 50.3 (SD = 10.5) and the range was 33–65. For the healthy volunteers, the mean FSIQ was 113.2 (SD = 19.0) and the range was 71–145. All the participants were right handed and were Han Chinese in origin. All of the healthy volunteers and both parents of the MR patients gave standard informed consent for this study, which was reviewed and approved by the ethical committee of the Xuanwu Hospital of the Capital University of Medical Sciences.

**Genotyping**

Genomic DNA was extracted from 250 μl of whole blood using a DNA direct kit (Omega Bio-tek, Doraville, GA). The val158met (rs4680) was genotyped using the conditions described in Qian et al. [2003].

**DTI 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/mm²) and one non-diffusion-weighted image (b = 0 s/mm²), employing a single shot echo planar imaging sequence (TR = 6000 ms, TE = 87 ms). The integrated parallel acquisition technique (iPAT) was used with an acceleration factor of 2. The acquisition time was able to be reduced by the iPAT method with less image distortion from susceptibility artifacts. Forty-five slices were collected from each participant. The field of view was 256 mm × 256 mm, the acquisition matrix was 128 × 128 and was zero-filled into 256 × 256. The number of excitations (NEX) was 3, and the slice thickness was 3 mm with no gap, which resulted in voxel-dimensions of 1 mm × 1 mm × 3 mm.

**FA Images**

Diffusion is anisotropic in brain white matter since diffusivity is potentially faster along the axons than in the perpendicular direc-
tion. FA was used as a measure of the degree of diffusion anisotropy, which varies between 0, representing isotropic diffusion, and 1, representing unidirectional diffusion.

Distortions induced by eddy currents and simple head motions were corrected using FMRIB’s Diffusion Toolbox (free software from Oxford Centre for Functional MRI of the Brain, UK). The SPM2 software package (http://www.fil.ion.ucl.ac.uk/spm/) was used to normalize the DTI images into a standard space. For each subject, the non-diffusion-weighted image was normalized to the SPM stereotactic space, using the EPI template, and then the transfer parameters were applied to the FA images.

**Statistical Analysis**

A voxel-based linear regression analysis on the normalized FA images of all 95 subjects was performed across the whole brain to seek regions where the correlation coefficient between the FA and FSIQ values was significantly greater than zero. An SPM-2 simple regression model with the FSIQ as the covariate and the FA as the dependent variable was used; only clusters with \( P < 0.05 \) (FDR corrected) and size \( >30 \) voxels were considered as significant.

The same regression analysis was performed to evaluate the influence of the genotypes of val158met on the relationship between the FA value and FSIQ. All participants were divided into two groups according to their genotypes on val158met: 41 carriers of the met allele and 54 homozygous for the val allele (9 MR patients and 45 volunteers). The same regression analysis was performed for each group.

**RESULTS**

**Significant Regression Between FA and IQ**

According to our voxel-based regression analysis of all 95 subjects, significant correlation between FA and FSIQ was found in the bilateral prefrontal lobe (PFL) and in the bilateral hippocampus formation (HF, mainly the parahippocampal gyrus, also including the hippocampus) (Fig. 1a). The MNI coordinates of the peak voxel in these regions are given in Table I.

**Influence of val158met: Voxel-Based Analysis**

Based on their val158met genotypes, all subjects were divided into 41 carriers of the met allele and 54 homozygous for the val allele. These two groups showed no significant differences in age, sex, IQ (all \( P > 0.05 \) as well as FA values \( P < 0.0001 \) uncorrected, cluster size >30 voxels). In the met carrier group, no significant correlation between FA and FSIQ was found; whereas in the val homozygous group, a significant correlation was once again found in the bilateral PFL and the HF (all \( P < 0.0001 \); Table I and Fig. 1b).

**Influence of val158met: Region of Interest (ROI)-Based Analysis**

To further establish the role of val158met in the correlation between FA and FSIQ, the above four regions found in the regression analysis of 95 subjects were extracted as ROIs and the mean FA values in the four ROIs were calculated. Then, in the left HF, a significant association between the mean FA and FSIQ was found in the val homozygous subjects \( (P < 0.0005) \), but not in the met carriers \( (P = 0.137) \). Moreover, the associations between the mean FA of other ROIs and the FSIQ were significant in both groups; however, the slope showing the relationship between the FSIQ and the mean FA values was steeper for the val homozygous subjects than for the met carriers (Fig. 2).

**DISCUSSION**

This study regressed whole brain FA values on FSIQ by pooling the MR and the healthy subjects. The bilateral PFL and bilateral HF showed significant correlations with FSIQ. These results indicate that the white matter architecture in both the PFL and the HF may contribute to variances in individual IQ. Our result was partially consistent with a volumetric MRI study [Haier et al., 2004] which showed significant correlations between white matter volumes of both the frontal and temporal lobes and IQ.

