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Alternative Neuropsychological and Magnetic Resonance Imaging Measures in Multiple Sclerosis.

Exploring the relation between brain lesion measured by diffusion tensor magnetic resonance imaging and interhemispheric communication and processing speed in multiple sclerosis.

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Thesis submitted in fulfilment of the requirements

For the degree of Doctor in Medical Sciences

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Dedicated to Steven for his patience,

And to our beloved daughter Noor

Table of Contents

List of abbreviations

ADC	Apparent Diffusion Coefficient
CUD	Crossed-Uncrossed Difference
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EDSS	Expanded Disability Status Scale
FA	Fractional Anisotropy
FLAIR	Fluid-Attenuated Inversion-Recovery
MD	Mean Diffusivity
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
PASAT	Paced Auditory Serial Addition Test
PET	Positron Emission Tomography
RF	Radio Frequency
RG	Redundancy Gain
RT	Reaction Time
SDMT	Single Digit Modalities Test

List of Publications used in this Thesis

Warlop, N.P., Fieremans, E., Achten, E., Debruyne, J., Vingerhoets, G. (2008). Callosal function in MS patients with mild and severe callosal damage as reflected by diffusion tensor imaging. *Brain Research, 1226, 218-225.*

Warlop, N. P., Achten, E., Debruyne, J., Vingerhoets, G. (2008). Diffusion weighted callosal integrity reflects interhemispheric communication efficiency in multiple sclerosis. *Neuropsychologia, 46(8),* 2258-2264.

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Aim of this thesis

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The main aim of this thesis is to explore the relation between neuropsychological deficits and sclerotic lesions in multiple sclerosis. Thus far, the strongest psychometric-morphometric correlations have been found between the Paced Auditory Serial Addition Test (PASAT) and magnetic resonance imaging (MRI) derived total lesion volume. Although the PASAT, a neuropsychological test measuring processing speed, is viewed as one of the most important measures of cognitive dysfunction in MS, its reported relation with disease severity as measured by total lesion load is modest, not always significant and thus remains controversial.

Several reasons may explain these contradictory results. On the psychometric side it can be argued that the PASAT is a questionable measure. It measures the end result of a host of cognitive functions (sustained and divided attention, working memory,...) not necessarily related to disrupted intra- or interhemispheric processing caused by demyelinating lesions. In this thesis we propose an alternative, more direct cognitive measure of interhemispheric processing. The redundancy gain paradigm is a well known paradigm in the literature on interhemispheric communication; it has proven its value in getting a good insight into interhemispheric processing in different populations (dyslexic patients,...). In this thesis we explore the redundancy gain effect in MS. This paradigm has by the best of our knowledge not yet been tested in an MS population before.

On the morphometric side it can be argued that MRI derived total lesion load is a crude measure of brain pathology that also includes lesions that do not necessarily underlie cognitive (dys)function. Moreover, with classic MRI techniques only visible lesions can be quantified. Recently a bulk of studies shows the presence of normal appearing white matter (NAWM) in MS: white matter tissue appearing normal, but nevertheless affected by MS related pathological processes. In this thesis we propose the use of the relatively new MRI technique, more specific the diffusion tensor imaging (DTI) technique, by which it is possible to detect abnormalities in NAWM. DTI measures the preferred directionality of the diffusion of water molecules in the brain. The free water diffusion is constrained by the direction and density of the fiber tracts. Recent studies show altered diffusion parameters in MS-patients compared to healthy controls. The relation between neuropsychological deficits in MS and DTI parameters is however not yet profoundly investigated and this will be the challenge of this thesis. Additionally, given the recent emphasis on transverse diffusivity as possible specific indication of MS brain pathology, this DTI derived parameter was also investigated in MS. This is of great interest in matching the obtained results with the recent literature and in providing further evidence that transverse diffusivity is specific to the demyelination pathology in MS.

This work commences with a comprehensive introduction. In the first part of the introduction we describe the different paradigms used to investigate interhemispheric communication and the theoretical framework of the redundancy gain paradigm. Next the pathological and clinical aspects of

multiple sclerosis are described. The last part of the introduction will introduce different magnetic resonance techniques and will go into detail on the technical aspects of the diffusion tensor imaging technique.

The different papers included in this work are presented in the second and third chapter of this thesis. The first two studies deal with interhemispheric communication in MS investigated by the redundancy gain paradigm. These studies also report on the results of the investigated relation between the redundancy gain effect (behavioural measure for interhemispheric communication) and DTI parameters (morphometric measure) in the corpus callosum. These two first studies focus on the specific aspect of callosal communication between the two hemispheres in MS. In the third study we enlarge our view and investigate the relation between different cognitive measures for processing speed and DTI parameters in the whole brain.

We conclude in chapter four with a general discussion and conclusion on the results with recommendations for future research with the promising DTI technique in research on MS.

Chapter 1

Introduction

1.1 Interhemispheric Communication

1.1.1 General introduction

The human brain is clearly divided into two hemispheres. The corpus callosum is by far the largest neural pathway that connects both brain halves. The basic function of the between 200 and 800 million axon fibers (Banich, 1995) of the corpus callosum is information transfer between the cerebral hemispheres. How the two hemispheres interact has been the topic of a lot of research and different paradigms have been developed to investigate interhemispheric processing velocity and efficiency. These paradigms are of great benefit to explore interhemispheric communication in healthy controls, but also in patients. Dysfunctions that occur in interhemispheric communication associated with specific callosal damage are crucial for understanding the role of the corpus callosum.

1.1.2 The Poffenberger paradigm and the crossed-uncrossed difference

The Poffenberger (1912) paradigm has been developed to measure interhemispheric relay time. This detection task requires a subject to manually respond as quickly as possible when he or she detects a unilateral presented target signal (flash of light). Visual and motor projections are contralateral with left visual hemifield stimulation resulting in contralateral right retinotopic brain activation and vice versa. Motor responding of the left hand is controlled by the right hemisphere and vice versa. A schematic picture of this process can be seen in Figure 1. The difference in reaction time between ipsilateral or uncrossed conditions (for example left visual hemifield stimulation requiring left hand responding) and contralateral or crossed conditions (for example left visual hemifield stimulation requiring right hand responding) is a good estimate for interhemispheric transfer time. This measure is calculated by subtracting the average median reaction time for the uncrossed conditions (right visual hemifield and right hand response or left visual hemifield and left hand response) from the average mean reaction time for the crossed conditions (left visual hemifield and right hand response or right visual hemifield and left hand response) and dividing the result by two (Poffenberger, 1912) and is also referred to as the crossed-uncrossed difference (CUD). The CUD ranges between 2 and 6ms in healthy controls. A prolonged CUD has been reported in patients with lesion of the posterior body of the corpus callosum (Peru et al., 2003), and in patients with posterior section of the corpus callosum (Corballis et al., 2002).

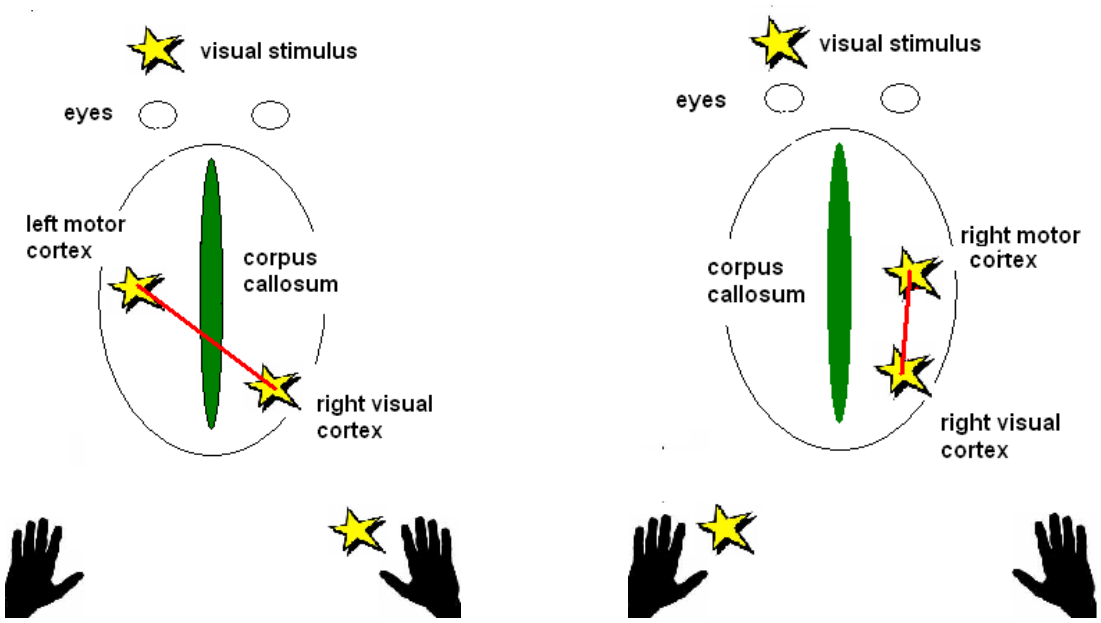

Figure1 Schematic overview of crossed and uncrossed conditions in the Poffenberger paradigm (Poffenberger, 1912). Visual stimulation and the associated visual and motor projection are indicated by a star. Transfer from the visual cortex to the motor cortex is indicated by a red line and the corpus callosum is represented by a green oval. On the left, the crossed condition is depicted and on the right the uncrossed condition is depicted.

1.1.3 The redundancy gain effect

One limitation of the CUD measure is that, when calculated for each hand separately, the CUD is partly confounded by hemispheric processing time differences (Corballis, Hamm, Barnett, & Corballis, 2002; Iacoboni, & Zaidel, 2000). The redundant stimuli task, which accounts for this confound, is considered to be more reliable.

This task is essentially the same as the Poffenberger paradigm, with this difference that stimuli also can be presented bilateral, one in each hemisphere simultaneously. In healthy controls reaction times to bilateral or redundant stimuli are faster than to unilateral stimuli. This effect is referred to as the redundancy gain (Corballis, 1998; Reuter-Lorenz, Nozawa, Gazzaniga, & Hughes, 1995) and reflects the difference between response time to uni- and bilateral presentations. The redundancy gain can be calculated by the formula proposed by Corballis (2002). The formula is given by $[(RT_c + RT_i)/2] - RT_b$ with RT_c the median reaction time to contra-lateral stimuli, RT_i the median reaction time to ipsilateral stimuli and RT_b the median reaction time to bilateral stimuli. In order to account for possible hand differences, the redundancy gain is calculated for each hand separately.

1.1.4 The race model

A possible explanation for the typically found redundancy gain effect is the probability summation model (Raab, 1962; Miller, 1982). For bilateral conditions, the processing of the two simultaneously bilateral presented stimuli race for response, with the fastest winning. For the unilateral condition, only one stimulus is to be processed, hence there is no race. Hence, for the bilateral condition there are two chances of getting a (fast) response, in comparison to the one chance in the unilateral condition. The probability of getting a fast response for the bilateral condition will consequently be higher (there are two chances for a fast processing resulting in a fast response) than for the unilateral condition (where there is only one chance for fast processing resulting in fast response). This race model assumption can statistically be tested as described by the methods by Corballis (1998).

The statistical procedure for testing this model can be explained as follows: At some given time, t, after a stimulus has been presented, let P_i be the probability summation of responding to ipsilateral stimuli (for example left visual stimulus and left hand response), P_c the probability summation of responding to contralateral stimuli (for example right visual stimulus and left hand response) and P_{ic} the probability summation of responding to stimuli in bilateral conditions. These probability summations for the three conditions can be calculated as follows. First, the reaction times to all stimuli (ipsilateral, contralateral and bilateral conditions) are sorted in ascending order and are divided in reaction time bins, with the first time bin containing the 20 fastest reaction times, the second bin the next 20 fastest reaction times and so on. Second, in each time bin the cumulative distribution proportion within all three conditions separately is calculated. The obtained values represent the probability summation for each condition (P_c, P_i, and Pic) within each time bin. The race model predicts that in bilateral conditions the hemifield stimuli race independently for response, resulting in the following expression $P_{ic} = P_i + P_c – P_iP_c$; this is the probability of responding to bilateral stimuli equals the sum of the probability summation of responding to a contralateral stimulus and the probability summation of responding to an ipsilateral stimulus minus the product of the multiplication of the probability summation of a response to ipsilateral stimuli and the probability of a response to contralateral stimuli. The expression $P_{ic} – (P_i + P_c – P_iP_c)$ can be calculated within each reaction time bin and averaged over both response hands.

Violations of the race model are indicated by higher probabilities for bilateral conditions than predicted by the formula $(P_{ic} – (P_i + P_c – P_iP_c) > 0$. Or in other words, if the cumulative distribution of reaction times to bilateral stimuli is faster than can be accounted for by the race model (probability summation) then an *enhanced* redundancy gain is observed. Additionally, in the model proposed by Miller (1982) the assumption of stochastic independency between both processes initiated by the two stimuli, this is reflected in the product term P_iP_c, is relaxed. Here it is assumed that the joint probability that both stimuli have been responded to (P_iP_c) must lie between 0 and 1. This gives rise to the formula

$P_{ic} - (P_i + P_c)$. Again, results that are larger than zero for this formula indicate probability (*race*) model violations, an *enhanced* redundancy gain.

1.1.5 Theories explaining the enhanced redundancy gain in populations with callosal problems

As assumed in the race model both hemispheres could operate independently and the presence of a redundancy gain does not necessarily imply interhemispheric communication. However, the redundancy gain in patients with callosal problems (callosotomy and callosal agenesis patients) is *enhanced* compared to healthy controls (Corballis, 1998; Corballis, Corballis, & Fabri, 2004), suggesting callosal involvement in the redundancy gain effect. Various theories have been offered to explain this rather paradoxical observation.

The first model assumes that the *enhanced* redundancy gain is due to reaction time slowing to unilateral stimuli (Reuter-Lorenz et al., 1995). In the intact brain, response readiness of both hemispheres is ensured through the corpus callosum, which activates a hypothetical logical "and" gate. The "and" gate mechanism removes response inhibition only when response preparation signals were received from both hemispheres. Following callosal section, the "and" gate mechanism will not be activated for unilateral stimuli, and response readiness is generated in one hemisphere only. This results in an interhemispheric conflict with inhibition and slowing of response. In contrast, for bilateral conditions, the "and" gate will be satisfied, no conflict ensues and response is facilitated with speeding of reaction time.

A somewhat similar but simpler theory suggests that reaction time is influenced by neural summation, rather than by an "and" gate mechanism (Roser and Corballis, 2002). Interhemispheric transfer creates neural summation in the intact brain even when input is unilateral. Summation in the split brain only arises when input is bilateral.

