VBM–DTI Correlates of Verbal Intelligence: A Potential Link to Broca's Area

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Abstract

■ Human brain lesion studies first investigated the biological roots of cognitive functions including language in the late 1800s. Neuroimaging studies have reported correlation findings with general intelligence predominantly in fronto-parietal cortical areas. However, there is still little evidence about the relationship between verbal intelligence and structural properties of the brain. We predicted that verbal performance is related to language regions of Broca's and Wernicke's areas. Verbal intelligence quotient (vIQ) was assessed in 30 healthy young subjects. T1-weighted MRI and diffusion tensor imaging data sets were acquired. Voxel-wise regression analyses were used to correlate fractional anisotropy (FA) and mean diffusivity values with vIQ. Moreover, regression analyses of regional brain volume with vIQ were performed adopting voxel-based morphometry (VBM) and ROI methodology. Our analyses revealed a significant negative correlation between vIQ and FA and a significant positive correlation between vIQ and mean diffusivity in the left-hemispheric Broca's area. VBM regression analyses did not show significant results, whereas a subsequent ROI analysis of Broca's area FA peak cluster demonstrated a positive correlation of gray matter volume and vIQ. These findings suggest that cortical thickness in Broca's area contributes to verbal intelligence. Diffusion parameters predicted gray matter ratio in Broca's area more sensitive than VBM methodology. ■

INTRODUCTION

Intelligence is described as the ability to adapt purposively to, shape, and select real-world environments. The intelligence quotient (IQ) is a score derived from standardized tests attempting to measure intelligence. Mostly, two factors of general intelligence are described: fluid intelligence as the ability to solve new problems, independent of acquired knowledge, which corresponds to the performance IQ (pIQ). On the other hand, crystallized intelligence is regarded as the ability to analyze problems using language-based skills, knowledge, and experience—corresponding to the verbal IQ (vIQ).

The size of human brain structures may partly determine cognitive functional abilities. The history of the study of brain structure–function relationships dates back to post-mortem studies in the late 1800s (Spitzka, 1903). Human lesion studies lead to more evidence on the biological roots of cognitive functions. In particular, the French surgeon Pierre Paul Broca and the German neurologist Karl Wernicke investigated the correlation of language deficits with lesions in particular brain areas (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007; Lanczik & Keil, 1991; Broca, 1861). The relationship of brain anatomical asymmetries and cognitive and language abilities has been investigated as well (Geschwind & Galaburda, 1987).

Neuroimaging methods for in vivo investigations of the association between cognitive performance and human brain size and structure have recently extended our knowledge considerably. Traditional concepts assumed that the anatomical structure of the adult human brain does not undergo changes, except for changes in morphology caused by aging or pathological conditions. Although, during the last years, neuroimaging investigation findings indicate that learning-induced cortical plasticity is also reflected at the structural level (Draganski et al., 2004). Andreasen et al. suggested that the size of several cerebral structures measured by MRI may account for a significant proportion of the variance in human intelligence (Andreasen et al., 1993). Jung and Haier reviewed 37 recent structural and functional neuroimaging studies to address the question if there is a characteristic biology of intelligence of the normal human brain (Jung & Haier, 2007). They suggested that variations in a distributed network predict individual differences that are observed in intelligence and reasoning tasks. This network includes primarily the dorsolateral pFC, the inferior and superior parietal lobule, and ACC (Jung & Haier, 2007). Correlations of white matter (WM) structural integrity and total IQ were primarily found in the left superior longitudinal fasciculus (SLF), revealing a stronger correlation with vIQ than with pIQ (Schmithorst, Wilke, Dardzinski, & Holland, 2005). Several authors already

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suggested that crystallized intelligence (as measured by vIQ) may particularly be influenced by brain structure, and there is actually some evidence for a higher correlation of vIQ with brain size and structure than for pIQ correlation (Witelson, Beresh, & Kigar, 2006; Haier, Jung, Yeo, Head, & Alkire, 2004, 2005; Schmithorst et al., 2005).

