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White-matter microstructure and language lateralization in left-handers: A whole-brain MRI analysis

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ABSTRACT

Most people are left-hemisphere dominant for language. However the neuroanatomy of language lateralization is not fully understood. By combining functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), we studied whether language lateralization is associated with cerebral white-matter (WM) microstructure. Sixteen healthy, left-handed women aged 20–25 were included in the study. Left-handers were targeted in order to increase the chances of involving subjects with atypical language lateralization. Language lateralization was determined by fMRI using a verbal fluency paradigm. Tract-based spatial statistics analysis of DTI data was applied to test for WM microstructural correlates of language lateralization across the whole brain. Fractional anisotropy and mean diffusivity were used as indicators of WM microstructural organization. Right-hemispheric language dominance was associated with reduced microstructural integrity of the left superior longitudinal fasciculus and left-sided parietal lobe WM. In left-handed women, reduced integrity of the left-sided language related tracts may be closely linked to the development of right hemispheric language dominance. Our results may offer new insights into language lateralization and structure–function relationships in human language system.

1. Introduction

The incidence of left-handedness, ranging from moderate through strong left-handed is about 10% in the population (Gilbert & Wysocki, 1992; Hardyck & Petrinovich, 1977). Several type of factors may affect the development of left-handedness including maternal handedness and familiar history of sinistrality (Annett, 1983; Knecht et al., 2000; McKeever, 2000), gender (Gilbert & Wysocki, 1992), testosterone level (Tan, 1991) and history of early brain injury (Satz, Orsini, Saslow, & Henry, 1985). Genetic theories of handedness and brain asymmetry were also suggested assuming a genetic predisposition toward right-handedness and left-hemispheric dominance for language (Annett, 2002; McManus, 2002). Left-handedness may be related to certain psychiatric diseases (especially schizophrenia and bipolar disorders) (Klar, 1999; Satz & Green, 1999), developmental disorders (Dane & Balci, 2007; Goez & Zelnik, 2008) and central nervous system disorders (Llaurens, Raymond, & Faurie, 2009).

Left-hemispheric preference for language processing is one of the most consistent early findings (Auer et al., 2009; Josse & Tzourio-Mazoyer, 2004). Hemispheric language lateralization has shown to be systematically associated with handedness: 94–96% of right-handed subjects showed left-hemispheric dominance, while 4–6% showed a bilateral pattern (Pujol, Deus, Losilla, & Capdevila, 1999; Springer et al., 1999). In contrast, the incidence of atypical (bilateral or right-hemispheric) language lateralization was found to increase in left-handers to approximately 15–30% (Josse & Tzourio-Mazoyer, 2004; Knecht et al., 2000; Pujol et al., 1999). Despite the fact that hemispheric language lateralization of the human brain is a hot topic in neuroscience for a long time, its neuroanatomy is not fully understood (Propper et al., 2010; Vernooij et al., 2007).

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Diffusion tensor imaging (DTI) is a technique in which at least seven images must be acquired (six diffusion-weighted images along non-collinear directions and one image with no diffusion weighting). From these images mean diffusivity (MD) and fractional anisotropy (FA) can be calculated, which represent the magnitude and directionality of water diffusion, respectively and provide unique insights into white-matter (WM) microstructure. Increased MD may result from loss of barriers such as myelin sheaths, cell membranes or axons (Beaulieu, 2002), while FA thought to be related to tract integrity and may reflect the alignment of neuronal fibers (Johansen-Berg & Behrens, 2009). Higher MD and lower FA values may indicate lower microstructural organization.

Some studies reported relationship between functional language lateralization and the morphometric magnetic resonance imaging (MRI) findings of arcuate fasciculus (Propper et al., 2010), corpus callosum (Josse, Seghier, Kherif, & Price, 2008; Moffat, Hampson, & Lee, 1998), insula (Keller et al., 2011), right hippocampus (Jansen et al., 2010) or left planum temporale (Josse, Mazoyer, Crivello, & Tzourio-Mazoyer, 2003; Moffat et al., 1998; Tzourio, Nkanga-Ngila, & Mazoyer, 1998). WM microstructure in relation to language lateralization has also been recently investigated using the combination of functional magnetic resonance imaging (fMRI) and DTI techniques (Häberling, Badzakova-Trajkov, & Corballis, 2011; Powell et al., 2006; Vernooij et al., 2007; Westerhausen et al., 2006). These studies tested for associations between the lateralization of fMRI activations and various diffusion tensor measures (fractional anisotropy, relative anisotropy, relative fiber density, mean diffusivity) in prespecified tracts of interest i.e. the corpus callosum and the arcuate fasciculus. Häberling et al. (2011) found that atypical hemispheric dominance for language was associated with higher mean fractional anisotropy (FA) of the corpus callosum, but this finding is somewhat in conflict with those of Westerhausen et al. (2006), who found a trend towards higher FA values for subjects with strongly left-lateralized language representation (Häberling et al., 2011; Westerhausen et al., 2006). In right-handed subjects both the relative fiber density asymmetry index of arcuate fasciculus and the mean FA asymmetry index of connections between Broca's and Wernicke's areas were found to be positively correlated with the degree of functional language dominance (Powell et al., 2006; Vernooij et al., 2007). A recent paper by Häberling et al. investigated the arcuate fasciculus asymmetry and its relationship to language dominance in monozygotic twins. They found that twin pairs with discordant language dominance showed reversed asymmetry of anisotropic diffusion in the arcuate fasciculus. The left-cerebrally dominant twins showed leftward and the right-cerebrally dominant co-twins showed rightward asymmetry of anisotropic diffusion, indicating a strong nongenetic influence in arcuate fasciculus asymmetry (Häberling, Badzakova-Trajkov, & Corballis, 2013).