Both models described above assume that *enhanced* redundancy gain arises because reaction time to unilateral input is slowed. An alternative approach has been taken by Iacoboni et al. (2000), who suggested that the *enhanced* redundancy gain in the split brain is rather due to speeded reaction time to bilateral stimuli. In this model the basic mechanism is the inhibitory function of the corpus callosum, with neural summation operating at the subcortical level via the superior colliculli. This whole process is fed by visual input, with large input sending strong signals from the extrastriate cortex to the premotor cortex resulting in speeded response. With bilateral stimuli, the degree of activation of the superior colliculli depends on whether the activity in the striate cortex is synchronised or not and this in turn depends on interhemispheric conduction time. Summed over time, asynchronous activity (conduction delay of more than 15 ms) would result in a larger input to the colliculli, which then feed a stronger signal back to the extrastriate cortices. The striate cortex in turn sends stronger activation to the premotor cortex, speeding the response. In patients with callosal transfer dysfunction resulting in slowed transfer, this process happens and results in an *enhanced* redundancy gain. Albeit interesting,

this hypothesis does not fit with the finding that in healthy subjects, the redundancy gain decreases at increasing time delays between two redundant stimuli (Miller and Ulrich, 2003).
An alternative model states that not asynchronous input to the superior colliculli, but dual attention is responsible for the effect (Corballis et al., 2004). In the intact brain the inhibitory function of the corpus callosum ensures the restriction of attention to one or other visual field. In split-brain, attention restriction is not possible which results in dual attention capacities. Consequently, enhanced activation in both hemispheres arises and neural summation either at the superior colliculus or at the motor level could arise.

1.1.6 Independence of CUD and redundancy gain

Previous research (Corballis, 2002) investigating interhemispheric communication by measuring the CUD as well as the redundancy gain with the methods as explained above, showed that both effects were uncorrelated. This finding suggests that the underlying functional mechanism of both measures depends on different independent processes. Furthermore, brain imaging research (Omura et al., 2004) revealed that different brain mechanisms are involved in the crossed-uncrossed difference and the redundancy gain. Research on interhemispheric processing can thus profit of the investigation of both effects in order to get a profound insight on interhemispheric communication processes.

1.1.7 Gender and Handedness

Gender differences in callosal function and anatomy of the corpus callosum are extensively described (Clarke and Zaidel, 1994; Bishop and Wahlsten, 1997; Westerhausen et al., 2004). Gender differences indicate a larger relative corpus callosum in women compared to men (Johnston et al., 1994; Clarke & Zaidel, 1994). Moreover, animal studies demonstrate the effect of hormones on corpus callosum anatomy (Fitch et al., 1990; 1991). Diffusion studies showed decreased fractional anisotropy in the female compared to the male corpus callosum (Westerhausen et al., 2004; Shin et al., 2005). A thorough discussion on gender differences in the corpus callosum anatomy can be found in Bishop and Wahlsten (1997).
Gender differences in callosal function are also described (in dichotic listening see Hughdal, 2003; evoked potential studies see Burnison et al., 1993). A major point of discussion is the impact of gender on corpus callosum anatomy (size) over brain size (Jäncke & Steinmetz, 2003), with the size of the corpus callosum depending mainly on brain size and not per se on gender or handedness.
The effect of handedness on corpus callosum size and function, interacting with gender, remains questionable, with some authors showing evidence for handedness effects (Clarke and Zaidel, 1994; Moffat et al., 1998) and others not (Steinmetz et al., 1992, 1995; Jäncke et al., 1997).

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1.2 Multiple Sclerosis

1.2.1 Pathology

Multiple sclerosis (MS) is a chronic inflammatory disease of the white matter in the central nervous system resulting in multifocal brain and/or spinal cord damage. The neuropathology in MS is characterised by multiple discrete areas in which neurons have absence of myelin. This demyelinating process results in the formation of demyelinated plaques in the central nervous system, ranging in size from 1 mm to several centimetres. The destruction of myelin, the fatty sheet around the axons providing fast electrical signal propagation, in MS is thought to occur because of the disturbance in auto-immunological response. The demyelinated areas interfere or block neural transmission and cause symptoms specific to the location of these areas.

In the first stage of the disease, the axons are relatively spared within the plaques. Axonal degeneration is a secondary pathologic process in MS that occurs in some degree in almost all plaques. Progressive axonal loss leads to tract degeneration and atrophy. Axonal injury in the central nervous system can occur trough at least two general mechanisms: a) as a consequence of direct injury, for example within focal areas defined by acute inflammatory pathology and b) as a result of degeneration distant to the focal lesion for example Wallerian degeneration that is characterised by axonal injury enduring without inflammation.

1.2.2 Clinical Picture

MS is one of the most common neurological diseases of non-traumatic origin of young and middle-age adults occurring in approximately 60 of every 100.000 individuals. The prevalence in MS is higher in women than in men (ratio 3:2) (Baum and Rothschild, 1981).

The neuropathology marks a series of physical symptoms (tremor, loss of sensitivity, optic neuritis…) typical to MS. The Expanded Disability Status Scale (EDSS) (Kurtze, 1983) is a scale that aims to quantify MS related disability in eight functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder related, visual, cerebral and other) (refer to Figure 2). In addition to the physical problems, it is estimated that half of the MS patients suffer from cognitive problems that have an impact on daily life (Rao, Lean, Bernardin, & Unverzagt, 1991).

0	Normal neurological examination
1.0	No disability, minimal signs in one functional system
1.5	No disability, minimal signs in more than one functional system
2.0	Minimal disability in one functional system
2.5	Mild disability in one functional system or minimal disability in two functional system
3.0	Moderate disability in one functional system, or mild disability in three or four functional system. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one functional system and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10	Death due to MS

Figure 2 Kurtzke Expanded Disability Status Scale (EDSS)

Along the course of the disease three different subtypes can be differentiated. The relapsing-remitting type is characterized by relapses and remissions. 60% to 65% of all MS patients suffer from this subtype. The secondary progressive subtype is found by patients who initially have the relapsing-remitting type of the disease. After a certain time, the relapses do not occur anymore, but slow regular progression with gradual loss of functions appears. For primary progressive MS functional loss occurs gradually from the start of the disease onwards. For a schematic overview of the MS subtypes, refer to Figure 3.

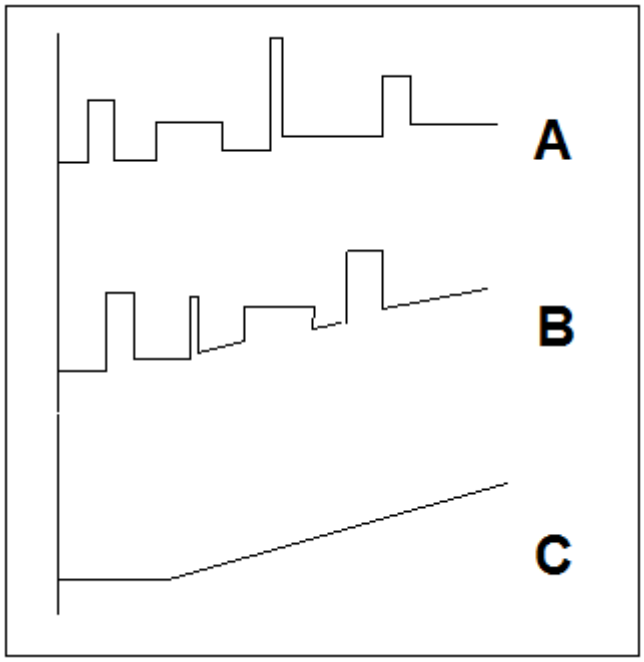

Figure 3 Schematic overview of the MS subtypes. Ascending lines indicate a relapse, descending lines a remission. A) depicts relapsing remitting MS, B) the secondary progressive subtype, and C) the primary progressive subtype.

The study of clinical populations with callosal damage is important for research on interhemispheric interaction. MS involves degeneration of white matter throughout the central nervous system, but with a predilection for specific target zones that include the corpus callosum (Ge et al., 2004). On the basis of magnetic resonance imaging (MRI) scans, callosal lesions are seen in 55% to as high as 93% of MS patients (Simon et al., 1986). Hence, MS subjects represent a group with varying degrees of callosal involvement.

1.2.3 Interhemispheric Communication in Multiple Sclerosis

The first studies assessing cross-callosal communication in MS used mainly dichotic listening tasks. In this task, two similar, but not identical verbal or non-verbal sound stimuli are simultaneously presented, one to each ear, and the tasks include recall (in which the listener has to repeat the stimuli) or detection tasks (in which the subject has to detect a given stimulus). Dichotic tests with verbal

stimuli show a right ear advantage in healthy subjects. This effect has been attributed to the left hemisphere language specialization and to the dominance of the contralateral auditory pathway when the two ears are in competition (Kimura, 1967). This hypothesis received support from studies on patients with surgical section of the corpus callosum (Milner et al., 1968; Sparks and Geschwind, 1968). Based on these findings, Zaidel (1986) proposed that dichotic listening assesses interhemispheric transfer according to the 'callosal relay' model that assumes a left hemisphere supremacy in language auditory signal transmission. According to this model, speech stimuli that enter the right (non-language) hemisphere will require callosal transfer to the left (language) hemisphere in order to be processed, thus requiring extra transfer time, responsible for the finding of longer reaction time to verbal left-ear stimuli (Hughdahl et al., 1997). Conversely, the 'direct access' model proposes that speech stimuli from the left ear will be directly analyzed in the right auditory cortex, albeit less efficiently than in the left cortex (Zaidel, 1986).

In MS patients, left ear suppression was shown for the dichotic listening task (Jacobson, Deppe & Murray, 1983). This finding was attributed to attentional factors. The left ear suppression was replicated in further research, with different explanations (Rubens, Froehling, Slater & Anderson, 1985; Lindeboom & Ter Horst, 1998). The observed left ear suppression was found to be independent of the tendency to direct attention to the right ear, or of MS related disability as measured by the EDSS.

Rao et al. (1989) was the first to extend the evaluation of interhemispheric transfer in MS to visual tasks. Impairment in interhemispheric transfer was found for the visual task as well as for the dichotic listening task. The results were also compared to the size of the corpus callosum, with patients with callosal atrophy presenting a greater impairment in both auditory and visual tasks requiring callosal involvement. The most extensive study evaluating interhemispheric transfer in MS was carried out by Pelletier et al. (1993). Not only auditive and visual tasks were used, tactile and bimanual coordination tasks were administered too. Performance on all tasks correlated with callosal atrophy. In 2001 a longitudinal study of interhemispheric dysfunction in MS was reported by the same research group (Pelletier et al., 2001). Transfer of motor, auditory and sensory information was evaluated and the correlation with disability and callosal lesion load was investigated. As all correlations were significant, the suggestion was raised that callosal dysfunction could be a surrogate marker of disease progression in MS.

A more recent study that extensively studied interhemispheric communication in MS (and other neurological diseases) is the study by Brown (2003). A range of measures of interhemispheric interaction was administered in MS patients and compared to the performance of patients with other pathology involving the corpus callosum (commissurotomy patients, patients with agenesis of the corpus callosum, dyslexic adults). Assessment of the contributions of callosal dysfunction were evoked potentials of interhemispheric transfer time, bilateral field advantage, bimanual coordination test, tactile performance test, finger localisation test and tactile maze. Deficits in interhemispheric

interactions were evident in MS patients on all measures in the battery, except for the bilateral field advantage and the tactile maze. This finding indicates deficits in interhemispheric interaction in MS. Interestingly however, in the patients with indications for callosal transfer delay as measured by visual evoked potentials, the performance on the bimanual coordination test and the tactile performance test was relatively larger than for the patients who showed a normal cross-callosal evoked potential. The heterogeneous condition for (callosal) cerebral damage in MS is well-known and the study by Brown (2003) indicates the importance of taking this into account when investigating callosal transfer in MS. Generalising over all MS patients when studying callosal deficits implies that the heterogeneous condition in MS patients is not taken in account, ignoring the complex individually different neuropathology.

To the best of our knowledge, the crossed-uncrossed difference and the redundancy gain paradigm were not yet used to study interhemispheric transfer in MS. However, these paradigms, especially the redundancy gain paradigm, showed to be sensitive for even subtle callosal damage and these paradigms has been successfully used in other populations to demonstrate callosal dysfunction.

Badzakova-Trajkov, Hamm, and Waldie (2005) could show violations of the race model in dyslexic children, consistent with the accumulating literature that suggests callosal dysfunction among individuals with dyslexia (Davidson and Saron, 1992). In alcoholics an enlarged crossed-uncrossed difference as well as a small redundancy gain could be found for those subjects with callosal thinning, related to alcohol use (Schulte, Sullivan, Muller-Oehring, Adalsteinsson, and Pfefferbaum, 2005). In addition Schulte, Pfefferbaum and Sullivan (2004) showed probability summation for the redundancy gain in aging people related to an age related smaller corpus callosum.

1.2.4 Multiple Sclerosis and Information Processing Speed

The contribution of callosal function to neurocognitive abilities in MS is not yet known. There is however, at present, a good agreement about the nature of the cognitive problems in MS. Different neuropsychological tests indicate disturbances in memory, information processing, higher order visual-perception, attention and executive function, and to a lesser extent, in language processing (Hannay et al., 2004). For a thorough review on cognitive dysfunction in MS we refer to Bobholz and Rao (2003).

Different neuropsychological screening batteries have been proposed for MS, all composed of several cognitive tests covering different cognitive domains (Benedict et al., 2002). The most robust results were found on tests primarily measuring information-processing speed and working memory (Nocentini et al., 2006). MS patients across various disease types or in the very early phase of the disease show lower scores on neuropsychological tests measuring these aspects of cognition (DeSonneville et al., 2002; Feuillet, Reuter, Audoin, & Malikova, 2007). Recent research even suggests that the effectiveness of these single tests as a screening instrument for cognitive dysfunction

in MS is equal to that of more time-consuming comprehensive test batteries (Parmenter et al., 2007; Deloire et al., 2006; Sepulcre et al., 2006). Two commonly used tests measuring processing speed in MS are the Paced Auditory Serial Addition Test (PASAT) (Gronwall, & Sampson, 1974) and the Symbol Digit Modalities Test (SDMT) (Smith, 1982).

In fact the PASAT is a cognitive task developed to measure working memory, information processing speed and sustained and divided attention. In this test a series of sixty-one single digit numbers from one to nine are randomly presented. Participants are instructed to consecutively add pairs of numbers such that each number is added to the one that immediately preceded it. For example, if the stimulus "2" followed by "7" is presented, the participant must respond by saying out loud "9"; if the next stimulus is "4" the participant must respond "11" (this is by adding the "4" to the previous digit "7", not to the participant's own answer of "9"), and so on. This response requirement is sustained over numerous items until the end of the trial. The time between two presented digits, or in other words the interstimulus interval, can differ dependent on the administered version of the test (3s/2s or 2.4s/2.0s/1.6s/1.2s). Classic administration of the PASAT includes decreasing interstimulus interval with repetition of the same process. The PASAT thus incrementally increases processing demands over trials by increasing the speed of stimulus input and decreasing the available response time. Administration time depends on the version used with an average time of about six to eight minutes.

The most commonly used metric for PASAT performance is the total number of correct responses. With sixty-one digits presented, a maximum of sixty correct answers can be given. A response is treated as incorrect if the response is given after the next digit is already presented (i.e. the answer "9" to the digits "2" and "7" is given while the next digit "3" is already presented). Normative data on the PASAT or given by Stuss et al. (1988) and Scherer et al. (2007), and test performance is considered normal if it falls within one standard deviation of the mean score of the appropriate norm group. If the performance falls below minus one standard deviation above minus two standard deviations form the mean score of the appropriate norm group, the performance is considered to indicate a mild impairment on the designated measure. If the performance falls below minus two standard deviations from the mean of the appropriate norm group but above minus three standard deviations from the mean of the appropriate norm group, the performance is considered to indicate a severe impairment on the designated measure.