In recent years, specific MRI methods became available for more refined investigations of human brain structure and microstructure, and these methods provided a substantial contribution to the linkage of brain structure and behavioral measures: Voxel-based morphometry (VBM) became a widely used method to examine regional brain volume and density. Several VBM studies have demonstrated correlations of regional brain volume with measures of intelligence primarily in prefrontal areas and cingulate cortices (Gong et al., 2005; Frangou, Chitins, & Williams, 2004; Wilke, Sohn, Byars, & Holland, 2003). Although, these VBM studies did not investigate correlations with verbal intelligence as a separate measure.

In addition, diffusion tensor imaging (DTI) became available to investigate human brain microstructure. With DTI, diffusion of water molecules can be characterized by two diffusion parameters: (1) mean diffusivity (MD), which measures the rotationally invariant magnitude of water diffusion, and (2) fractional anisotropy (FA), which provides an index of directional selectivity of water diffusion (Beaulieu, 2002). Recently, an ROI-based DTI study of the corpus callosum (CC) demonstrated that higher vIQ was associated with decreased FA in the genu of the CC (Hutchinson et al., 2009). By now, no whole-brain DTI study has been conducted that explored the relationship between intelligence and microstructural properties in healthy adult persons. Most notably, no study has yet been performed that addressed the relationship between vIQ and structural properties of the language processing Broca's and Wernicke's areas.

A large number of studies have shown high heritability of human intelligence and indicate that many genes may contribute to IQ (Deary, Spinath, & Bates, 2006). Known genetic effects only account for a small part of the variance of intelligence, however. Moreover, little is known about the role of epigenetics in determining the normal variation in human intelligence, but epigenetic mechanisms have been implicated in syndromes associated with mental impairment (Haggarty et al., 2010). There is evidence from animal studies that genomic imprinting as an epigenetic process has an important impact on neurodevelopment and on higher-level cognitive functions (Davies, Isles, Humby, & Wilkinson, 2007). Accordingly, it is still unknown which of these mechanisms during brain development and which brain region particularly determine intelligence.

Here, we explored whether regional brain structural and microstructural properties contribute to verbal cognitive performance in a sample of young healthy subjects adopting VBM and DTI methodology. As an exploratory study, we adopted a voxel-wise approach for whole-brain investigation, being aware of the relevant risk of a Type I error. We predicted that verbal performance is related to the left-hemispheric classic language regions of Broca's and Wernicke's areas and their connecting WM structures, primarily the left SLF.

METHODS

Participants

Thirty healthy subjects (mean age = 22.8 years, *SD* = 1.5 years) were investigated (Table 1). Only unrelated white subjects were included in the study. Participants were only investigated if there was no evidence for any medical or neurological condition that could interfere with the purpose of the study or if there was no history for any psychiatric DSM-IV Axis I or II disorder including current or recent drug or alcohol abuse as assessed by a structured clinical interview (First, Spitzer, Gibbon, & Williams, 1995), a formal medical and neurological examination including urine toxicology for illegal drug abuse screening, routine blood tests, and a clinical EEG session. All subjects were right-handed as assessed with the Edinburgh inventory (Oldfield, 1971).

Intelligence Testing

IQ was assessed by the Hamburg–Wechsler Intelligenztest (HAWIE-R) Scale (Tewes, 1991), including six verbal and five performance subtests to measure full-scale IQ, vIQ, and pIQ. HAWIE-R is largely equivalent with the full-scale WAIS-R (Kaplan, Fein, Morris, & Delis, 1991). The raw scores are converted to scaled scores on the basis of a reference group, with the median score set to 100 and an *SD* of 15.

