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Diffusion weighted callosal integrity reflects interhemispheric communication efficiency in multiple sclerosis

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ABSTRACT

We aimed to investigate the relation between damage in the corpus callosum and the performance on an interhemispheric communication task in patients with multiple sclerosis (MS). Relative callosal lesion load defined as the ratio between callosal area and the total lesion load in the total corpus callosum, and the diffusion tensor imaging (DTI) derived measures fractional anisotropy (FA) and transverse and longitudinal diffusivity were calculated in sixteen female MS patients and sixteen age and education matched female controls. The redundancy gain task was used to behaviorally evaluate interhemispheric communication efficiency. During this task, simple reaction times to uni- and bilateral presented stimuli are recorded. The advantage in reaction time for bilateral as compared to unilateral trials, the redundancy gain, was significantly larger for the MS-group. The DTI data showed significantly decreased FA and increased diffusivity parameters in the corpus callosum for the MS patients compared with the control group. Moreover, we found a significant correlation between the DTI-derived measures in the corpus callosum and the redundancy gain effect. Callosal damage in MS, as measured by DTI and defined as transverse diffusivity, is associated with alterations in a behavioral task that relies on interhemispheric transfer and communication.

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1. Introduction

Individuals diagnosed with MS are at an increased risk of cognitive deficits (Rao, Leo, Bernardin, & Unverzagt, 1991). The cognitive profile of patients with MS is characterized by memory decline, attention deficits, slowed information processing, and reduced executive skills and visuo-spatial abilities (Bobholz & Rao, 2003). The extent of diffuse tissue damage, lesion localization, neural connectivity deficiency due to white matter damage, and the efficiency of the process for cortical reorganization have been associated with increased risk for cognitive decline in this patient group (Ranjeva et al., 2006). Although gray matter abnormalities in MS have been described, the predominant pathology underlying MS is white matter degeneration. This degeneration in MS is characterized by a gradual destruction of the myelin sheets insulating the nerves. The process of demyelination results in interference or blocking of the fast conduction of electrophysiological signals along the nerves in the affected neuronal fibers. Degeneration of conductive capacities results in reduced communication between separate cortical regions.

In MS, white matter degeneration is observed throughout the central nervous system, but a predilection for specific target zones that include the corpus callosum has been described (Ge et al., 2004). The corpus callosum that connects both cerebral hemispheres is by far the largest fiber tract in the brain. Gender differences point to a larger relative corpus callosum in women compared to men (Clarke & Zaidel, 1994; Johnson, Farnworth, Pinkston, Bigler, & Blatter, 1994). Moreover, animal studies demonstrate the effect of hormones on corpus callosum anatomy (Fitch, Berrebi, Cowell, Schrott, & Denenberg, 1990; Fitch, Cowell, Schrott, & Denenberg, 1991). Diffusion studies showed decreased fractional anisotropy in the female compared to the male corpus callosum (Shin et al., 2005; Westerhausen et al., 2004). For a thorough discussion on gender differences in the corpus callosum structure, we refer to Bishop and Wahlsten (1997).

As the callosal structure is preferentially involved in MS, the impact of MS on interhemispheric communication is not surprising. Clinical evidence for functional impairment of callosal tracts comes from different investigations (Larson, Burnison, & Brown, 2002; Pelletier et al., 2001). Neuropsychological evaluations demonstrate reduced performance in callosal-mediated tasks in MS (for example

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the interhemispheric transfer time, the bimanual coordination task, the tactile performance test and the finger localization test; Brown, 2003). Evoked potentials demonstrate longer latency and lower cross-callosal amplitude in an MS-subgroup compared to healthy controls. In addition, gender differences in callosal functioning are also described (in dichotic listening see Hugdahl, 2003; in evoked potential studies see Burnison, Larson, & Brown, 1993).

The redundancy gain paradigm has been used extensively to gather reliable information about interhemispheric processing in normal volunteers and callosotomy patients. In this task the reaction times of responses given with both the right and the left hand to stimuli presented to the left, right, or both visual fields simultaneously are recorded. One way to estimate the interhemispheric transfer time is defined as the crossed-uncrossed difference (CUD) (Poffenberger, 1912). Based on visual reaction times with the right or the left hand to right or left visual field presented stimuli the contra- and ipsilateral interhemispheric transfer time can be estimated. A marked overall lengthening of the CUD is found in partial callosal lesion patients (Marzi, Bongiovanni, Miniussi, & Smania, 2003).

In healthy controls reaction times to bilateral or redundant stimuli are faster than reaction times to unilateral presentations. This effect is referred to as the redundancy gain (Reuter-Lorenz, Nozawa, Gazzaniga, & Hughes, 1995). A possible explanation for the redundancy gain effect is given by the probability summation model (Miller, 1982). In analogy with horses racing, the two stimuli race for response, with the fastest winning. In the bilateral condition, there are two chances of getting a fast response, in comparison to the one chance in the bilateral condition. This model can be mathematically tested and violations were found in callosotomy and callosal agenesis patients (Corballis, Corballis, & Fabri, 2004). This demonstrates an enhanced redundancy gain, implying neural summation between the hemispheres. A possible explanation for this paradoxical finding is that the corpus callosum serves as an inhibitor of neural interhemispheric interaction, with neural summation operating at subcortical level via the superior colliculi (Corballis, 2002). An magnetic resonance imaging (MRI) study indicated that the CUD and the redundancy gain were best predicted by diffusivity parameters in the corpus callosum (Schulte, Sullivan, Müller-Oehring, Adalsteinsson, & Pfefferbaum, 2005).