The advantages of the PASAT are that the participant can perform this test without holding a pen or can perform the test with impaired vision, which could be important in MS patients suffering from motor hand deficits or optic neuritis. A major disadvantage of the PASAT is however the frustration level of the test. Many patients dislike the test resulting in a high dropout rate, especially in patients, but also in healthy subjects (Diehr et al., 2003). In addition, individuals completing the PASAT may employ different strategies to decrease task difficulty and the score on the PASAT may not reflect adequate testing of the purported cognitive domain (Coo et al., 2005). To account for this

shortcoming alternative scoring methods have been proposed (Tombaugh, 2006; Coo et al., 2005; Balzano et al., 2006).

A valuable surrogate for the PASAT is the SDMT (refer to Figure 4). The SDMT assesses divided attention, visual scanning and motor speed. In this test, a coding key is presented consisting of nine abstract symbols, each paired with a number. The participant is required to scan the key and match unpaired symbols as quick as possible by voicing the answer while the examiner records the answers spoken by the participant. To account for the possible extra effort in the oral version of the test due to extra eye-scanning movements, the participants are allowed to indicate with their hand/finger where they are. The limited time given for this test is 90 seconds and the total number of correct answers given in this time bin is the score. Normative data for the SDMT are given by Jorm et al. (2004). In addition, Parmenter et al. (2007) indicated by Bayesian statistics in a MS population that a cut-off score of 55 or lower on the SDMT accurately categorized 72% of the patients as cognitively impaired or not, yielding sensitivity of 0.82, specificity of 0.60. This result indicates that the SDMT is an effective screening test for cognitive impairment in MS. As in this oral version of the test the patients do not need to write down the answers, performance is minimally influenced by motor slowness. Moreover, in contrast to the PASAT, the frustration level is very low for the SDMT.

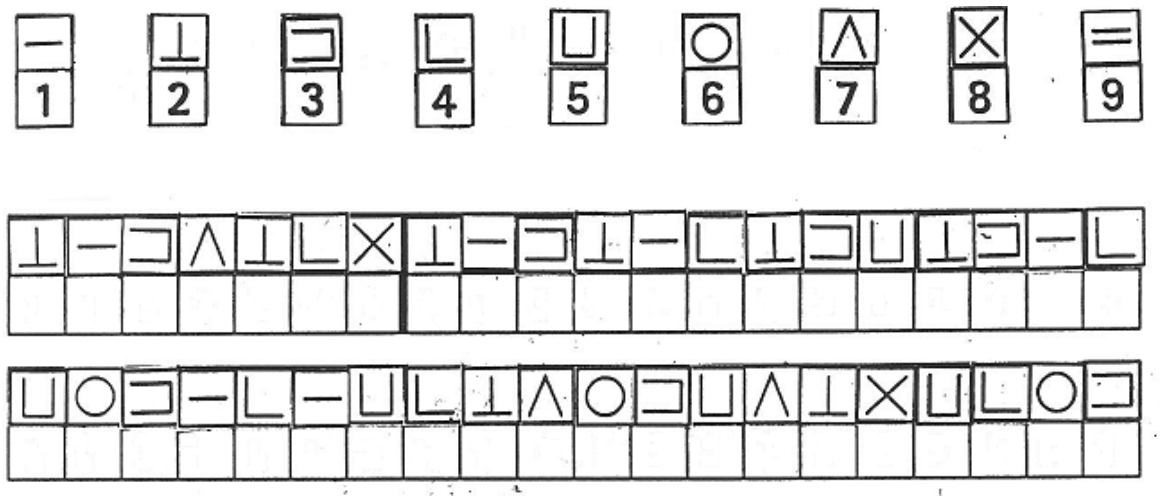

Figure 4 Extract of the Symbol Digit Modalities Test (SDMT) (Smith, 1982).

1.2.5 Relationship between Brain Damage and Information Processing Speed in Multiple Sclerosis

One of the first studies examining the relation between cognitive impairment and brain pathology in MS was the study by Rao and collaborators (1989). Total lesion load was found to be a robust predictor for cognitive dysfunction (recent memory, abstract/conceptual reasoning, language and visuo-spatial problem solving). The atrophy measure (ventricular brain ratio) predicted mental processing speed and rapid problem solving measurements. Since this first study, a bulk of studies on the neural correlates of cognitive dysfunction in MS were published, using different cognitive tests or

batteries to assess the cognitive abilities (Comi et al., 1995; Filippi et al., 2000; Rovaris et al., 2000; Rovaris et al., 2002; Zivadinov et al., 2001; Lazaron et al., 2005). A whole range of techniques has been used to obtain information on the neuropathological damage in the brain, from conventional T2 or T1 weighted images with or without gadolinium contrast enhancement (Comi et al., 1995; Lazeron et al., 2005; Zivadinov et al., 2001) over fluid-attenuated inversion-recovery (FLAIR) (Rovaris et al., 2000) to Positron Emission Tomography (PET) (Paulesu et al., 1996; Blinkenberg et al., 2000) and diffusion tensor imaging (Rovaris et al., 2002). These techniques can all be used to quantify lesioned brain area in MS. At least some authors state that inflammatory demyelination is not the main pathogenetic aspect of MS (Brück, 2005), but that axonal degeneration which leads to cortical atrophy is at least as important and this process may be partly independent of demyelination (Kutzelnigg et al., 2005). Consequently there are various studies that investigate the effect of brain atrophy on cognition in MS. In a review article by Lanz, Hahn and Hildebrandt (2007) nine studies were mentioned that investigate the effect of brain atrophy on performance on the PASAT, and eight investigations on the effect of brain atrophy on SDMT performance. For an extensive overview of the results in the different studies we refer to the review article by Lanz et al. (2007). In summary the overall conclusion is that PASAT and SDMT performance correlates with whole brain atrophy, but to a lesser degree with ventricular size and that both correlations are stronger as MS progresses. Correlation in the earliest stages of the disease all showed negative results.

The bulk of the studies however concentrate on lesion load. It is notable that, of all cognitive domains tested, processing speed consistently has the highest correlation with brain damage, independent of the technique used to quantify cerebral damage (Fulton et al., 1999; Randolph et al., 2005; Sperling et al., 2001; Rovaris et al., 2002). T2 lesion volume in the whole brain correlated with performance on the SDMT, but not with PASAT performance in the study by Fulton et al. (1999). The research by Randolph et al. (2005) revealed that total lesion load measured by FLAIR sequence accounted for 56% of the variance in cognitive performance (processing speed and verbal memory), with the largest association for processing speed (SDMT). Sperling et al. (2001) explored the contribution of regional cerebral damage and cognitive performance. Their study indicates a highly consistent association between MRI lesion burden on T2 weighted images in fronto parietal white matter and cognitive performance. The association was most strong with the PASAT. An explorative study by Rovaris et al. (2002) assessed the magnitude of correlation between diffusion tensor imaging derived measures and cognitive impairment. Again, the correlation for processing speed (SDMT) was, however only moderate, the strongest of all assessed cognitive measures. The correlation with mean diffusivity in the lesions, mean diffusivity in the total brain, mean diffusivity in the normal appearing brain tissue, in the normal appearing white matter and in the normal appearing grey matter were all significant. Very recently, the strongest but still moderate association between diffusion derived measures and different cognitive domains was found between mean diffusivity entropy and performance on the SDMT and

the PASAT (Benedict et al., 2007). Diffusivity entropy is a new diffusion derived analysis defined as the calculation of diffusion measures within the cerebral parenchyma.

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1.3 Diffusion Tensor Imaging

Over the past decades MRI has evolved with a considerable speed. One of the most recent evolutions in this field is the diffusion weighted imaging technique which is based on the difference in diffusion of water molecules within the brain. The first important application of diffusion weighted imaging (DWI) in the early 1990's was for detection of stroke in its acute phase (Moseley et al., 1990). Diffusion tensor imaging (DTI) is a form of diffusion weighted imaging which allows better evaluation of white matter fiber tracts in vivo. One of the major advantages of DTI is that with this technique it was possible to demonstrate that 'normal-appearing' brain tissue in many instances is affected.

In what follows we will give a short overview of the basic principles of MRI, DWI and DTI, furthermore the use of diffusion imaging in MS will be discussed.

1.3.1 Magnetic Resonance Imaging

Atoms like hydrogen consist of a nucleus and a shell, which is made of electrons. In the nucleus there are protons that have a positive electrical charge that spin around the axis. This moving electrical charge is in fact an electrical current accompanied by a magnetic field. In an external electrical field all these protons align with the external magnetic field either along an axis parallel to the magnetic field or along an axis antiparallel to the magnetic field. The state that needs less energy, that is parallel to the magnetic field, is preferred. The protons precess along the axis of the magnetic field. The stronger the magnetic field, the higher the precession frequency. The parallel and anti-parallel orientated protons can cancel each others forces out. As there are more parallel protons on the lower energy level, the net magnetization of a system of spins is a vector parallel to the magnetic field. When a patient is in the MRI scanner, an electromagnetic pulse, also called radio frequency (RF) pulse, causes longitudinal magnetization to decrease and establishes a new transversal magnetization. More protons are now anti-parallel and the protons precess in phase resulting in transversal magnetization. This change in magnetization over time in the transverse plane causes the magnetic resonance (MR) signal which can be measured by a detector coil. When the RF pulse is switched off, the longitudinal magnetization increases again and this longitudinal relaxation is described by a time constant T1 and the transversal magnetization decreases and disappears as described by a time constant T2. These two processes are different, independent processes with for example T1 longer than T2 and different relaxation times for different brain tissue (water has long T1, fat has short T1). The intensity signal of the signal received by the receiver coil indicates the concentration of the particular substance in the brain but by itself cannot provide information on the location in the brain from which the signal is coming. This information is provided by the third magnetic field, the gradient field, which varies in intensity over the area being imaged. It provides a way to identify particular locations within the static field, thus enabling identification of the location from which signals are emanating. The combination

of spatial information from the gradient field and the signal intensity received after a series of radio-frequency pulses allows a three-dimensional image of the brain to be reconstructed.

1.3.2 Principles of diffusion weighted imaging

Magnetic resonance can be made sensitive to diffusion through a pair of sharp magnetic field gradients pulses, the duration and the separation of which can be adjusted. In diffusion weighted images, instead of a homogeneous magnetic field, the homogeneity is varied linearly by a pulsed field gradient. Since precession is proportional to the magnet strength, the protons begin to precess at different rates, resulting in dispersion of the phase and signal loss. Another gradient pulse is applied in the same direction but with opposite magnitude to refocus or rephase the spins. The refocusing will not be perfect for protons that have moved during the time interval between the pulses, and the signal measured by the MRI scanner is reduced. The reduction in signal due to the application of the pulse gradient can be related to the amount of diffusion that is occurring.

A new weighting scheme is thus introduced in diffusion weighted imaging. The intensity of this image is weighted by translational motion (diffusion) of water molecules. The microscopic motion of water molecules is based on the measurement of Brownian motion related to the thermal energy carried by these molecules. The faster the diffusion process is, the darker the image becomes. In practice, the contrast created in diffusion-weighted images is more complicated. The absolute image intensity of diffusion weighted images is determined not only by the extent of diffusion, but also by proton density reflected in T1 and T2. Moreover, in biological systems water does not diffuse equally in all directions in highly ordered organs such as the brain.

In a free medium with molecules travelling randomly in space, molecular displacements will obey a three-dimensional Gaussian distribution – the molecules will move in space over a distance that is statistically described by a diffusion coefficient. This coefficient depends only on the size of the molecules, the temperature and the nature (viscosity) of the medium. As the water molecules can move freely in all directions, this is called “free” or isotropic diffusion.

In the brain, water diffuses preferentially along axonal fiber directions. In the white matter of the brain, molecules move on a microscopic level, well beyond the usual (millimetric) image resolution. In about 50-100 ms the molecules travel distances of around 1-15 μm, while bouncing off, crossing and interacting with many tissue components, such as cell membranes, fibres and macromolecules. The impediment of such obstacles leads to a reduced actual diffusion distance compared to that of free water movement. Water diffusion is thus restricted, resulting in so-called anisotropic diffusion. The diffusion process in white matter is three-dimensional and water molecular mobility is anisotropic, not necessarily the same in all directions.

Application of DWI to an MRI pulse sequence encodes all forms of motion. Quantification from DWI is therefore described in terms of the **apparent diffusion coefficient** (ADC) which incorporates these

different motions as well as the fact that any pixel is so macroscopically large in dimensions that it comprises a number of underlying diffusion environments (intra-, extracellular and intravascular spaces) and processes, which are averaged together as an ensemble represented by the single ADC term. **Mean Diffusivity** (MD), another diffusion weighted measure, characterizes the overall mean-squared displacement of molecules (average ellipsoid size) and the overall presence of obstacles to diffusion (orientation of the ellipsoid). Mean diffusivity is rotationally invariant and represents the total diffusion within a voxel.

1.3.3 Magnetic Resonance Diffusion Tensor Imaging

The gradient pulses for diffusion can be applied on any of the gradient axes, so the resultant image can be made sensitive to diffusion processes in different directions. This is of particular utility in the characterization of anisotropic diffusion. Acquiring diffusion weighted images with diffusion sensitization in different directions allows both the magnitude and orientation of anisotropy to be determined. In order to accurately depict the direction and degree of anisotropy DTI is used. This technique refers to a technique in which diffusion is considered as a tensor quantity rather than a scalar. To 'solve' the diffusion tensor, at least six different directions of diffusion encoding are needed. The tensor is usually described in terms of three coordinate axes with the principal axis being the direction of preferred diffusion. It is difficult to depict tensor data, but the concept of 'diffusion ellipsoid' has been proposed to make it imaginable (Basser, Mattiello, and Le Bihan; 1994). This three-dimensional ellipsoid is a representation of the diffusion distance covered in space by molecules in a given diffusion time. In the case of isotropic diffusion, the ellipsoid is simply a sphere. In the case of anisotropic diffusion, the ellipsoid becomes elongated (cigar shaped) if one diffusion direction predominates, or flat (pancake shaped) if one direction contributes less than the others. The **eigenvectors** define the orientation of the anisotropic diffusion 'ellipsoid', the diffusion tensor **eigenvalues** describe the degree of directional preference in a region. The three diffusion directions are labelled as approximately along the direction of maximum diffusion (λ_1), along the direction of minimum diffusion (λ_2), and along the third direction (λ_3), which is orthogonal to the other two directions. The main diffusion eigenvalue along the principal direction is often referred to as the **longitudinal diffusivity** (λ_1), whereas the mean of the non-principal eigenvalue is known as the **transverse diffusivity** (mean of λ_2 and λ_3). The isotropic **Apparent Diffusion Coefficient** (ADC) (see also above) is the average of the three diffusion eigenvalues (refer to Figure 5). **Fractional Anisotropy** (FA) is the widely used scalar invariant reflecting the variance of the three diffusion tensor eigenvalues, or in other words the description of degree of white matter anisotropy. This variable varies between 0 and 1. The highly ordered white matter has high fractional anisotropy values, whereas grey matter has lower fractional anisotropy.