**TABLE I. Brain White Matter Regions With Significant Correlations Between FA Values and IQ**

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Corrected  ( P ) value</th>
<th>Cluster size (mm(^3))</th>
<th>Peak coordinate ( (x, y, z) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left PFL</td>
<td>(&lt;0.0001)</td>
<td>509</td>
<td>(-18, 32, -12)</td>
</tr>
<tr>
<td>Right PFL</td>
<td>(&lt;0.0001)</td>
<td>867</td>
<td>(20, 32, -14)</td>
</tr>
<tr>
<td>Left HF</td>
<td>(&lt;0.0001)</td>
<td>299</td>
<td>(-34, -14, -20)</td>
</tr>
<tr>
<td>Right HF</td>
<td>(&lt;0.0001)</td>
<td>867</td>
<td>( -34, -12, -22)</td>
</tr>
<tr>
<td>Val homozygous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left PFL</td>
<td>(&lt;0.0001)</td>
<td>509</td>
<td>(-20, 34, -12)</td>
</tr>
<tr>
<td>Right PFL</td>
<td>(&lt;0.0001)</td>
<td>301</td>
<td>(16, 26, -12)</td>
</tr>
<tr>
<td>Left HF</td>
<td>(&lt;0.0001)</td>
<td>1115</td>
<td>(-34, -16, -16)</td>
</tr>
<tr>
<td>Right HF</td>
<td>(&lt;0.0001)</td>
<td>533</td>
<td>(32, -10, -28)</td>
</tr>
</tbody>
</table>

Met carriers. No voxels survive after correction.
For PFL, Schmithorst et al. [2005] also used the DTI technique and found a positive correlation between IQ and the FA in several regions of the frontal lobe. Previous fMRI and PET studies have well established the role of the PFL in higher cognitive functions, such as working memory, attention control, reasoning, temporal ordering of spatial and nonspatial events, etc., and the activation of PFL under some of these cognitive tasks was related to IQ [Duncan et al., 2000; Gray et al., 2003]. These previous findings may explain the correlation between the white matter FA in the PFL and IQ that we found.

For HF, two structural MRI studies have found correlations between hippocampal volume and IQ [Andreasen et al., 1993; Amat et al., 2008]. The prominent function of the HF is memory [Scoville and Milner, 1957], so, it is possible that the correlation between IQ and FA in the HF may be due to the fact that many subsets of the IQ test used in this study contain memory components, for example, the subsets about general information, vocabulary, digit span, digit symbol and a variety of others that involve information storage and retrieval. All of these subsets belong to the verbal IQ test, which may be the reason why the hippocampal volume correlated with verbal IQ, but not performance IQ, in Schumann and colleagues' study [Schumann et al., 2007].

Moreover, the PFL and HF are reciprocally connected via both monosynaptic and polysynaptic pathways, and these pathways are involved in cognitive processes [Bertolino et al., 2006; Schott et al., 2006]. To some extent, the FA reflects the integrity of white matter fibers, which is related to nerve conduction speed. Thus, the correlations between IQ and the FA of both the PFL and the HF may indicate that a better developed white matter in these brain regions induces faster nerve conduction within and between these regions and thus a higher individual IQ.

The most important results of this study were that the association between FSIQ and FA in the PFL and HF was significant in subjects who were val homozygous, and thus not met carriers, and that the val homozygous subjects showed steeper slopes for regression of the FA value on the FSIQ score than did the met carriers, even though no significant difference was found in whole brain FA values between the val homozygous and the met carriers. These results indicate that val158met may modulate the association between IQ and the FA values in both the PFL and HF. Val homozygous subjects may need to mobilize more white matter resources to achieve the same IQ augmentation as met carriers. This concept supports the notion that val homozygosity may enable a less efficient use of the available white matter resources. Both the PFL and HF are regions where COMT is highly expressed [Schacter and Wagner, 1999]. Many previous studies have found that val homozygous subjects exhibited reduced function and structure of the PFL compared with met carriers [Blasi et al., 2005; de Frias et al., 2005]. As for the HF, Taylor et al. [2007] reported that val homozygous subjects showed significantly smaller hippocampal volumes. Children with 22q11.2 deletion syndrome (whose deletion of the COMT gene results in decreased COMT activity) showed decreased hippocampal volume,
and the decrease in hippocampal volume was significantly associated with low FSIQ and verbal IQ in these patients [Shashi et al., 2006].

Val158met is critical for the determination of COMT activity. Previous studies have demonstrated that the val allele is associated with a high COMT activity and thus a low synaptic dopamine level as well as low dopaminergic neuronal firing [Lotta et al., 1995]. Since neuronal activity may facilitate myelination of nerve fibers [Demerens et al., 1996], we speculate that val158met may affect the myelination of white matter fibers through modulating the activity of dopaminergic neurons. In val homozygous subjects, decreased synaptic dopamine levels may cause decreased activity of dopaminergic neurons and therefore decreased myelination of dopaminergic nerve fibers and nerve conduction, which may explain the lower efficiency of val homozygous subjects in the current study.

It should be noted that we could not find significant effects of val158met polymorphism on IQ, although a significant effect of this polymorphism was found in the association between IQ and FA in some specified brain regions. This phenomenon has been commonly seen in previous studies. In the genetic study of complex cognitive problems, brain structural and functional features have been considered to be intermediate phenotypes, or endophenotypes, and may be more sensitive and nearer to the effect of a genotype than performance at the behavioral level, such as on IQ tests. This difference makes it easier to find the role of gene polymorphisms, such as val158met, in the brain basis for IQ than in the IQ itself.

In summary, we found that the COMT val158met polymorphism may modulate the association between IQ and white matter architecture in both the PFL and HF. Besides val158met, several other SNPs, for example rs4633, rs737865 and rs165599 also affect the gene expression, and haplotypes comprising these SNPs may exert a more reliable effect on gene expression than val158met alone [Bray et al., 2003; Zhu et al., 2004]. Further study is needed to subdivide the subjects according to COMT haplotypes and to explore their roles in the association between brain structural and functional properties and IQ.

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REFERENCES