Neuroimaging Procedures

Image Acquisition

MRI scanning was performed with a 1.5-T Siemens Sonata® system at the Institute of Neuroradiology of the University Medical Center of the Johannes Gutenberg University Mainz, Germany. High-resolution T1-weighted MRI volume data set was acquired using a magnetization prepared rapid gradient-echo sequence. The acquisition matrix was 256 × 256;

Table 1. Demographic Data and IQ Scores

Subjects (*n*)	30
Age (years)	22.8 ± 1.5
Male, female (*n*)	16, 14
Education (years)	14.9 ± 2.7
Total IQ	118.5 ± 10.7
pIQ	115.2 ± 11.4
vIQ	116.2 ± 11.4

Given are mean values and standard deviations.

176 slices were acquired with 1-mm slice thickness and 15° flip angle. Repetition time was 2860 msec; echo time was 3.9 msec.

DTI was conducted with EPI sequences. The images were acquired in six noncollinear diffusion-sensitizing gradient directions with diffusion sensitivity of b = 1000 mm^2/sec and one acquisition without diffusion encoding (b = 0 mm^2/sec). A generalized autocalibrating partially parallel acquisition reconstruction algorithm was used. Slices were positioned along the AC–PC line. The diffusion acquisition parameters were as follows: The acquisition matrix was 128 × 128 with a field of view of 192 × 192 mm^2 and a resolution of 1.5 × 1.5 × 2.0 mm^3. Slice thickness was 2 mm, and 64 axial slices were acquired to cover the whole brain without interslice gap. Other parameters were repetition time of 8000 msec and echo time of 100 msec. A total of 10 acquisitions was performed and averaged; the total duration of the DTI measurement was 20 min.

Image Preprocessing

All scans were visually inspected. DTI series from four subjects were excluded because of gross motion artifacts or because of technical problems; DTI data sets from 26 subjects (Table 1) and T1 data sets from 30 subjects remained. Original MR diffusion and T1- and T2-weighted images were registered in DICOM format and converted to ANALYZE format using MRIcro software (University of Nottingham, UK).

DTI Analysis

The T2-weighted images were normalized to the Montreal Neurological Institute (MNI) T2 template using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) software implemented in MatLab 6.5 (Mathworks, Inc., Natick, MA). Identical normalization parameters were used for warping of the diffusion-weighted images such that each voxel represents the same part of the brain in every subject. For the calculation of FA maps, the FMRIB's Diffusion Toolbox tool of the FMRIB's software library was used. The obtained FA maps were then smoothed with a 6 × 6 × 6 mm^3 FWHM Gaussian kernel to improve signal-to-noise ratio and normalization. The choice of using a 6-mm filter was based on evidence from imaging studies that the smoothing filter should be at least two to three times larger than the voxel size. Voxel-based t statistic regression analyses were then done to correlate FA and MD with vIQ. Following established procedures (Konrad et al., 2010; Konrad, Vucurevic, Musso, Stoeter, Dahmen, et al., 2009; Konrad, Vucurevic, Musso, Stoeter, & Winterer, 2009; Shin et al., 2005), contrast maps were thresholded at a $p < .001$ without correction for multiple comparisons, and the extent threshold for significant clusters was set to 50 voxels. We prepared an FA template according to the procedure described by Smith et al. (2006), which was then overlaid with the statistically significant SPM clusters using MRIcro software for graphical presentation in neurological convention (R = R). The MNI coordinates of the peak voxels were used to determine the FA (MD) values in these peak voxels in each subject's data set and to depict these data in scatter plots.

VBM Analysis

VBM was carried out with an optimized VBM protocol (Ashburner & Friston, 2000) using SPM5 software implemented in MatLab 7.1. The high-resolution T1-weighted MRI data sets were first normalized to a standard template. The procedure then performed segmentation of the normalized images into gray matter (GM) and WM. The segmented images were then smoothed with a 6-mm isotropic FWHM kernel. Voxel-wise t statistic regression analyses of the normalized, segmented, and smoothed data were then performed to test for significant correlations of local brain tissue concentration and volume with vIQ scores ($p < .001$, uncorrected).