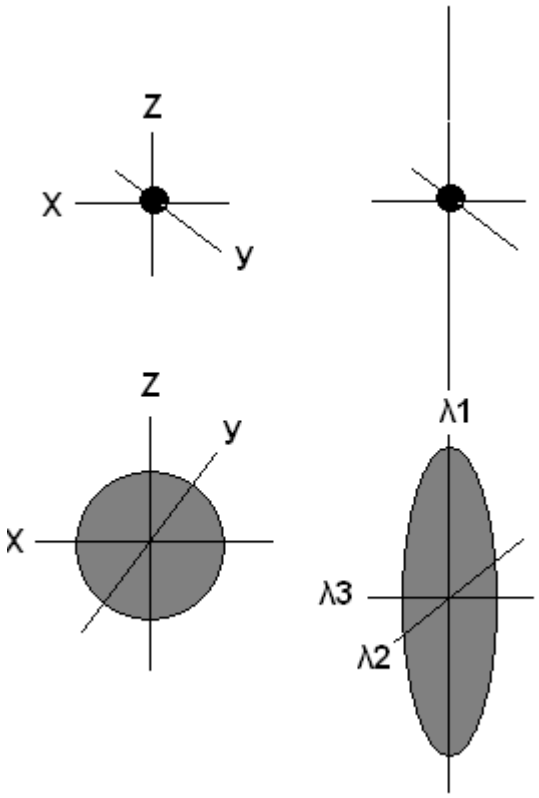

Figure 5 Relation between anistropic diffusion (upper row) and diffusion ellipsoid (bottom row). When the environment is isotropic (left) water diffuses equivalently in all directions. The diffusion ellipsoid of this system is spherical. When the environment is anisotropic water diffusion has directionality (right). The diffusion ellipsoid of water is elongated (for instance in a cylinder) and has three principal axes, λ_1, λ_2 and λ_3.

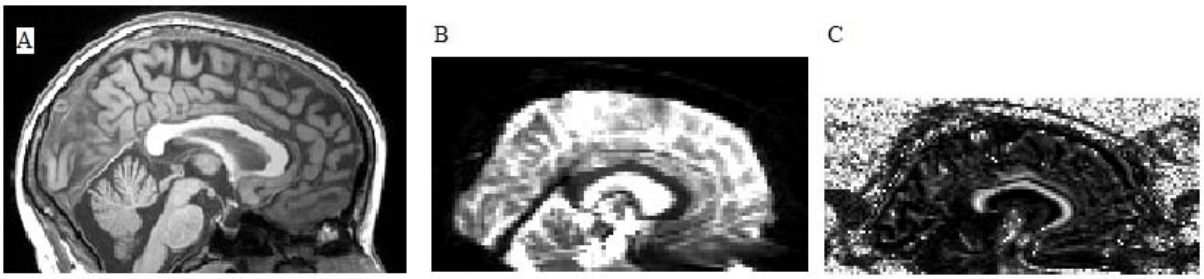

Figure 6 Example of an MRI image, T_1-weighted image (a), an DWI image acquired with a b value of 0 s^2/mm (b) and a pixel-by-pixel FA map (c). All images are from the same MS patient.

1.3.4 Diffusion weighted imaging and diffusion tensor imaging in multiple sclerosis

The first report of diffusion weighted imaging in MS was by Larsson et al. in 1992 showing an elevated mean diffusivity coefficient in T2 visible lesions. Not surprisingly, all studies have shown elevated mean diffusivity in different brain areas in MS patients compared to healthy controls (Cercignani et al., 2000). In MS patients the mean diffusivity was markedly higher in MS induced lesions as seen on T2 weighted scans, than in the normal appearing white matter (Horsfield et al.,

1996; Droogan et al., 1999; Werring et al., 1999; Bammer et al., 2000; Cercignani et al., 2000). The degree of elevation depends on different factors (clinical course, disease subtype,…). In some lesions however a diffusivity close to that of pure water at body temperature could be found. Comparison of diffusion measures with other MR derived measures like T1 weighted hypointense lesions or lesions with low magnetisation transfer ratio values indicates that lesions with more destructive pathology are generally shown to have the most strongly elevated diffusivity (Horsfield et al., 1996; Droogan et al., 1999; Werring et al., 1999; Bammer et al., 2000; Cercignani et al., 2000; Nusbaum et al., 2000). Numerous diffusion weighted imaging studies of MS have also consistently shown that the apparent diffusion coefficient or the mean diffusivity values of normal appearing white matter (non-lesion containing tissue) are higher than those of white matter from healthy controls, but lower than those in T2 visible lesions (Cercignani et al., 2002; Cercignani et al., 2001; Filippi et al., 2001; Ciccarelli et al., 2001; Werring et al., 2001).

Several diffusion tensor studies show that diffusion fractional anisotropy is generally reduced in MS lesions (Werring et al., 1999; Bammer et al., 2000). Reduced diffusion anisotropy could result from damage to and removal of highly aligned cellular structures such as axons or from replacement of axonal fibers with more amorphous cells such as glial cells. In addition, research showed that fractional anisotropy of normal appearing white matter in MS is lower than of corresponding white matter from controls and higher than those of T2 visible lesions (Werring et al., 1999; Filippi et al., 2000; Bammer et al., 2000; Ciccarelli et al., 2001; Filippi et al., 2001; Cercignani e al., 2001). The magnitude of correlation between diffusion imaging derived metrics reflecting water diffusivity (MD) and those reflecting tissue anisotropy (FA) in the normal appearing white matter is highly variable from one study to another (Ciccarelli et al., 2001; Filippi et al., 2001; Cercignani et al., 2001), being moderate at best. This suggests that the study of water diffusivity and anisotropy can provide complementary information, but also that MS tissue damage may affect diffusion tensor imaging derived indices differently in accordance with the heterogeneous aspects of normal appearing white matter pathology.

Researchers recently have suggested that the reduction in fractional anisotropy within the normal appearing white matter is primarily due to an increase in transverse diffusivity rather than a change in the magnitude of the principal eigenvector (Henry et al., 2003; Oh et al., 2004). This is of special interest as similar changes were demonstrated in animal models of demyelination (Song et al., 2002, 2005) and Wallerian degeneration (Beaulieu et al., 1996; Stanisz et al., 2001). These results could thus indicate a specific marker of structural changes related to the neuropathology in MS.

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1.4 Aim and Overview

The main aim of this thesis is to explore the relation between MS related cerebral damage as defined by diffusion magnetic resonance techniques and neuropsychological problems related to the disease. This aim is related to more specific goals:

- **Chapter 2.1** Investigate the usefulness of the redundancy gain paradigm to evaluate interhemispheric communication in MS. This paradigm is tested in seventeen mildly to severely disabled MS patients (EDSS 0 to 7) and seventeen matched healthy controls.

- Replicate earlier research indicating decreased FA and increased MD in MS, more specifically in the corpus callosum. Define FA and MD in the corpus callosum of MS patients and compare the obtained values with DTI derived values in matched healthy controls.

- Explore the relation between pathological callosal white matter damage and the redundancy gain which is the behavioural measure for interhemispheric communication. Define callosal FA and MD in the MS and matched healthy control subgroup, and compare the behavioural performance for the high and low callosal injured MS group to find out if more callosal damage is reflected in more violations of the race model.

- Define the crossed-uncrossed difference, another important behavioural measure for interhemispheric conduction delay in both MS and healthy controls to find out if MS patients have a prolonged CUD.

- **Chapter 2.2** Measure transverse and longitudinal diffusivity in the corpus callosum of sixteen MS patients and sixteen matched healthy controls to replicate previous studies that indicate increased transverse diffusivity and not longitudinal diffusivity in MS as a benchmark of MS related pathology.

- Explore the correlation between redundancy gain and diffusion derived measures (FA, longitudinal and transverse diffusivity) and investigate the additional predicting value of callosal lesion load defined by conventional MRI in explaining the redundancy gain.

- **Chapter 3** Evaluate processing speed in 15 MS patients using the two most common neuropsychological tests (PASAT and SDMT). Compare the performance on PASAT and SDMT.

- Explore the contribution of brain damage related in MS, defined with diffusion derived metrics (FA, transverse and longitudinal diffusivity) to processing speed.

Personal contribution of Nele Warlop

Nele was responsible for the set up, the used methodology, all statistical analyses, and the writing of the manuscripts in this thesis. She personally tested and scanned all patients and controls included in the study.

Chapter 2

Diffusion Weighted Callosal Integrity Reflects Interhemispheric Communication Efficiency in Multiple Sclerosis

2.1 Introduction

The two papers included in this chapter focus on interhemispheric communication in MS. The redundancy gain paradigm is used in both studies. The aim of the first study is to evaluate the use of this paradigm in an MS group and compare the redundancy gain effect in the MS group with the effect in a matched control group. Callosal damage is evaluated in the MS group by use of the diffusion tensor imaging technique, by measuring callosal fractional anisotropy and callosal mean diffusivity. By combining the information on the behavioural measure and the MRI measures (FA and MD) the relation between the redundancy gain and callosal damage is investigated.

The relation between the redundancy gain and callosal FA and MD, as indicated in the first paper, is further explored in the second paper. This newly found correlation is compared with the correlation for more classic measures of callosal lesion load (lesion load). Moreover, next to correlations for FA and MD, correlations for longitudinal and transverse diffusivity, two DTI parameters that recently get a lot of attention in the light of the specific MS related pathology, are explored.

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BRAIN RESEARCH

Research Report

Callosal function in MS patients with mild and severe callosal damage as reflected by diffusion tensor imaging

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ABSTRACT

In this study, callosal function was behaviourally tested in MS patients with a redundant stimuli task. Reaction times to uni- and bilateral visual stimuli are recorded. Normal subjects respond faster to bilateral than to unilateral stimuli. This effect is called the redundancy gain effect. In patients with agenesis of the corpus callosum, the redundancy gain exceeds that predicted by probability summation, suggesting a mediating influence of the corpus callosum in healthy controls. The aim of this study is to investigate the effect of callosal damage on the redundancy gain in MS patients by investigating the probability summation model. Seventeen MS patients and as many matched healthy controls performed the redundancy gain task. In order to objectify callosal damage in our MS group, diffusion tensor imaging (DTI) derived measures such as fractional anisotropy (FA) and mean diffusivity (MD) in the corpus callosum were obtained. Callosal FA and MD significantly differed in our MS group compared to the healthy controls, indicating pathological callosal involvement. Since the amount of callosal damage was highly variable within the MS group, the MS cohort was split into a low and a high callosal-injured group as quantified by FA. The high FA group performed like the healthy controls, whereas violations of the probability (*race*) model were found for the low FA group. We conclude that behavioural measures obtained by the redundancy gain paradigm reflect callosal pathology in MS as measured by DTI.

1. Introduction

The redundancy gain paradigm, a task where visual stimuli are presented to the left, right, or both visual hemifields simultaneously, offers reliable information about interhemispheric processing (Corballis, 1998; Reuter-Lorenz et al., 1995). In healthy controls, response to bilateral conditions is faster than to unilateral conditions (Corballis, 1998). This effect is called the redundancy gain effect. It is suggested that the effect emerges due to probability summation (Raab, 1962) which reflects a 'race' between two independent processes. In analogy with horses racing, the visual input from both hemifields in each hemisphere independently races through all processing, with the fastest resulting in the given response. Thus in the bilateral condition, there are two chances of getting a fast response in comparison to the one chance in the

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unilateral condition: faster mean reaction times will be recorded for bilateral conditions rather than for unilateral conditions. Probability calculus can be explored by the statistical methods first described by Corballis (1998) in order to test if the predictions of the probability (*race*) model are violated. The assumption is that violations of the model indicate neural interaction between the responses to the two stimuli, or in other words neural summation between both hemispheres. If the cumulative distribution of reaction times to bilateral stimuli is faster than can be accounted for by probability summation, the probability (*race*) model is violated, an *enhanced* redundancy gain is observed and neural summation between the two hemispheres is assumed (Corballis, 1998; Corballis et al., 2002).

Different possible explanations are proposed for the *enhanced* redundancy gain effect, somewhat paradoxically found in split-brain patients and in patients with corpus callosum agenesis (Corballis, 1998; Corballis et al., 2003; Iacoboni et al., 2000; Reuter-Lorenz et al., 1995). A first model states that the enhanced redundancy gain is primarily due to speeded bilateral reaction time (Iacoboni et al., 2000). The basis mechanism in this model is the inhibitory function of the corpus callosum, with neural summation operating at subcortical level via the superior colliculi. This whole process is fed by visual input, with large input sending strong signals from the extrastriate cortex to the premotor cortex resulting in speeded response.

An alternative model proposed by Reuter-Lorenz et al. (1995) assumes that the enhanced redundancy gain is due to reaction time slowing to unilateral stimuli. Reuter-Lorenz et al. (1995) suggest that the corpus callosum ensures response readiness (release of response inhibition) of both hemispheres, which activates a logical AND gate. Activation of the AND gate requires input from both hemispheres. Whereas in healthy subjects unilateral stimuli will activate the AND gate via the well functioning corpus callosum, in split-brain patients unilateral stimuli do not activate the AND gate, and consequently the motor commands of both hemispheres conflict, resulting in inhibition. In bilateral conditions the AND gate will be satisfied as the stimuli in both hemispheres generate response readiness. A somewhat similar model is the neural summation model which assumes that interhemispheric transfer creates bilateral neural summation even when the input is unilateral in healthy controls, but not for split-brain patients. In these patients neural summation only emerges in bilateral conditions (Roser and Corballis, 2002).

In addition to the test for probability (*race*) model violations, a quantitative outcome measure of the redundancy gain paradigm is the crossed–uncrossed difference (CUD). This is the mean difference between reaction times for the crossed conditions (for example, visual stimuli presented to the left visual field and right-hand response or vice versa) and the uncrossed conditions (for example, left visual hemifield representation and left-hand response or vice versa). This measure is used as an indication for the callosal transfer time. In healthy controls, it has been shown that the CUD ranges between 2 and 6 ms (Poffenberger, 1912). Research in callosotomy patients indicated that the CUD in those patients was significantly larger than in healthy controls (Corballis et al., 2003). It can be hypothesized that the more injured the corpus callosum, the longer the interhemispheric transfer times will be.

The aim of this study is to investigate interhemispheric communication efficiency in Multiple Sclerosis (MS) patients compared to healthy controls using the redundancy gain paradigm. Due to the preferential pathological impact of the disease on the corpus callosum (Ge et al., 2004), there are good reasons to hypothesize an enlarged effect in this population compared to healthy controls. Although the strength of the redundancy gain paradigm lies in its simplicity and the ability to calculate different measures for interhemispheric functional efficiency based on reaction times, research with this paradigm in MS is scarce.

To objectify callosal damage in MS, we used the Diffusion Tensor Imaging (DTI) technique. With this technique in vivo measures of subtle white matter tract integrity can be provided, which is extremely valuable in studying MS. Fractional anisotropy (FA) reflects the coherence of the orientation of white matter tracts. This is typically lower in inhomogeneous tissue fibre. Mean diffusivity (MD) quantifies the overall amount of water diffusion at a voxel, regardless of the direction of diffusion. MS-related pathological changes like demyelination can modify the integrity of white matter tracts, leading to DTI detectable changes. In MS, it has been shown that FA values of white matter lesions are decreased, whereas MD is increased (Larsson et al., 1992; Christiansen et al., 1993; Werring et al., 1999; Bammer et al., 2000; Filippi et al., 2001; Ge et al., 2004;). Moreover, earlier reports highlighted DTI derived anisotropy decline, even in normal appearing white matter (Christiansen et al., 1993; Werring et al., 1999; Bammer et al., 2000; Cercignani et al., 2001; Lin et al., 2007). Callosal damage in MS patients, indicated by DTI measures, is expected to result in an enhanced redundancy gain effect. The purpose of the present study is to examine if the redundancy gain paradigm is a valuable behavioural measure to investigate callosal damage in MS. Hence, it is hypothesized that the amount of callosal damage in MS patients as measured by DTI will be reflected in the performance on the redundancy gain paradigm, with patients with more callosal damage showing more behavioural indications for callosal deficiency (enhanced redundancy gain effect).