However, none of these studies provided insights into the relationship of WM microstructure and language lateralization at the *whole-brain level*. Tract-based spatial statistics (TBSS) is a new approach aiming to improve the sensitivity, objectivity and interpretability of whole-brain analysis of multisubject diffusion data (Smith et al., 2006). TBSS attempts to combine the strengths of voxel-based morphometry-style (VBM-style) analysis (being able to analyze the whole brain without prespecifying regions-of-interest) with the strengths of tractography-based methods (being confident that the estimates of FA are truly taken from the relevant voxels). Unlike conventional VBM-style analysis, TBSS does not rely strongly on perfect cross-subject alignment or smoothing, thus allowing for unbiased whole-brain analysis of diffusion tensor properties between multiple subjects.

In the present study, we investigated WM microstructure using DTI at the *whole-brain level* (without prespecifying regions of interest), in relation to hemispheric language lateralization established with fMRI.

In order to increase the chances of including individuals exhibiting atypical language lateralization (Szaflarski et al., 2002) and to avoid confounding effects of handedness (Buchel et al., 2004; Westerhausen et al., 2003, 2004), aging (Abe et al., 2008; Camara, Bodammer, Rodriguez-Fornells, & Tempelmann, 2007; Hsu et al., 2008) or sex-specific differences in WM integrity (Catani et al., 2007; Hagmann et al., 2006; Menzler et al., 2011; Thiebaut de Schotten et al., 2011) as well as the impact of interaction between gender and handedness (Hagmann et al., 2006), only left-handed, healthy, young women were recruited. Our sample was as homogenous as possible.

2. Methods

2.1. Subjects

Eighteen healthy, left-handed, Caucasian, female, graduate or postgraduate university students between age of 20 and 25 without history of brain disorders were recruited through advertisements placed on notice boards across the University of Pécs. The handedness of all subjects was assessed by the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Two individuals were excluded due to excessive head movements during the fMRI and/or DTI protocols. Thus, we included a total of 16 healthy, young (mean age: 21.8 ± 1.7; range: 20–25 years), left-handed (mean EHI score: −79 ± 18.4; range: −50 to −100) women. The study was approved by the Regional Ethical Committee of the University of Pécs and performed in accordance with the ethical standards described in the Declaration of Helsinki (Rickham, 1964). All subjects got detailed information about the investigation in both oral and written forms and gave written informed consent prior to the study.

2.2. Imaging data acquisition and visual analysis

All measurements were performed on a 3T Magnetom TIM Trio human whole-body MRI scanner (Siemens AG, Erlangen, Germany) with a 12-channel head coil.

Functional images were acquired using a 2D single-shot gradient-echo echo-planar imaging (EPI) sequence (TR/TE = 2000/36 ms; Flip Angle = 76°; 23 axial slices; slice thickness = 4 mm; no interslice gap; FOV = 192 × 192 mm^2; matrix size = 92 × 92; receiver bandwidth = 1360 Hz/pixel; interleaved slice order to avoid crosstalk between contiguous slices). A total of 210 volumes were acquired during the verbal fluency task.

DTI data were measured using a 2D single-shot diffusion-weighted spin-echo EPI sequence (TR/TE = 6700/78 ms; 60 axial slices; slice thickness = 2 mm; no interslice gap; FOV = 211 × 260 mm^2 matrix size = 104 × 128; diffusion gradients were applied in 20 directions with a *b*-value of 700 s/mm^2 and a single volume was collected with no diffusion gradients applied; bandwidth = 1698 Hz/pixel; number of averages = 3).

Anatomical images were obtained using a T1-weighted three-dimensional MPRAGE sequence (TR/TI/TE = 1900/900/3.41 ms; Flip Angle = 9°; 144 axial slices; slice thickness = 0.9 mm; no interslice gap; FOV = 201 × 230 mm^2; matrix size = 215 × 256; receiver bandwidth = 180 Hz/pixel).

Visual analysis of the images identified no brain abnormalities.

2.3. Functional MRI stimulation paradigm

As in our previous studies, a standard verbal fluency task with a block design was used to assess functional hemispheric language lateralization (Auer et al., 2009; Janszky et al., 2003). Although