ROI Analysis of Structural MRI

A mask was created out of the peak cluster in Broca's area resulting from the voxel-based analysis of FA data sets (see below) using the MarsBar toolbox implemented in SPM5. This mask was then used as an ROI for analyses of the GM and WM portion within the peak cluster. In addition, the correlations of GM and WM portion within the ROI and vIQ were calculated.

RESULTS

Intelligence Testing

Mean vIQ was 116.2, and *SD* was 11.4 (Table 1).

Correlation of vIQ and DTI Parameters

SPM analysis revealed significant negative correlations ($p <$ .001, uncorrected) between vIQ and FA predominantly in the left-hemispheric Broca's area (Figure 1; Table 2). Moreover, correlation analysis of vIQ and MD demonstrated a significant positive correlation in a smaller cluster again in the left-hemispheric Broca's area (Figure 1; Table 2). Although, we did not find any significant correlation between DTI parameters and vIQ neither in Wernicke's area nor in the SLF or any other brain region.

Volumetric Analyses

Correlation analysis of regional brain volume (GM, WM) with vIQ did not reveal any significant ($p < .001$, uncorrected) results. However, in the subsequent ROI analysis of the peak cluster from voxel-based FA regression

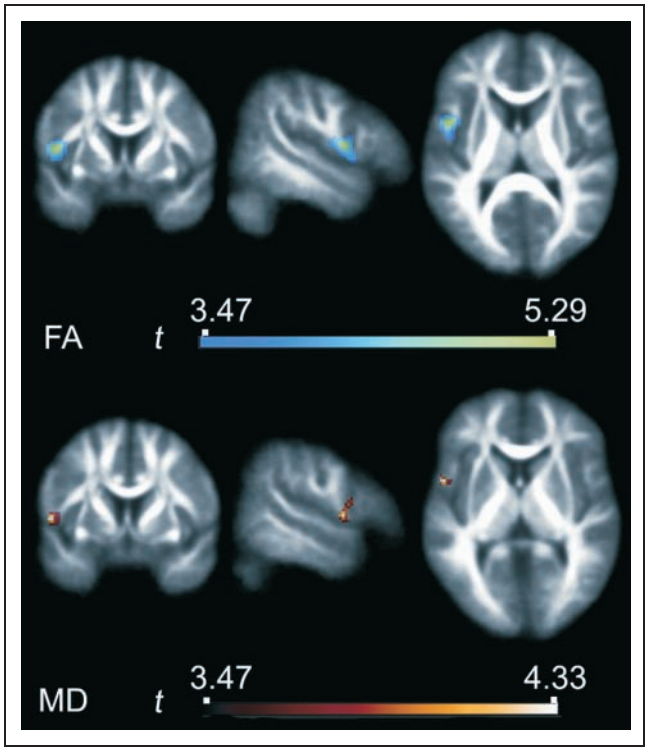

Figure 1. Correlation of verbal intelligence and DTI measures. Voxel-wise *t* statistic regression analysis showing significant negative correlations between vIQ and FA in Broca's area (left; peak voxel MNI: −52, 6, 8). Significant positive correlations between vIQ and MD in Broca's area (peak voxel MNI: −56, 6, 2). Results are thresholded at $p < .001$, uncorrected. Images are represented in neurological convention (R = R).

analysis with vIQ in the left-hemispheric Broca's area, we found a significant positive correlation of the GM portion in the ROI with vIQ ($p = .0055$, $t = 2.75$).