As functional and anatomical gender differences for the corpus callosum are described (Clarke and Zaidel, 1994; Bishop and Wahlsten, 1997; Westerhausen et al., 2004), this explorative study was limited to one gender. Gender differences point to a larger relative corpus callosum in women compared to men (Johnson et al., 1994; Clarke and Zaidel, 1994). Moreover, animal studies demonstrate the effect of hormones on corpus callosum anatomy (Fitch et al., 1990, 1991). Diffusion studies showed decreased fractional anisotropy in the female compared to the male corpus callosum (Westerhausen et al., 2004; Shin et al., 2005). For a thorough discussion on gender differences in the corpus callosum structure we refer to Bishop and Wahlsten (1997). In addition, gender differences in callosal functioning are also described (in dichotic listening see Hughdal, 2003; evoked potential studies see Burnison et al., 1993). As women are more often affected by MS (Noseworthy et al., 2000), we opted to only include women. The effect of handedness on CC size and function, interacting with gender, remains questionable, with some authors

showing evidence for handedness effects (Clarke and Zaidel, 1994; Moffat et al., 1998) and others not (Steinmetz et al., 1992, 1995; Jäncke et al., 1997). For this reason and for reasons of sample homogeneity we only included right-handed subjects.

2. Results

2.1. *Diffusion derived measures: fractional anisotropy and mean diffusivity*

A t-test revealed that the FA for MS patients was significantly lower than for the healthy control group in the corpus callosum ($t(32) = B2.10$; $p<0.05$). Mean diffusivity also differed significantly for the MS patients compared to the control group as revealed by a t-test ($t(32) = -4.19$; $p<0.001$). These results are in line with other research indicating lower FA and higher MD in the corpus callosum for MS patients (Filippi et al., 2000; Coombs et al., 2004).

For mean DTI measures, refer to Table 1. The DTI measures (FA and MD) were not correlated with the Kurtze Expanded Disability Status Scale (EDSS) (Kurtze, 1983), a measure of disability (mean EDSS 2.25, with SD 0.24).

2.2. *Redundancy gain task*

A first inspection of the behavioural data revealed that, on average, MS patients did not miss significantly more trials of the redundancy gain task than the healthy controls ($t(16) = -0.86$; $p=0.40$). 1.75% (SD = 1.45) of all trials were missed for the MS patients against 1.27% (SD = 2.08) for the healthy controls. In all further analyses, reaction times shorter than 100 ms and longer than 1500 ms were considered as anticipatory and attentional errors and were removed from the analysis.

A 2 (group) × 2 (visual hemifield) ANOVA repeated measures was performed on mean reaction time data. The first factor "group" is a between-subject factor referring to the control versus the MS group. The second factor "visual hemifield" is a within-subject factor referring to the unilateral left, unilateral right and bilateral stimuli condition. The overall mean reaction time for healthy controls is 153.52 ms with SD = 59.89. MS patients responded on average in 191.69 ms (SD = 48.59). The mean response time did not significantly differ for those two groups, however there was a trend ($F(1,30) = 4.02$, $p=0.054$).

The overall mean response latency to unilateral right stimuli conditions was 177.76 ms (SD = 52.14), to unilateral left stimuli response was given on average in 179.50 ms (SD = 52.14) and to the bilateral presentation response was given on average in 160.55 ms (SD = 54.31). The ANOVA analysis revealed that the response latencies for the three conditions did significantly differ ($F(2,60) = 30.366$; $p<0.001$). Additional t-tests showed that the overall mean reaction time to unilateral left stimuli conditions was significantly longer than the overall mean reaction time to bilateral stimuli ($t = -7.051$, $p<0.001$), and that the overall mean reaction time to unilateral right stimuli was significantly longer than the overall mean reaction time to bilateral stimuli conditions ($t = -8.826$, $p<0.001$). The overall mean reaction time to unilateral left stimuli did not significantly differ from the overall mean reaction time to unilateral right stimuli ($t = -0.006$, $p=0.995$).

It was also investigated if the difference in reaction time between the uni- and bilateral stimuli condition differed between the MS group and the healthy control group. This interaction failed to reach significance ($F(2,60) = 1.67$; $p=0.19$), the reaction time difference between uni- and bilateral stimuli conditions was similar for both groups.

2.3. *Testing the probability (race) model*

The probability (*race*) model inequality was investigated by calculation of both the formula given by Corballis (1998), $P_{ic} - (P_i + P_c - P_i P_c) > 0$, with P_{ic} the probability of responding to the stimuli in bilateral conditions, P_i the probability of responding to ipsilateral stimuli and P_c the probability of responding to contralateral stimuli, and the formula proposed by Miller (1982) $P_i P_c - (P_i + P_c) > 0$. See Experimental procedures Section 4.2.2 for more details on these formulas.

As can be seen in Figs. 1 and 2, it is clear that for both formulas the curve lies below zero for the control group; in other words, there are no indications for a violation of the probability (*race*) model. For the whole MS group, no violations were found either.

In order to filter out the MS patients with little or no callosal damage as defined by DTI-measures, we dichotomized our MS group. A median split was performed to divide the MS group into two subgroups, a high and a low FA group (FA higher or lower than 0.68). The mean FA in the low FA group differed significantly from the mean FA in the control group ($t(24) = -4.73$; $p<0.001$), whereas the mean FA for the high FA group did not differ from the control group ($t(23) = 0.55$; $p=0.55$). Mean FA for the high FA group was 0.73 (SD = 0.043) and mean FA for the low FA group was 0.63 (SD = 0.045). An independent t-test was performed in order to compare the EDSS score in the low and high FA MS subgroup. The physical disability as measured by EDSS did not differ between both groups ($t(15) = 1.52$, $p=0.15$, mean for the low FA group of 3, with SD of 2.52 and for the high FA group of 1.44, SD = 1.64).

The probability (*race*) model was tested with the formula given by Corballis for both the low and high FA group, and the results are plotted in Fig. 1. The difference between the two plots is obvious: the model is violated for the low FA group, but not for the high FA group. Violations of the model were situated in the fastest response bins, and overall the curves were parallel for both groups for the slower reaction times. Testing the probability (*race*) model by the formula proposed by Miller (1982) revealed the graphs as depicted in Fig. 2. Again violations of the model were limited to the low FA group of MS

Table 1 – Characteristics of the high and low FA subgroup

	Controls	MS	Significance
Age	37.41 (9.46)	37.76 (8.35)	NS
Years of education	15.35 (2.69)	14.47 (3.02)	NS
Fractional anisotropy	0.72 (0.045)	0.68 (0.061)	$p<0.05^{*}$
Mean diffusivity	0.83 (0.11)	1.04 (0.17)	$p<0.001^{**}$
EDSS		2.25 (0.24)	

EDSS was reported for the MS group.

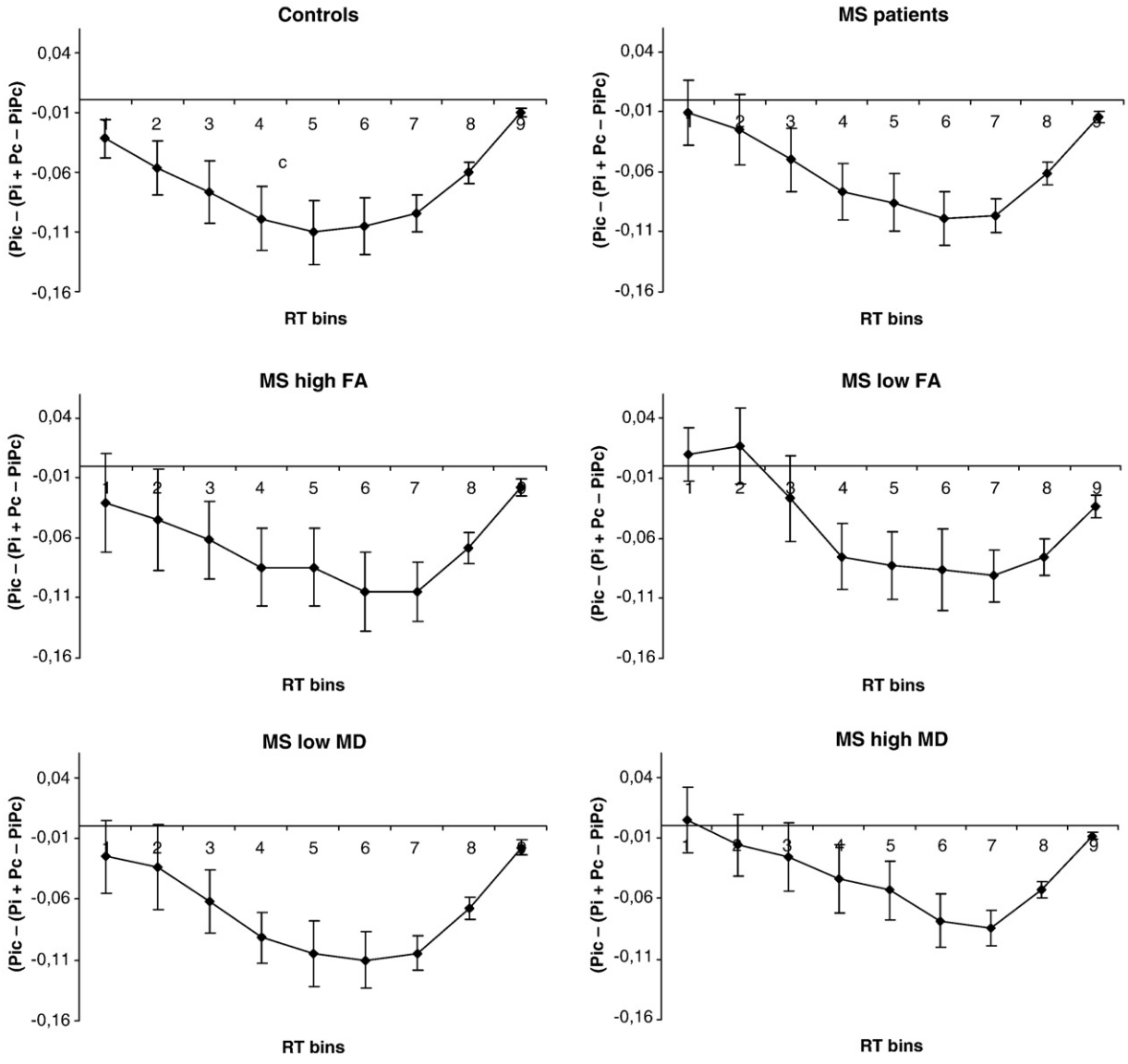

Fig. 1 – Cumulative plots of expression $P_{ic}-(P_i+P_c-P_i\,P_c)$ for the control and the MS group (top). Plots for the MS patients, split up by high (centre left) and low (centre right) FA, or by MD (low MD, bottom left and high MD, bottom right). Violations of the probability (*race*) model are indicated by points above the zero line, that is when the expression $P_{ic}-(P_i+P_c-P_i\,P_c)$ exceeds zero.

patients. For the shortest three response bins the curve lies above zero but the curve is parallel to the curve for the controls. For the high FA group the curve is almost similar to the curve for the healthy controls.

Similar analyses were performed for MD in order to explore the probability (*race*) model in different MS subgroups. For these additional analyses, we performed a median split (median=.96*10^{-3} mm^2/s) split within the MS group based on MD, the low MD group had a mean diffusivity of 0.92*10^{-3} mm^2/s (SD=0.039*10^{-3} mm^2/s) and the high MD group had a mean diffusivity of 1.2*10^{-3} mm^2/s (SD=0.15*10^{-3} mm^2/s). The difference between MD for the high and low MD group reached significance ($t(15)=-3.20$; $p<0.05$). Probability (*race*) model violations could be found for high MD group, but not for the low MD group (refer to Figs. 1 and 2).

2.4. *Crossed–uncrossed difference (CUD)*

The CUD was calculated by subtracting median reaction time for the uncrossed conditions (right visual hemifield (RVH)/right hand (RH), left visual hemifield (LVH)/left hand (LH)) from the crossed conditions (RVH/LH, LVH/RH) and dividing the result by two (Poffenberger, 1912). The overall CUD did not differ between the MS patients and the healthy controls and was within the normal range (2.5–4 ms) for both groups (Bashore, 1981; Marzi et al., 1991). The mean CUD within the control group was 2.28 ms (SD=6.86), whereas the mean CUD for the MS group was 2.78 ms (SD=12.86). The CUD was not significantly different between both groups ($t(16)=-0.14$; $p=0.89$). To investigate if there was a relation between CUD and each of the obtained DTI

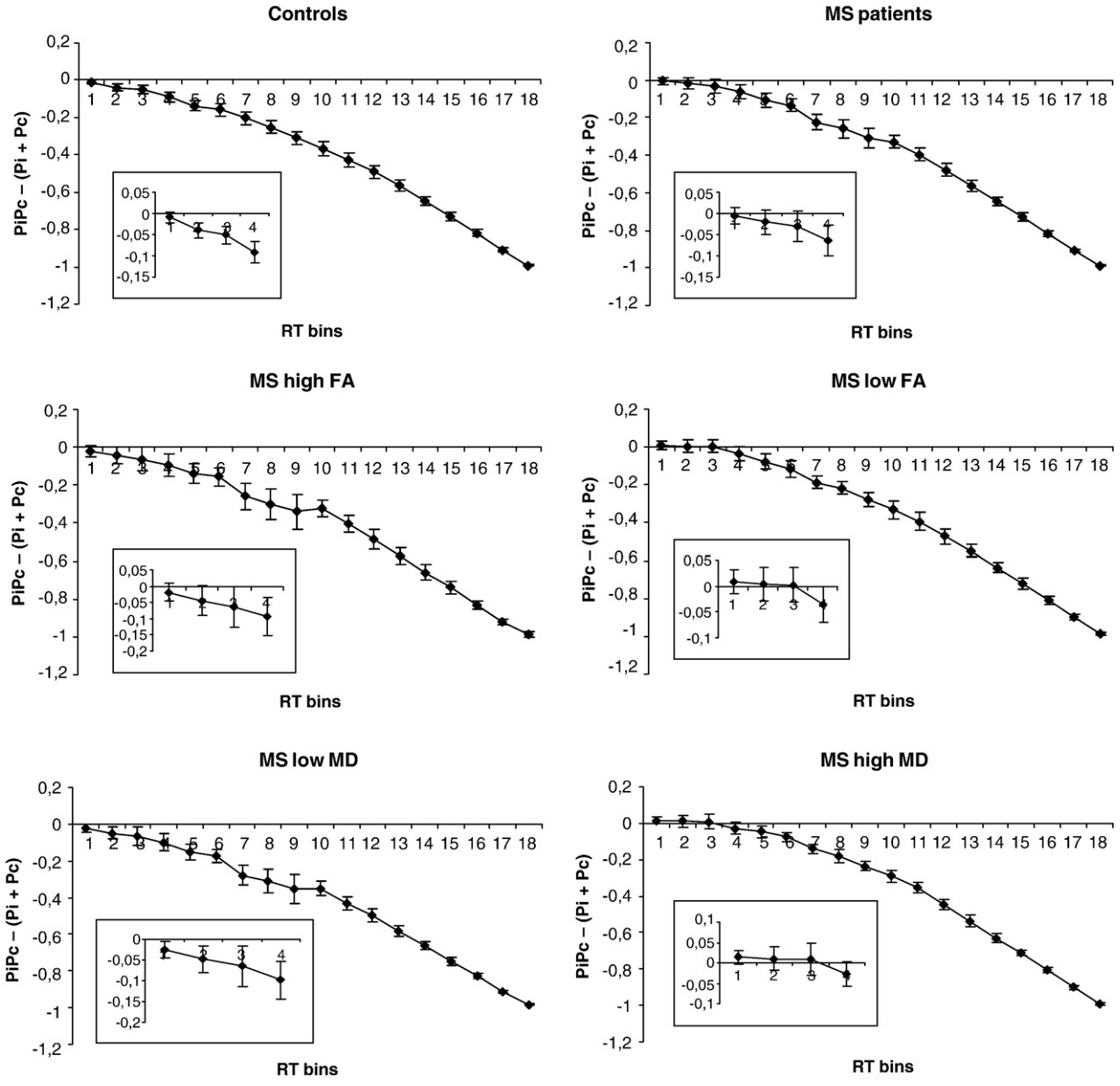

Fig. 2 – Cumulative plots of mean values of $P_iP_c-(P_i+P_c)$ (see text) over 18 response bins for the control group and the MS patients (top). At the bottom the plots for the high (left) and low (right) FA MS subgroup are depicted at the centre, and for low MD (left) and high MD (right) at the bottom. Violations of the Miller formula are indicated by points above the zero line, that is when the expression $P_iP_c-(P_i+P_c)$ exceeds zero. In the box at the left bottom of each graph an enlargement for the fast responses is shown.

measures, a series of correlation analyses was performed, more specifically between CUD and FA and MD. None of the correlations reached significance.

