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The association of macro- and microstructure of the corpus callosum and language lateralisation

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Abstract

The present study aimed to examine how differences in functional lateralisation of language are related to interindividual variations in interhemispheric connectivity. Utilising an fMRI silent word-generation paradigm, 89 left- and right-handed subjects were subdivided into four lateralisation subgroups. Applying morphological and diffusion-tensor MRI, midsagittal cross-sectional area as well as quantitative measures of molecular diffusion (anisotropy, mean diffusion) of the corpus callosum were determined to assess interhemispheric connectivity. Statistical analyses revealed group differences in molecular diffusion but not in callosal size, which may be interpreted to reflect a stronger and/or faster interhemispheric connection in strongly left-lateralised subjects as compared to moderately left-lateralised, bilateral, or moderately right-lateralised subjects.

Keywords: Corpus callosum; Laterality; Language; Verbal fluency; fMRI; Diffusion-tensor imaging; Anisotropy; Mean diffusion; Handedness; Sex

1. Introduction

The major commissural tract connecting the two cerebral hemispheres is the corpus callosum (CC). It is primarily responsible for the functional integration of the hemispheres, as demonstrated by research on commissurotomised patients (for a review see Gazzaniga, 2000). However, not only complete destruction but also the naturally occurring interindividual variations of the callosal connections in healthy subjects are related to function. For example, the midsagittal surface area of the CC was reported to be associated with interhemispheric transfer time (Schulte, Pfefferbaum, & Sullivan, 2004), reaction time (Jäncke & Steinmetz, 1994), or the lateralisation of movement-related potentials (Stancák, Lücking, & Kristeva-Feige, 2000).

Until now, only little work has been done concerning the relationship between language lateralisation and interhemispheric connectivity. Particularly among healthy subjects, only a few studies have correlated scores obtained in the behavioural dichotic-listening task with the midsagittal area of the total CC or its subregions. Some of these investigations found that the degree of right-ear advantage for dichotically presented verbal material (commonly taken to reflect leftward cerebral lateralisation of language perception) is associated with smaller callosal area (Hines, Chiu, McAdams, Bentler, & Lipcamon, 1992; O'Kusky et al., 1988; Yazgan, Wexler, Kinsbourne, Peterson, & Leckman, 1995). However, these results need to be interpreted with caution. It is not only that several other studies failed to find any such association (Clarke, Lufkin, & Zaidel, 1993; Jäncke & Steinmetz, 2003; Kertesz, Polk, Howell, & Black, 1987; Moffat, Hampson, & Lee, 1998), but also that the indices of auditory lateralisation obtained with

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dichotic listening cannot unequivocally and exclusively be regarded as indicating language lateralisation. According to the widely accepted structural model of dichotic listening (Kimura, 1967; alternative models are reviewed in Hugdahl, 2003), information presented to the ear contralateral to the language-dominant cerebral hemisphere is directly transferred to the dominant (usually left) hemisphere, whereas stimuli delivered to the ipsilateral ear take an indirect path via the opposite hemisphere and the CC. The inferior performance of the ear ipsilateral to the dominant hemisphere is attributed to a delay and/or loss of information during the longer route including the callosal relay. Thus, the correlation between callosal size and lateralisation indices obtained from dichotic-listening tasks may (at least to some degree), be attributed to callosal relay rather than merely to language lateralisation.

An alternative approach to dichotic listening, functional magnetic resonance imaging (fMRI), is now widely utilised to locate cerebral language areas and to assess language lateralisation non-invasively and more directly (Binder & Price, 2001). In recent years, various language tasks have been administered in functional imaging studies, including the frequently used word-generation task (e.g., Friedman et al., 1998; Frith, Friston, Liddle, & Frackowiak, 1991; Pujol, Deus, Losilla, & Capdevila, 1999; Rueckert et al., 1994; Tzourio-Mazoyer, Josse, Crivello, & Mazoyer, 2004). The task involves visual or auditory presentation of a letter or a word, and the subject is instructed to produce words that are semantically related or phonologically similar to a presented stimulus. Across studies, activation in the region of the left inferior frontal gyrus (Brodmann area, BA 44, 45, 46/47) was consistently found during a word-generation task. The posterior part of the middle frontal gyrus, precentral gyrus, and the cingulate cortex are other frequently reported areas of activation. Furthermore, a high correlation between lateralisation of frontal activation in an fMRI word-generation task and the language lateralisation status obtained with the invasive sodium amytal test have been reported by Lehéricy et al. (2000), indicating a good validity of the method.

Structural assessment of the interhemispheric connection is typically performed by measuring the cross-sectional surface area of the CC on a midsagittal slice of an anatomical magnetic resonance imaging scan. Although the resulting measures of callosal size are commonly used as an indicator for the "strength" of the interhemispheric connections, the relationship of midsagittal area to the number of axons remains unclear, since the empirical results are scarce and contradictory (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; but see LaMantia & Rakic, 1990). Moreover, the influence of other variables such as myelination, axon diameter or inter-axonal space on callosal size is poorly established. For example, a greater callosal area may result from wider inter-axonal space without any increase in axon number. Thus, it may well be misleading to regard only the midsagittal area, whereas the additional inspection of the callosal microstructure may be a favourable approach to gain further and more valid information about interhemispheric connectivity and its functional relevance.

Following the development of the novel diffusion-tensor magnetic resonance imaging (DTI) technique, the analysis of callosal microstructure is no longer limited to post-mortem examinations (LeBihan et al., 2001; Pierpaoli, Jezzard, Basser, Barnett, & DiChiro, 1996). The DTI technique provides quantitative information about the random motion of water molecules (diffusion). In brain tissue, water diffusion is more or less impeded by obstacles such as cell membranes or myelin sheaths. For example, in sections of brain white matter with strongly aligned axons, molecules preferentially move parallel to the orientation of the axons rather than perpendicular to them. Thus, the measurement of the molecular displacement in different directions gives indirect information about the microstructural architecture of the tissue.

The diffusion process in each voxel of a volume can be described by a symmetrical three-by-three matrix, the so-called diffusion tensor. In DTI, the elements of this tensor are estimated by utilising diffusion-weighted MRI in at least six directions. Quantification of the diffusion process can be obtained by mathematical diagonalisation of the tensor, which reveals three orthogonal eigenvectors (the principal frame) and three corresponding eigenvalues (λ_1, λ_2, and λ_3). The eigenvalues can be interpreted as the diffusion coefficients in the three principal coordinate directions, and provide the basis for the computation of scalar indices which quantify different characteristics of the diffusion process in each voxel (Pierpaoli & Basser, 1996). The most common parameters are indices of diffusion anisotropy (e.g., relative anisotropy, RA) and the index of mean diffusion (MD; see Fig. 1). Anisotropy indices represent the directionality of the water diffusion (deviation from free and undirected diffusion), which in white matter is thought to reflect the degree of alignment of the axons. MD indicates the mean overall or total diffusion in a voxel, and is interpreted as an indicator for the existence of diffusion barriers such as cell membranes or myelin sheaths, irrespective of the spatial orientation of these barriers.

The aim of the present study was to examine whether and how differences in functional lateralisation of language production are related to interindividual variations in interhemispheric connectivity. Language lateralisation was assessed using a reliable fMRI word-generation paradigm, while interhemispheric connectivity was determined by utilising a combination of high-resolution morphological MRI and DTI measurements of the CC. Thus, by inspecting the interhemispheric