DISCUSSION

Correlation of DTI Parameters with vIQ in Broca's Area

This study shows for the first time that verbal intelligence, as measured by six subtests of the HAWIE-R (Tewes, 1991), is directly correlated with diffusion parameters FA and MD in Broca's area, which is located in the left frontal lobe, around the opercular and triangular sections of the inferior frontal gyrus. Broca's area was first described by Paul Broca, who investigated two aphasic patients with lesions in the language network (Dronkers et al., 2007; Broca, 1861). Broca's aphasia is characterized by nonfluent speech, few words, short sentences, and many pauses (Mohr et al., 1978). Moreover, surface anatomy and asymmetry of the pars triangularis as a portion of Broca's area has been shown to predict language laterality determined from Wada testing (Foundas, Leonard, Gilmore, Fennell, & Heilman, 1996). There is evidence that Broca's area contributes to sentence processing via verbal working memory (Grodzinsky & Santi, 2008). An increase in activity as a function of syntactic complexity in Broca's area has been demonstrated in an fMRI study (Rogalsky, Matchin, & Hickok, 2008). Moreover, the functional and structural properties of Broca's area and their subdivisions have recently been described in detail providing a new anatomical basis for the interpretation of functional imaging studies of language (Amunts et al., 2010). In particular, the authors contribute to a better understanding of the relations between Broca's area and motor areas (Amunts et al., 2010). Considering the particular functional impact of Broca's area on language processing and verbal working memory (Chein, Fissell, Jacobs, & Fiez, 2002), our findings of correlation between diffusion parameters and vIQ appear conclusive. Language processing and verbal working memory are of particular relevance for verbal performance as measured by the vIQ. Interestingly, we saw no significant correlations of vIQ with DTI measures in Wernicke's area or in the SLF as the connecting tract between Broca's and Wernicke's areas, further suggesting a specific contribution of Broca's area to vIQ.

Previous Studies Investigating Correlations of Brain Structure and (Verbal) IQ

Until now, only two DTI studies have investigated vIQ. A recent ROI-based study of the CC demonstrated a negative correlation of vIQ and FA in the genu of the CC (Hutchinson et al., 2009). Brain language regions have not been included in this analysis. Another single voxel-based DTI study in 47 healthy children demonstrated significant positive correlations of total IQ scores with FA bilaterally in frontal and parieto-occipital WM association areas including parts of the SLF (Schmithorst et al., 2005). In this study, the authors also reported a comparatively stronger (positive) correlation of FA with vIQ than with pIQ in the SLF. No voxel-based correlation analysis between FA and vIQ was conducted in this study

Table 2. Clusters Showing Significant Correlation of vIQ with FA and MD

Brain Area	*DTI Measure*	*Peak Voxel MNI*	*Peak Voxel r*	*Peak Voxel t Value*	*Peak Voxel p Value*	*Cluster Size (Voxels)*
Left Broca	FA	−52, 6, 8	−0.73	5.29	2×10^{-5}	276
Left Broca	MD	−56, 6, 2	0.66	4.33	2×10^{-4}	56

Given are significant ($p < .001$, uncorrected) clusters. *r* = Pearson's correlation coefficient.

(Schmithorst et al., 2005). Accordingly, it is difficult to compare these two studies with our study because, in both cases, Broca's area was not a target of investigation. On the other hand, these two studies indicate that brain regions outside Broca's area may play a role in vIQ—a relationship that might have remained undetected with our voxel-based correlation analysis approach.

A previous volumetric imaging study in healthy individuals demonstrated a significant correlation between total IQ, vIQ, and pIQ with overall GM volume but not with WM or CSF volume (Andreasen et al., 1993). A VBM study in a large sample of children revealed a significant positive correlation between total IQ and anterior cingulate volume (Wilke et al., 2003). Frangou et al. (2004) investigated a sample of 40 healthy young people and demonstrated positive correlations between total IQ and GM density in several brain areas including the OFC and the cingulated gyrus. Although, none of these VBM studies investigated the correlation with vIQ as a separate measure, and therefore, a direct comparison with our results is not possible. In this context, it is noteworthy that a VBM study in symphony orchestra musicians revealed increased GM volume in the Broca's area compared with nonmusicians (Sluming et al., 2002).