3. Discussion

In this study, the redundancy gain was assessed in MS patients relative to age- and education-matched healthy controls in order to investigate callosal efficiency in MS. Bilateral trials were responded to faster than unilateral trials for both the control and the MS group. Earlier research using letter stimuli similarly found a significant bilateral field advantage in healthy controls and MS patients (Brown, 2003). The CUD, a measure for interhemispheric transfer time, was also investigated in our sample. We were unable to find a prolonged CUD for the MS group. The interhemispheric transfer time was within the normal range for the controls as well as for the MS group (Bashore, 1981; Marzi et al., 1991). This is in line with the results of the study by Tomaiulo et al. (2003) that also did not find evidence for a longer CUD in MS compared to controls.

As interhemispheric communication is best understood by examination of cumulative distributions (Corballis et al., 2002) we found the probability (*race*) model suitable to be investigated for this purpose. For the control group, plots testing the probability (*race*) model revealed no violations of the model, consistent with previous findings in healthy

controls (Corballis, 2002; Reuter-Lorenz et al., 1995). However, when testing the probability (*race*) model in MS patients, a slight violation of the model could be demonstrated, limited to the fastest response bins. Since callosal white matter damage in MS is accepted to be a heterogeneous condition (Wilson et al., 2001), callosal damage in the MS group was quantified by DTI measures. In our study, callosal FA and MD significantly differed between the MS group and the control group, indicating that callosal damage was apparent in our MS population. This result is in line with earlier findings indicating that MS-related pathological changes (demyelination and axonal loss) modify the integrity and permeability of white matter in MS patients' brains (Werring et al., 1999; Ge et al., 2004; Filippi et al., 2001).

In order to explore the relation between probability (*race*) model violations and callosal damage, we performed a median split based on FA and MD to dichotomise the MS group into a low and high callosal-damaged group. Probability (*race*) model violations were restricted to the patient subgroup with low FA. The high FA subgroup performed the same as our healthy control group. When we dichotomised the MS group on MD, only the high MD-subgroup showed violations of the model, this effect was however weaker. Based on these results, it is suggested that testing the probability (*race*) model offers an adequate reflection of callosal damage as measured by DTI indices.

In addition, these results indicate that the redundancy gain cannot be explained by a simple race between the processes in the left and right hemisphere and that additional interhemispheric neural mechanisms are responsible for the redundancy gain effect. The fact that reaction times to bilateral stimuli are generally shorter than predicted from a simple race suggests an inhibitory process of the normal functioning corpus callosum. Probability (*race*) model violations within the MS group for this study were only found for the fastest response bins. This could indicate that the fastest processes are primarily affected in MS. In that view overall slowness of cognitive processing is well documented in MS (Olivares et al., 2005). It is possible that the inhibitory (and/or excitatory) processes mediated by the corpus callosum are slowed down, resulting in diminished callosal intervention for the fastest reaction times indicated by probability (*race*) model violations.

This study shows that the redundancy gain paradigm is a valuable behavioural measure to examine callosal efficiency in MS. Moreover, the results of the present study show that performance on the redundancy gain paradigm reflects callosal damage in MS as measured by diffusion magnetic resonance techniques. MS patients with indications for high callosal damage (low FA or high MD) showed a different performance pattern on the redundancy gain paradigm compared to healthy controls or compared to patients with low callosal damage as indicated by DTI (high FA or low MD). A weakness of this study is the exclusion of male patients. Further research should be performed to replicate the results in males. Another shortcoming of this study is that, although interesting, the corpus callosum was not subdivided in regions. It was believed that the cohort of MS patients included in this study was too small to perform this additional analysis. Further research is warranted.

4. Experimental procedures

4.1. *Patients and control participants*

There were seventeen right-handed female MS patients recruited from the outpatient population of the department of Neurology at Ghent University Hospital. All patients were diagnosed according to the McDonald criteria (McDonald et al., 2001) and had the relapsing–remitting MS type. The EDSS ranged between 0 and 7 (mean ± standard deviation: 2.25 ± 0.24). These MS patients did not suffer from other neurological problems. At the time of testing none of the patients had visual optic neuritis as tested by a medical doctor (J.D.B.) or motor deficits in the upper extremities. Some characteristics of the high and low FA group are summarised in Table 2.

An age- and education-matched control group of seventeen right-handed women was also included in this study. The mean age and years of formal education for both groups can be found in Table 1. None of our healthy participants had neurological problems. All participants gave written informed consent to participate in the study according to the institutional guidelines of the Ethics Committee of Ghent University Hospital.

4.2. *Redundancy gain paradigm*

4.2.1. *Acquisition*

The visual stimuli (disks) with a diameter of 2.5 cm (visual angle 2.38°) were presented 6 cm (visual angle 5.7°) from the centre of the screen where a small fixation cross was shown. All stimuli were flashed for 130 ms synchronized with the refresh rate of the computer screen and with a random intertrial interval (300, 400, 500, 600 or 700 ms). Stimulus onset asynchrony consequently was the duration of the stimulus (130 ms) plus the duration of the variable intertrial interval. Stimulus presentation and response recording were supported by a commercially available experiment generator (E-prime, Psychological Software Tools Inc., Pittsburg, PA) (Schneider et al., 2001). Each experimental run consisted of 100 trials in a random order with 30 unilateral right, 30 unilateral left and 30 bilateral trials. Ten catch trials were also included where no stimulus

Table 2 – Mean values (standard deviations between brackets) for chronological age (in years), years of education, fractional anisotropy and mean diffusivity (10^{-3} mm^2/s) for the MS and control group

	Low FA group	High FA group	Significance
Fractional anisotropy	0.63 (0.045)	0.73 (0.043)	$p<0.001^{**}$
Disease duration	3.44 (1.59)	8.00 (3.42)	$p=0.003^{**}$
EDSS	1.28 (1.68)	3.19 (2.34)	$p=0.070$
Steroids	5	8	
Optic neuritis	2	1	

Disease duration is defined as the time (in years) that relapsed that MS was diagnosed in the patients. Standard deviations are between brackets. The number of patients that are on steroids is given for both groups, as well as the number of patients that has a history of optic neuritis. Mean EDSS and FA are given for both groups.

was shown. Subjects were instructed to keep their eyes fixed on the fixation cross and to press the response box as soon as possible when a stimulus appeared. Each participant ran the experiment four times, in two of the runs responses were made with the left hand, and in the other two with the right hand. The hand with which they started was counterbalanced. Before the experimental testing, we presented some test trials in order to check if all patients were able to see the shortly presented stimuli. The experiment took about 15 min to complete.

4.2.2. *Analyses*

The method proposed by Corballis (1998) was used to test the probability (*race*) model inequality: $P_{ic}-(P_i+P_c-P_i\ P_c)$. The cumulative distributions of ipsi-, contra- and bilateral conditions were calculated. All reaction times were sorted in ascending order and divided in reaction time bins, with the first time bin containing the 20 fastest reaction times, the second bin the next 20 fastest reaction times and so on. Nine time bins were defined for each participant. Within each bin the cumulative distribution proportion within all three conditions was calculated. The probability (*race*) model predicts that in bilateral conditions the hemifield stimuli race independently for response resulting in the following expression $P_{ic}=P_i+P_c-P_iP_c$. Violations of the probability (*race*) model are indicated by higher probabilities for bilateral conditions than predicted by the formula $(P_{ic}-(P_i+P_c-P_iP_c)>0)$. Additionally, in the model proposed by Miller (1982) the assumption of stochastic independency between both processes initiated by the two stimuli is relaxed. Here it is assumed that the joint probability must lie between 0 and 1, resulting in the formula $P_iP_c-(P_i+P_c)$. Again, results that are larger than zero for this formula indicate probability (*race*) model inequality. For this analysis we calculated the formula over 18 response bins, these time bins were defined the same way as described above for the formula by Corballis with the only difference that each bin only contained 10 reaction times.

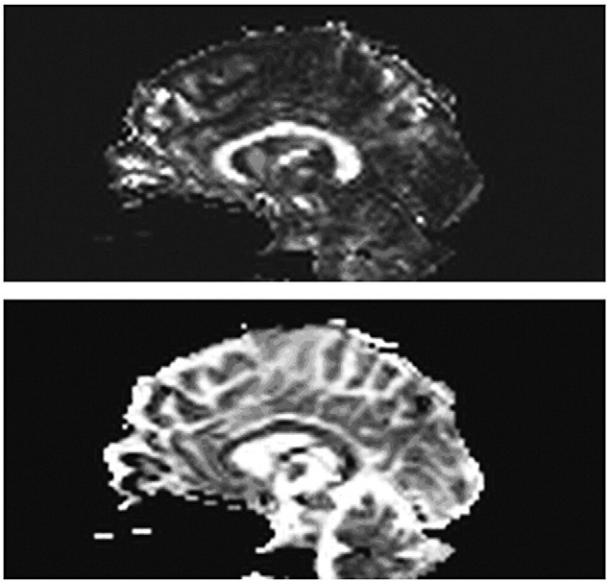

Fig. 3 – Full midsagittal FA (top) and MD (bottom) image of an MS patient.

4.3. *Magnetic resonance imaging*

4.3.1. *Acquisition*

The volunteers all underwent magnetic resonance imaging (MRI) scans, performed on a 3 T Siemens Trio MRI scanner. They were positioned head first and supine in the magnet. Participants were instructed to lie as still as possible to prevent motion artefacts and to restrict head movements, their heads were gently fixed in place by foam cushions. Diffusion weighted imaging was performed in 60 directions with an echo-planar imaging (EPI) sequence with a receiver bandwidth (BW) of 1300 Hz/pixel. A total of 60 slices was acquired in a repetition time (TR) of 10.10 s and with an echo time (TE) of 100 ms. To minimize the influence of eddy currents, a twice-refocused spin echo (TRSE) preparation was used with a *b*-factor of 700 s/mm^2. In addition, 10 averages were taken to obtain a diffusion unweighted image ($b=0$ s/ mm^2). The resolution was 2 mm × 2 mm × 2 mm, with a field of view of 256 mm. No parallel imaging was used and the acquisition time of this sequence was approximately 12 min.

4.3.2. *Image analyses*

FA and MD images were calculated using the DTI task card developed by MGH (for a reference about the algorithms used in this software see Jones et al., 1999). To outline the entire corpus callosum, regions of interest were manually drawn on the midsagittal images obtained with a *b*-value of 0 in the same echo-planar sequence used to provide anatomical landmarks. This method is based on the procedure described by Snook et al. (2005, 2007). The entire corpus callosum was marked on the midsagittal slice and two adjacent slices. Using the image software MRIcro (Rorden and Brett, 2000), the regions of interest were transferred to the FA and MD images and the mean FA and MD in the designated region was calculated. A midsagittal FA and MD slice can be seen in Fig. 3.

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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.

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.

2.2. Redundancy gain task

Visual stimuli (disks) were presented in white on a black LCD-screen controlled by a laptop computer. A commercially available experiment generator (E-prime, Psychological Software tools Inc., Pittsburgh, PA) was used for stimulus presentation and response recording (Schneider, Eschman, & Zuccolotto, 2001). The stimuli had a diameter of 2.5 cm (visual angle 2.38°) and were presented 6 cm (visual angle 5.7°) right and/or left of the middle of the screen where a little fixation cross was positioned. Stimuli were flashed for 130 ms with a random stimulus onset asynchrony (300, 400, 500, 600 or 700 ms). Each run consisted of 100 trials in a random order with 30 unilateral right, 30 unilateral left and 30 bilateral trials. Also included were 10 catch trials where no stimulus was presented. Subjects pressed on the response box as soon as they saw a stimulus either presented to the left, right or both hemifields simultaneously and were instructed to fixate on the fixation cross during the whole experiment. Each subject fulfilled a practice trial first (with uni- and bilateral trials included) in order to test if the participant was able to see the shortly presented stimuli and to respond manually. After the practice trials, four runs were completed. In half of the runs the participants responded with the right hand, the other half was responded to with the left hand. Response hand was counterbalanced between subjects. The experiment took about 15 min to complete.

2.3. Image acquisition

All scans were performed on a 3 T Siemens Trio MRI scanner equipped with echo planar imaging (EPI) capabilities, using an eight channel head coil for radio frequency transmission and signal reception. Participants were positioned head first and supine in the magnet. They were instructed to lie as still as possible in order to prevent motion artefacts. To further restrict head movements, participants' heads were fixed by foam cushions and ear clamps positioned behind the neck and around the head. All subjects had T1-weighted (receiver bandwidth of 180 Hz/pixel, TR/TE = 1550/2.89 ms, FOV 256 mm^2, 176 slices with a 0.9 mm slice thickness and gap 0.45 mm) and FLAIR (TR/TE = 6000/353 ms, FOV 240 mm^2, 160 slices with 1 mm thickness no gap and a matrix size of 256 × 256) images acquired prior to DTI.

Diffusion weighted imaging was performed in 60 directions with an echo-planar imaging (EPI) sequence with a receiver bandwidth (BW) of 1300 Hz/pixel. A total of 60 slices was acquired in a repetition time (TR) of 10.10 s and with an echo time (TE) of 100 ms. To minimize the influence of eddy currents, a twice-refocused spin echo (TRSE) preparation was used with *b*-factors of 0 and 700 s/mm^2. The resolution was 2 mm × 2 mm × 2 mm, with a field of view of 256 mm. The acquisition time of this sequence was about 12 min.