The neural summation model predicts that callosal damage results in decreased inhibition leading to a bigger redundancy gain (Corballis, 2002). In partial and complete callosotomy patients, as well as in callosal agenesis patients the extent of redundancy gain was related to the degree of disconnection; it was largest in subjects with complete forebrain commisurotomy, smaller in subjects with callosotomy and still smaller in acallosal subjects (Roser & Corballis, 2002). Even the subtler microstructural callosal white matter damage in alcoholics, as measured by DTI, was related to functional efficiency measures of interhemispheric processing (CUD) (Schulte, Pfefferbaum, & Sullivan, 2004). In phonological dyslexic children indications were found for a prolonged redundancy gain (Badzakova-Trajkov, Hamm, & Waldie, 2004). By our knowledge the redundancy gain paradigm has not yet been tested in an MS population. Given the MS induced callosal neurodegeneration, it appears plausible to hypothesize an enhanced effect in MS patients. We can also assume that the redundancy gain will be more pronounced as callosal damage is larger.

Damage to the corpus callosum in MS has been assessed by different MRI methods. A relatively new, quantitative, MRI based technique to assess white matter damage is DTI. The increased pathological specificity and its ability to assess in vivo the presence of tissue damage occurring outside the T_1-visible lesions makes DTI valuable especially in MS. Fractional anisotropy (FA) is a commonly used diffusion coefficient. FA reflects the coherence of the orientations of white matter tracts in the living brain and is computed from the diffusion properties within a voxel. It is a scalar invariant reflecting the variance of the three diffusion tensor eigenvalues. FA-values range from 0 to 1, high FA represents more organized tissues (anisotropic diffusion) such as white matter tracts, and low FA indicates a lack of directional tissues (isotropic diffusion). Although the exact mechanism underlying the anisotropy map is not completely understood, FA is believed to reflect many factors including the degree of myelination and axonal density and/or integrity (Arfanakis et al., 2002; Harsan et al., 2006; Song et al., 2002; Song et al., 2005). It has been shown that FA values of white matter lesions are decreased in MS (Ge et al., 2004; Filippi, Cercignani, Inglese, Horsfield, & Comi, 2001; Werring, Clark, Barker, Thompson, & Miller, 1999). DTI measures seem to be sensitive measures for cerebral damage as studies could find DTI-derived anisotropy declines even in the absence of macrostructural abnormalities (Werring et al., 1999). Recent studies provide further evidence that the reduction in FA within normal appearing white matter in MS is primarily caused by increased transverse diffusivity, that is the mean of the non-principal eigenvectors (λ_2 and λ_3) rather than by changes in diffusivity along the principal direction, or longitudinal diffusivity (λ_1) of the tract (Henry, Oh, Nelson, & Pelletier, 2003; Oh, Henry, Genain, Nelson, & Pelletier, 2004).

The aim of this study is to investigate the relationship between the redundancy gain and neuro-pathological damage in the corpus callosum in a sample of MS patients. MS patients represent a group with varying degrees of callosal involvement. Classic measures as lesion load and callosal size will be obtained using structural MRI as well as DTI measures (FA, longitudinal and transverse diffusivity). We will compare the relation between conventional structural measures (relative lesion load) and the DTI-derived measures with the behavioral redundancy gain performance. DTI is a potentially powerful technique for characterizing the effects of the pathology in MS and is highly sensitive to changes in the cellular and microstructural level. We expect to find more pronounced relations between DTI measures for callosal damage and redundancy gain than between the portended less sensitive conventional structural measures and redundancy gain, particularly in the white matter demyelination pathology associated with MS. We also expect that more MS induced callosal damage will lead to more behavioral problems reflected by the performance on the redundancy gain task. As described above, evidence for gender differences is given in both callosal anatomy and callosal function; therefore we chose to explore the redundancy gain effect in one sex. As MS merely affects women (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000), we decided to only include women in this explorative study.

2. Materials and methods

2.1. Patients

Sixteen right-handed female patients aged 21–46 years (mean age 36.4 years, mean years of education 14.8 years) with clinically definite MS according to McDonald criteria (McDonald et al., 2001) participated in the study. All MS-patients were recruited from the outpatient population of the department of Neurology at the Ghent University Hospital. The sixteen patients had relapsing-remitting MS, with a disability on the Kurtze expanded disability status scale (EDSS) (Kurtze, 1983) between 0 and 7 (mean ± S.D.: 2.25 ± 0.24). None of the patients suffered from other neurological problems or had a history of substance abuse. At the moment of the testing none suffered from upper limb motor problems or from optic neuritis as tested by a neurologist specialized in MS (J.D.). Sixteen right-handed age-, gender-, and education matched healthy controls were also included in this study (all controls were female with mean age = 37.1 years, mean years of education = 15.7 years). All patients gave written informed consent to participate in the study according to the institutional guidelines of the Ethics Committee of the Ghent University Hospital.

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