Neuroanatomical Correlates of Imaging Results

Both FA and MD have been described as parameters for WM integrity, but the biological determinants of diffusion parameters are not yet entirely understood (Konrad, Vucurevic, Musso, Stoeter, & Winterer, 2009; Schmithorst, Holland, & Dardzinski, 2007; Beaulieu, 2002; Papadakis et al., 1999). In brain WM, myelination properties, fiber organization, axonal diameter, fiber density, and ratio of intracellular/extracellular space contribute to differences in FA and MD (Beaulieu, 2002; Schmithorst, Wilke, Dardzinski, & Holland, 2002). In large fiber tracts, increased FA (and decreased MD) in general indicates higher structural integrity and has been shown to correlate with better performance in behavioral tasks (Konrad, Vucurevic, Musso, Stoeter, & Winterer, 2009). In our study, the significant cluster of voxels showing negative correlation between FA and vIQ (Figure 1) contains largely equal portions of GM and WM as shown by the volumetric ROI analysis, but because of limited resolution and distinctive gyral folding in this region, it is difficult to tell exactly which parts of the significant clusters are located in GM or WM. However, the FA peak voxel (Figure 2) is located in WM directly underneath the cortical folder. This is an important point because FA is generally much lower and MD is much higher in GM than in WM because the cell membranes are not oriented parallel in a preferential direction (Lee et al., 2009). On the other hand, diffusion parameters in GM may correlate with the dendritic architecture of pyramidal cells, the presence or absence of radial glial fibers, and the proportions of intracellular and extracellular compartments (Lee et al., 2009). Even so, there is currently only little evidence about the utility of DTI parameters with regard to understanding of GM microstructure (Pfefferbaum, Adalsteinsson, Rohlfing, & Sullivan, 2010).

We found no significant correlations between GM volume and vIQ in the Broca's area adopting VBM. The limitations of VBM in characterizing slight morphological differences between subjects have been described previously (Davatzikos, 2004; Friston & Ashburner, 2004; Mehta, Grabowski, Trivedi, & Damasio, 2003; Ashburner & Friston, 2001; Bookstein, 2001). Thus, the VBM method might not have been sensitive enough to detect small volumetric differences in the Broca's area between subjects in our study. It has to be noted that voxel-based MRI investigations (VBM and DTI) are less suitable than ROI analyses to register the full volumetric extent of a particular anatomical structure (Snook, Plewes, & Beaulieu, 2007).

However, when conducting a more focused ROI analysis in the Broca's area peak cluster from the FA analysis, we found that higher GM volume in Broca's area correlates significantly (positive) with vIQ. These slight volume effects may, in part, contribute to the DTI results: A higher