2.4. Image analysis

Lesion load in the corpus callosum and total brain lesion load were both calculated based on the white matter lesions that were detected on the FLAIR images using expectation maximization segmentation (Van Leemput, Maes, Vandermeulen, & Suetens, 1999). In all analyses the relative callosal lesion load was used. This was obtained by dividing the absolute lesion load by the total callosal area. Total callosal area was measured on the sagittal T_1 slice that best presented the midsagittal section, using in-house software for region-of-interest measurement. The outer edge of the corpus callosum was semi-automatically determined using a boundary-detection algorithm with a Canny Edge Filter (Canny, 1986). The number of pixels within this region of interest was summed automatically and multiplied by the pixel size to obtain absolute values (mm^2).

For DTI analyses all DTI images were transferred to an off-line Siemens Leonardo™ workstation. FA and eigenvector images were calculated using the DTI task card developed by MGH (for algorithms used in this software see Jones, Horsfield, & Simmons, 1999). The method for region of interest selection was based on the procedure described by Snook, Paulson, Roy, Phillips, & Beaulieu (2005) and Snook, Plewes, & Beaulieu (2007). Using image analysis software (MRIcro, Rorden & Brett, 2000) the corpus callosum was outlined following its contours on the anisotropy maps obtained with a *b*-value of 0 in the same echo planar sequence used to provide anatomic landmarks. We were very strict in defining the corpus callosum in order to eliminate partial volume effects as much as possible. The corpus callosum was marked on three slices, the midsagittal slice and the two adjoining slices. The obtained regions of interest were transferred to the FA and eigenvector images and the mean FA and eigenvectors (λ_1, λ_2, λ_3) in the designated region of interest were calculated. Transverse diffusivity was defined as the mean of the water diffusivity along the two non-principal directions (λ_2 and λ_3).

Our hypothesis that DTI-derived measures differ between MS patients and the control group was tested by multivariate ANOVA with transverse and longitudinal diffusivity, FA, and callosal size as dependent measures. Further correlation analyses were performed between FA and relative callosal lesion load, and between longitudinal diffusivity and transverse diffusivity and relative callosal lesion load in order to get a clear insight on the relation between both measures.

2.5. Behavioral analysis

For all analyses reaction time data were trimmed. Reaction times shorter than 100 ms and longer than 900 ms were considered as anticipatory and attentional errors and were removed from analyses. Omissions and responses to catch trials ('false alarms') were neither included in the analysis.

A 2 (visual half field, uni- versus bilateral stimuli) × 2 (response hand) × 2 (group) repeated measures ANOVA was performed on the mean reaction times, with visual half field and response hand as repeated within-subjects factors, and group as between subject factor. The difference between reaction time to uni- and bilateral stimuli, was calculated using the formula proposed by Corballis (2002). The formula is given by $[(RT_c + RT_i)/2] - RT_b$ with RT_c the median reaction time to contra-lateral stimuli, RT_i the median reaction time to ipsilateral stimuli and RT_b the median reaction time to bilateral stimuli. For each response hand the redundancy gain was calculated separately. Independent-sample *t*-tests were used to compare the redundancy gain between both groups. A larger redundancy gain was expected for the MS group.

The race model was tested as described by Corballis (1998). The cumulative distribution of ipsi-, contra- and bilateral conditions was calculated. All reaction times were sorted in ascending order and divided in reaction time bins, with the first time bin containing the 20 fastest reaction times, the second bin the next 20 fastest reaction times and so on. In each time bin the cumulative distribution proportion within all three conditions was calculated. The race model predicts that in bilateral conditions, the hemifield stimuli race independently for response, resulting in the following expression $P_{ic} = P_i + P_c - P_{ic}$ with P_{ic} the probability summation of responding to the stimuli in bilateral conditions, P_i the probability summation of responding to ipsilateral stimuli (left visual hemifield (LVH)/left hand (LH) or right visual hemifield (RVH)/right hand (RH)) and P_c the probability of responding to contralateral stimuli (LVF/RH or RVH/LH). Violations of the race model are indicated by higher probabilities for bilateral conditions than predicted by the formula $(P_{ic} - (P_i + P_c - P_i P_c) > 0$. This expression was calculated within each reaction time bin, we averaged the formula over both response hands.

CUD was calculated by subtracting median reaction time for the uncrossed conditions (RVH/RH, LVH/LH) from the crossed conditions (RVH/LH, LVH/RH) and dividing the result by two (Poffenberger, 1912).

2.6. Structural–behavioral associations

To investigate the possible relation between the structural brain imaging measures (FA, longitudinal and transverse diffusivity, and relative callosal lesion load) and the behavioral measures (redundancy gain, CUD), we will first present the results of the different Pearson correlation tests. In a second step we will perform a hierarchical multiple regression in order to contrast two regression models, the first with transverse and longitudinal diffusivity as predictors and the second with relative callosal lesion load as an additional predictor.

3. Results

3.1. Behavioral data

Inspection of the behavioral data revealed that there were 1.9% false alarms, with comparable percentages for both groups (2.1% false alarms for the healthy controls and 1.6% for the MS group). The percentage of missed trials was also comparable for both groups (1.35% omissions for the healthy control group and 1.79% for the MS group). No differences were found between response hands. Hence in total 98.38% of all data were included in further analyses.

The 2 (visual half field) × 2 (response hand) × 2 (group) ANOVA repeated measure revealed a main effect of visual half field ($F(1,30) = 132.32$, $p < 0.001$). Bilateral trials were responded to faster (mean = 158.61 ms, S.D. = 9.96) than unilateral trials (mean = 177.07 ms, S.D. = 10.18). The between subject factor group also showed a marginally significant main effect ($F(1,30) = 4.12$, $p = 0.051$), with a mean reaction time for the controls of 147.47 ms (S.D. = 14.195) and mean reaction time of 188.20 ms (S.D. = 14.195) for the MS patients. No main effect of hand was found. The interaction between visual half field and group also reached significance ($F(1,30) = 6.77$, $p < 0.05$). The interaction graph can be seen in Fig. 1. For both groups the difference in reaction time between bilateral and unilateral conditions was significant at the 0.001 significance level, with an increased redundancy gain for the MS group. The redundancy gain for the MS group lies outside the normal range (−10 to 16) (Corballis, 1998). A *t*-test revealed that mean redundancy gain was significantly larger for the MS than for the control

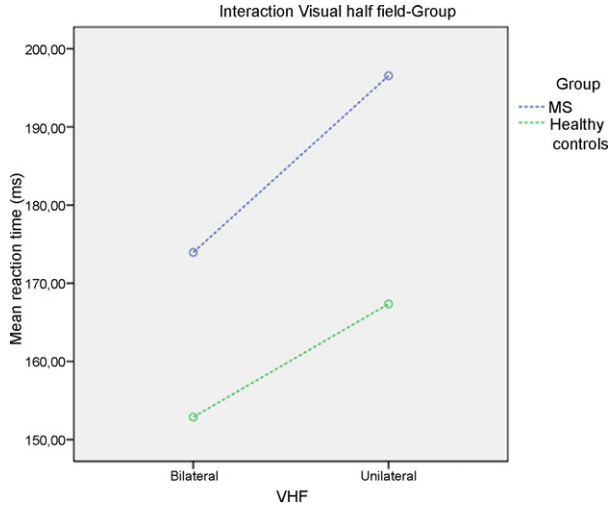

Fig. 1. Interaction between Group (MS and healthy controls) and Visual half field (bilateral and unilateral trials) with mean reaction times in milliseconds (ms) as dependent variable.

group ($t(30) = 2.31$, $p < 0.05$ with mean RG for MS 22.54 ms, S.D. 9.40 and mean RG for the controls 15.44 ms, S.D. 7.92). The race model was tested as described above. No violations of the model were observed for the controls. In MS patients, the formula testing the race model for the fastest two response bins were slightly bigger than zero (both were 0.00196). CUD measures were within the normal range (Marzi, Bisiacchi, & Nicoletti, 1991) for both controls as MS patients (2.39 ms for the controls and 2.95 ms for MS patients) and did not differ between both groups $F(1,30) = 0.062$, $p > 0.05$).

3.2. Structural data

An overview of all structural data for each group can be found in Table 1. In line with our expectations, the MANOVA revealed significant differences in DTI measures between MS patients and controls ($F(4,27) = 3.72$, $p < 0.05$). FA is significantly lower for the MS group compared to the control group ($F(1,30) = 4.83$, $p < 0.05$). Callosal size was significantly smaller for the MS patients ($F(1,30) = 5.20$, $p < 0.05$). There was a significant increase of transverse diffusivity, $(\lambda_2 + \lambda_3)/2$ ($F(1,30) = 12.56$, $p < 0.05$), and longitudinal diffusivity also differed significantly between both groups ($F(1,30) = 7.21$, $p < 0.05$). For transverse diffusivity there was an increase of 31% for the MS patients compared to the controls, whereas there was an increase of only 8% for longitudinal diffusivity in MS patients compared to the controls.

The correlation analysis shows that a lower FA is associated with relative callosal lesion load ($R = -0.505$, $p < 0.05$). Neither transverse nor longitudinal diffusivity correlated with relative callosal lesion load ($R = .445$ with $p = .096$ for λ_1 and $R = .47$ with $p = .079$ for $(\lambda_2 + \lambda_3)/2$).

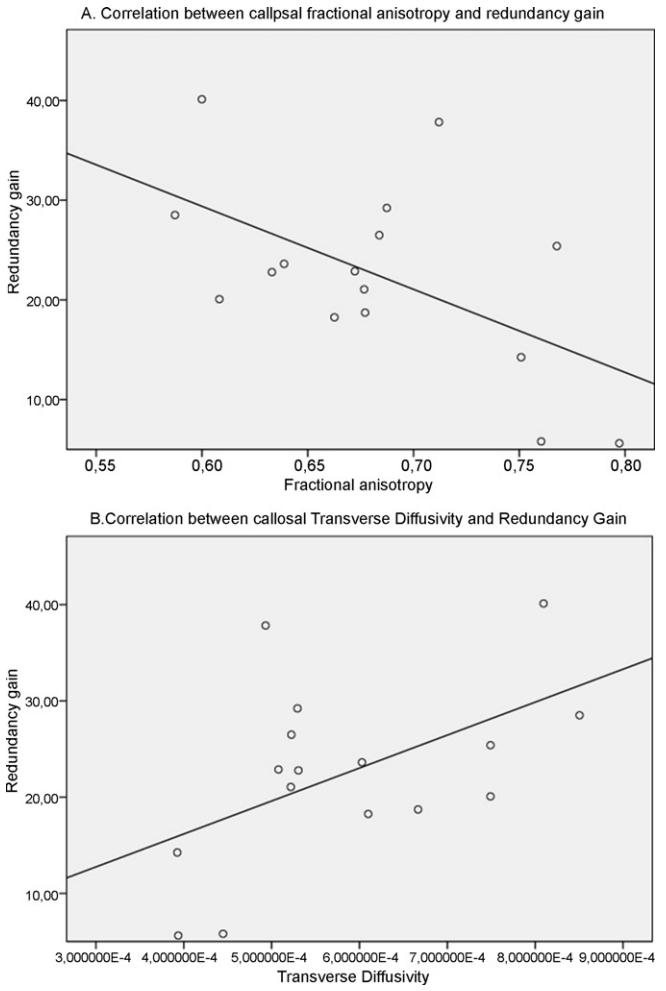

Fig. 2. (A) Correlation between callosal fractional anisotropy and redundancy gain for the MS group. (B) Correlation between callosal transverse diffusivity and redundancy gain in the MS group.

3.3. Structural–behavioral associations

Because both hands did not differ on mean redundancy gain, we performed subsequent analyses with the total average redundancy gain. The correlation analysis was split up by group.

Within the control group none of the correlations reached significance (redundancy gain and FA $R = -0.006$, $p = 0.98$, λ_1 $R = -.15$, $p = .56$ and for $\lambda_2 + \lambda_3/2$ $R = 0.04$, $p = 0.88$). For the MS group we found a correlation between FA and redundancy gain ($R = -0.56$, $p < 0.05$), the correlation is depicted in Fig. 2A. As expected this was a negative correlation indicating a larger redundancy gain as the FA decreases. As shown in Fig. 2B, this correlation was due to the correlation between redundancy gain and transverse diffusivity ($R = 0.52$, $p < 0.05$). The correlation between redundancy gain and longitudinal diffusivity was not significant ($R = 0.37$, $p = 0.16$). The slopes of

Table 1
Mean fractional anisotropy (FA), longitudinal diffusivity (λ_1), transverse diffusivity ($(\lambda_2 + \lambda_3)/2$), and size of the corpus callosum (mm^2) for controls and MS patients

	MS ($n = 16$)	Controls ($n = 16$)	Significance
FA	0.68 (0.062)	0.72 (0.045)	$p < 0.05$
Longitudinal diffusivity λ_1 ($\times 10^{-3}$ mm^2/s)	1.86(0.13)	1.72(0.17)	$p < 0.05$
Transverse Diffusivity $(\lambda_2 + \lambda_3)/2$($\times 10^{-3}$ mm^2/s)	0.57(0.14)	0.43 (0.10)	$p < 0.01$
Callosal area	644.75(115.96)	729.38 (92.57)	$p < 0.05$

Standard deviations are between brackets.

none of the correlations differed between MS and controls. Neither relative callosal lesion load nor total brain lesion load correlated with redundancy gain.

Finally, hierarchical multiple linear regression analyses for the MS group were performed with the following predictor variables: transverse and longitudinal diffusivity, and relative callosal lesion load. This analysis revealed that neither longitudinal diffusivity (R square = 0.28, $p = 0.12$), nor relative callosal lesion load (R square = 0.28, $p = 0.26$) was an additional factor of influence on the redundancy gain. Transverse diffusivity explained 27% of the variance in redundancy gain ($p < 0.05$). As FA and relative callosal lesion load correlate with each other ($R = -0.52$, $p < 0.05$), the linear regression with two predictor variables FA and relative callosal lesion load was not performed.

4. Discussion

The aim of the current study was to investigate the relation between structural callosal damage and behavioral evidence for abnormal interhemispheric processing as assessed by the redundancy gain paradigm. Callosal damage was defined in different ways. First of all, the conventional MR imaging measure of disease burden was defined as relative callosal lesion load, which is the amount of callosal lesion load corrected for corpus callosum surface. In addition, we calculated DTI-derived fractional anisotropy, and longitudinal and transverse diffusivity of the corpus callosum. DTI measures tend to be more sensitive to lesion burden than the conventional measures, especially in normal appearing white matter in MS (Guo, Macfall, & Provenzale, 2002; Vrenken et al., 2006).

4.1. Behavioral data

The results showed a redundancy gain effect for the MS patients: bilateral trials are responded to faster than unilateral trials. The redundancy gain turned out to be larger within the MS patients compared to the controls. Additional analyses testing the race model showed a slightly enhanced redundancy gain for the MS patients. Enhanced redundancy gain has previously been shown in patients with corpus callosum deficiency (callosotomy, callosal agenesis and split-brain patients) (Corballis, 1998; Corballis, Hamm, Barnett, & Corballis, 2002). It has been assumed that probability summation violations indicate some neural summation processes originating in the superior colliculi (Corballis, 2002). In the neural summation model, the corpus callosum has an inhibitory function and callosal damage is supposed to result in impaired inhibitory function of the corpus callosum leading to an enhanced redundancy gain. As evidence for callosal deficits was found in the tested MS group and callosal lesion load was correlated with redundancy gain resulting in an enhanced redundancy gain effect, some further evidence for the neural summation model is provided in this study.