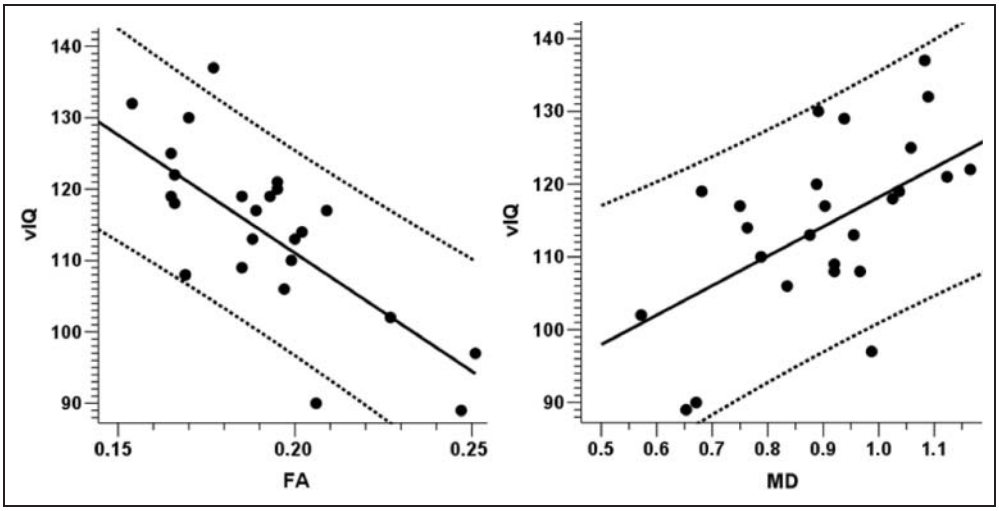

Figure 2. Regression between vIQ and diffusion parameters in the peak voxels in left Broca's area. Left: vIQ (*y* axis) as a function of FA (*x* axis; peak voxel MNI: −52, 6, 8; $r = -.73$). Right: vIQ (*y* axis) as a function of MD (*x* axis; peak voxel MNI: −56, 6, 2; $r = .66$). The solid line represents the linear fit, whereas the dashed line indicates the 95% confidence interval. r = Pearson's correlation coefficient.

amount of GM within the peak cluster results in lower FA and higher MD in this region. These partial volume effects and their impact on GM diffusion properties have been described recently (Koo et al., 2009). Furthermore, neuronal plasticity processes may also contribute to the results of our study. Several neuroimaging investigation findings indicate that learning-induced cortical plasticity is reflected at the structural level (Draganski et al., 2004; Sluming et al., 2002). Considering these findings, we could assume that the observed structural characteristics in Broca's area are not only causing differences in verbal performance but may rather be a consequence of different verbal intelligence. To put it in a simple way: May people with higher verbal intelligence be more eloquent, just talk more, and therefore, develop a discrete "hypertrophy" in Broca's area? Moreover, it is important to consider that larger brain areas do not necessarily correlate with better function. For example, bigger total brain volume in autism has been demonstrated (Piven et al., 1995), whereas a bilaterally enlarged planum temporale has been found in adults with persistent developmental stuttering (Foundas, Bollich, Corey, Hurley, & Heilman, 2001).

Age effects on GM, WM, and also on FA in healthy adults have been described previously (Madden et al., 2004; Good et al., 2001). As we included only subjects in a rather narrow age range (18–26 years), we were largely able to exclude age effects on brain volume and microstructure. The gender groups were almost of equal size (16 men and 14 women), but we did not perform subgroup analyses as the gender subgroups were not large enough for sufficient statistical power. Finally, it has to be mentioned that the IQ distribution in our sample was skewed toward more intelligent individuals, which is a quite common problem in neuroimaging studies of intelligence.

Limitations of the Study

The limited sample size is the most important limitation of this explorative study. Although false positive results cannot be excluded, the matching findings both in voxel-based DTI and in ROI-based morphometric investigations point to a correlation between vIQ and regional brain structure in the left Broca's area. Although, both voxel-based and ROI methodologies have to be interpreted carefully with respect to their correlation with anatomical structure. Both advantages and problems of these main methods of quantitative analysis have been widely discussed in the literature (Astrakas & Argyropoulou, 2010; Gonoi et al., 2010; Snook et al., 2007). Replication studies with larger sample sizes and refined imaging methodology are needed to confirm our findings.

Conclusion

On the basis of past postmortem anatomical studies and with reference to earlier neuroimaging studies, the novelty of this study is the re-examination of the biological roots of (verbal) intelligence adopting the newer MRI-based methodologies DTI and VBM. Despite the limitations of our study, our data support the notion that Broca's area morphology contributes particularly to verbal intelligence. We were able to demonstrate that slight cortical volume effects in the human cortex, as detected by ROI analysis, have a significant impact on DTI measures although they were not detected by VBM methodology. The investigation of components of human intelligence instead of "general intelligence" may be a promising strategy for further imaging studies to better understand the neuroanatomical and functional correlates of human cognitive performance.

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