We found no evidence for sensory-motor delay in the MS patients, as CUD was not enlarged for the MS patients compared to the control group. This result is in line with the results of Tomaiuolo, Nocentini, Grammaldo, & Caltagirone (2001), as they found no prolonged CUD in MS patients either. The enhanced redundancy gain without evidence for a prolonged CUD, suggests that the redundancy gain and the CUD rely on different (callosal) mechanisms. For fast responding to crossed stimuli efficient sensory transfer from the visual area in one hemisphere to the motor area in the other hemisphere is crucial. Our data suggest that this process was not delayed in our MS group. It may be that the mild deficits in the tested MS group (patients with mild disability, average EDSS = 2.25) did not lead to detectable sensory-motor delay. It is also possible that the redundancy gain paradigm measure is more sensitive than the CUD measure to pick up small callosal functional problems in MS. In this respect the redundancy gain paradigm offers good prospects to behaviorally explore interhemispheric problems in diseases with supposed callosal involvement like autism (for a review, see Palmen & van Engeland, 2004), schizophrenia (Brambilla et al., 2005), and attention deficit disorder (Valera, Faraone, Murray, & Seidman, 2007). In children with developmental dyslexia the redundancy gain paradigm was already successfully used to get a better insight in interhemispheric deficits (Badzakova-Trajkov et al., 2004).

Callosal involvement in MS is not a new finding; it has been indicated by different studies using different methodologies (Brown, 2003; Pelletier et al., 2001; Ortiz et al., 2000). However, to the best of our knowledge this is the first study investigating the redundancy gain in MS. Callosal damage in MS is subtler and more variable than in callosotomy, callosal agenesis or split-brain patients. The present study shows the sensitiveness of the redundancy gain paradigm in behavioral investigation of interhemispheric function. A limitation of this study is that we did not control the eye movements. It would be valuable to track eye-movements in order to secure fixation in the middle of the screen during the redundancy gain paradigm.

4.2. Structural data

Although the frequency of callosal lesions is particularly high in MS (93% of MS patients) (Gean-Marton et al., 1991), the amount of callosal damage is variable from patient to patient. Diffusion offers a valuable in vivo technique to detect structural abnormalities in normal appearing white matter brain tissue (Guo et al., 2002; Vrenken et al., 2006). In this study a significant decrease of fractional anisotropy for the MS patients was found, which was mainly induced by an increase of mean diffusivity along the non-principal directions. Longitudinal diffusivity, or the diffusivity along the principal direction, was also significantly higher for the MS patients compared to the controls, but appears to be much less affected than transverse diffusivity (31% change versus 8% change). These results are in line with previous studies (Oh et al., 2004; Lowe et al., 2006; Henry et al., 2003). In relapsing-remitting patients diffusivity parameters seemed to be increased compared to controls, with a more pronounced increase in transverse diffusivity than in longitudinal diffusivity. Animal models of MS showed an increased transverse diffusivity (Song et al., 2005). Increased transverse diffusivity thus seems to provide a distinct feature of MS related demyelination and the results of this study supports previous findings.

4.3. Relation between structural measures for callosal damage and redundancy gain

An interesting finding of this study is the significant positive correlation between the redundancy gain and the diffusion-derived measures for callosal involvement. The more callosal damage as defined by callosal fractional anisotropy, the bigger the redundancy gain. Transverse diffusivity was a significant predictor that explained 27% of the variance in redundancy gain. Relative callosal lesion load and longitudinal diffusivity did not significantly increase the proportion of explained variance. This result indicates that the occult MS-related callosal injuries, more specifically the increased transverse diffusivity, contribute to behavioral interhemispheric problems in MS.

Whether the observed callosal dysfunction in MS contributes to the neuropsychological profile of MS (memory decline, information processing slowness) needs further study. The redundancy gain paradigm offers a valuable method to investigate callosal func-

tioning, which is related to callosal damage in MS. Further research should also elaborate the effect of damage in specific callosal areas on interhemispheric communication efficiency. Some authors have suggested that the callosal functional correlate of the redundancy gain is situated in the posterior and anterior callosal areas (Iacoboni & Zaidel, 2003; Tassinari, Aglioti, Pallini, Belucchi, & Rossi, 1994), whereas others suggested that the body of the corpus callosum, connecting the motor cortices of the two hemispheres mediates interhemispheric transmission (Tomaiuolo et al., 2001).

One limitation of this study is that for reasons of sample homogeneity we opted to include right-handed female participants only. Previous research provided evidence for structural and functional gender differences in the corpus callosum (Clarke & Zaidel, 1994; Cowell, Allen, Zalatimo, & Denenberg, 1992; Johnson et al., 1994). Evidence for diffusion differences between men and women in the corpus callosum has also been provided (Shin et al., 2005; Westerhausen et al., 2004), with men showing higher anisotropy. Further research should corroborate the impact of MS pathology on the corpus callosum anatomy and function in men.

5. Conclusion

First of all this study showed, in replication to previous investigations, evidence for callosal damage reflected by callosal area quantifications and DTI-derived measures in a MS cohort compared to age and education matched healthy controls. In addition, we demonstrated that the redundancy gain task, a behavioral measure of interhemispheric communication efficiency, confirms the expected increase in redundancy gain in MS patients. Most importantly, we found a correlation between the DTI-derived measure transverse diffusivity and the performance on the redundancy gain task.

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Chapter 3

Directional Diffusion and Processing Speed in Relapsing-Remitting Multiple sclerosis

3.1 Introduction

This chapter includes the results of a study in which we investigated the relation between MS related brain damage as measured by DTI and performance on classic neuropsychological tests (PASAT and SDMT). There is little research that uses the relatively new DTI technique to investigate the relation between cognitive deficits and brain damage in MS. Moreover, in this chapter the relation between processing speed and longitudinal and transverse diffusivity in the whole brain, recently shown to be parameters of great relevance and specific to MS brain pathology, is explored.

3.2 Directional Diffusion and Processing Speed in Relapsing-remitting Multiple Sclerosis

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Abstract

In this study we investigate the relation between processing speed and brain damage in multiple sclerosis (MS). Cerebral damage in 15 relapsing-remitting MS patients was measured by diffusion tensor imaging. Fractional anisotropy, longitudinal and transverse diffusivity were defined in the cerebral parenchyma. Processing speed in MS patients was measured with the Symbol Digit Modalities test (SDMT) and the Paced Auditory Serial Addition Test (PASAT). A significant correlation was found between performance on the SDMT and the fractional anisotropy in the brain. This correlation was induced by transverse diffusivity, and not by longitudinal diffusivity. These results indicate that diffusivity along the non-principal diffusion direction contribute to processing speed in MS.

Introduction

Despite the many research the relationship between cognitive dysfunctions and cerebral damage in MS remains unclear. Neuropsychological investigations demonstrate that cognitive disorders occur in 45% to 65% of the MS patients (Rao, Leo, Bernardin, & Unverzagt, 1991), including disturbances in memory, executive function, higher order visual-perception, attention and information processing speed (Bobolz and Rao, 2003). In this study the focus will be on processing speed as deficits on tests that primarily measure information processing speed have been considered the most robust neuropsychological findings across various disease stage in MS (DeSonneville et al., 2002; Nocentini et al., 2006; Schulz, Kopp, Kunkel, & Faiss, 2006; Feuillet, Reuter, Audoin, & Malikova, 2007).

The Paced Auditory Serial Addition test (PASAT) (Gronwall, & Sampson, 1974) is commonly used test to measure information processing speed and working memory. This test is included in many cognitive batteries for MS and is, next to two psychical tests (9-hole peg test and the 25ft walk test) the chosen task for cognitive assessment in the MS Functional Composite (MSFC) (Fischer Rudick, Cutter, & Reingold, 1999). The PASAT, in which the patient is instructed to add auditory presented single digits to the previous one presented in the series, puts high load on information processing speed and working memory. Concerns have been raised about the high dropout rate and the scoring method of the PASAT (Tombaugh, 2006).

A good surrogate for the PASAT is the Symbol Digit Modalities test (SDMT) (Smith, 1982). This test involves matching numbers with symbols and assesses executive function, concentration and speed, with a lower dropout rate compared to the PASAT. Prompted studies question whether a single test can provide good results in estimating the severity of cognitive impairment. Recent research (Deloire et al., 2006; Sepulcre et al., 2006; Parmenter et al., 2007) identified single tests to be better suited for screening instruments for cognitive impairment than extensive test batteries. The SDMT has been proposed as a good screening test for cognitive impairment in MS (Parmenter et al., 2007).

The pathology in MS is defined by diffuse white matter damage, cerebral atrophy, grey matter damage, and ventricle enlargement have been associated with MS. The relationship between the MS related brain damage and cognitive impairment in MS has been a longstanding issue. When reviewing previous research, it is notable that when investigating the relation between brain damage and cognitive performance on a test battery, the correlation between processing speed is the strongest, independent of the brain imaging technique used (Fulton et al., 1999; Sperling et al., 2001; Rovaris et al., 2002; Randolph et al., 2005). New neuroimaging techniques nowadays provide unprecedented ways to examine cerebral damage in MS. In particular, the diffusion tensor imaging (DTI) technique appears very useful as it allows in vivo detection of acute and chronic white matter lesions, and tissue damage outside T_2 – visible lesions (normal appearing white matter) (Werring et al., 1999). Fractional anisotropy (FA) is a commonly used diffusion coefficient. This measure 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 eigen values. FA is typically reduced in MS related lesions and in normal appearing white matter in MS patients (Werring et al., 1999). Although the diffusion technique opens new ways to investigate cerebral damage in MS, research investigating the relation between DTI derived measures and cognitive performance in MS is scarce and not always leads to significant results. In an exploratory study by Rovaris et al. (2002), no correlation was found between SMDT or PASAT score and FA measures in cerebral lesions or FA in the whole brain tissue. In addition, FA differences, either in lesion or in whole brain tissue, between the cognitively impaired patients and intact patients failed to reach significance. In contrast, very recently a strong correlation between diffusion derived measures and performance in different cognitive domains was found between mean diffusivity entropy, a new diffusion derived analysis defined as the calculation of diffusion measures within the parenchyma, and performance on the SDMT (Benedict et al., 2007). The special characteristic of diffusivity entropy is that this measure is sensitive to individual signal intensities over all possible intensities, with increased entropy as the distribution of these intensities becomes more homogeneous. Furthermore, this study indicated that mean parenchymal diffusivity entropy differed significantly between cognitive intact and impaired patients.

The purpose of the present study is to further investigate the relation between diffusion tensor imaging measures in the brain parenchyma and processing speed as measured by the PASAT and the SDMT. Recent research indicated the importance of transverse diffusivity in MS (Song et al., 2002; Henry et al., 2003; Lowe et al., 2006). The reduction of diffusion anisotropy in MS is shown to be primarily due to an increase in transverse diffusivity, this is the mean of the non-principal eigenvectors (E_2 and E_3), rather than to changes in diffusivity along the principal diffusion direction (E_1), also referred to as longitudinal diffusivity (Lowe et al., 2006). As similar changes were demonstrated in animal models of demyelination (Song et al., 2002), these results could indicate a specific marker of structural changes related to the neuropathology in MS. The observed decrease in anisotropy in the normal-appearing brain matter of MS patients arose from increased diffusion transverse to the fibers without significant change along the fibers (Henry et al., 2003; Oh et al., 2004; Lowe et al., 2006). By our knowledge the only study investigating associations between transverse diffusivity and cognition in MS is the study by Lowe et al. (2006). A significant correlation was found between the MSFC (Fischer et al., 1999), and transverse diffusivity in a specific pathway namely the supplementary motor pathway in MS patients (Lowe et al., 2006). This correlation was however most likely induced by the relation between transverse diffusivity and the 9-hole peg test, a subtest measuring hand and finger coordination and dexterity. A direct correlation between the PASAT, the cognitive subtest in the MSFC, was not found. The SDMT was not included in the study by Lowe (2006). As mentioned above there are major concerns about the PASAT, and we hypothesize that the correlation between the SDMT, a test with a low frustration level in patients, and transverse diffusivity would be stronger.

Transverse diffusivity is defined in the brain parenchyma; as there is accumulating evidence that grey matter is also affected in MS (Stadelmann, Albert, Wegner, Bruck, 2008).

Methods

Participants

Fifteen right-handed female patients aged 21 to 49 years (mean age 37.6 years, mean years of education 13.93 years) with clinically definite MS according to McDonald criteria (Mc Donald 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. And all patients had relapsing-remitting MS, with a disability on the Kurtze expanded disability status scale (EDSS) (Kurtze, 1983) between 0 and 7 (mean ± SD= 2.47 ± 2.17). The mean disease duration was 5.13 years (SD = 3.38). None of the patients suffered from other neurological problems or had a history of substance abuse. 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.

Neuropsychological testing

The PASAT and the SDMT were assessed in all patients. The 3-s presentation rate version of the PASAT was selected. Participants were required to listen to 61 auditory presented single digits and to add each consecutive digit to the preceding one. Answers were given orally.

During the oral version of the SDMT a symbol-number coding key consisting of nine pairings was visually presented. The patients were required to scan the key and match unpaired symbols as quick as possible by voicing the answer. The time given for this task is 90 s and the number of correct answers given in this time bin was measured.

Magnetic Resonance Imaging

All scans were performed on a 3T Siemens Trio MRI scanner equipped with echo planar imaging (EPI) capabilities, using an eight channel head coil for radio frequency transmission and signal reception. Participants were positioned head first and supine in the magnet. They were instructed to lie as still as possible in order to prevent motion artefacts. To further restrict head movements, participants' heads were fixed by foam cushions and ear clamps positioned behind the neck and around the head. All subjects had FLAIR images (TR/TE = 6000/353 ms, FOV 240 mm^2, 160 slices with 1 mm thickness no gap and a matrix size of 256 x 256) acquired prior to DTI.

Diffusion weighted imaging was performed in 60 directions with an echo-planar imaging (EPI) sequence with a receiver bandwidth (BW) of 1300Hz/pixel. A total of 60 slices was acquired in a

repetition time (TR) of 10.10 s and with an echo time (TE) of 100 ms. To minimize the influence of eddy currents, a twice-refocused spin echo (TRSE) preparation was used with b-factors of 0 and 700s/mm^2. The resolution was 2mm x 2mm x 2mm, with a field of view of 256mm. The acquisition time of this sequence was about 12 minutes.

Total cerebral lesion load was calculated based on the white matter lesions that were detected on the FLAIR images using expectation maximization segmentation (EMS) (Van Leemput, Maes, Vandermeulen, & Suetens, 1999). The number of pixels that were defined as lesions by EMS were automatically summed using in-house software, and multiplied by the voxel size to obtain lesion load in mm^2.

For DTI analyses all DTI images were transferred to an off-line Siemens Leonardo^{TM} workstation. FA and eigenvector images were calculated using the DTI task card developed by MGH (for algorithms used in this software see Jones, Horsfield, & Simmons; 1999). Longitudinal diffusivity is defined as the first eigen value image (E_1), whereas the transverse diffusivity is defined as the mean image of the second and the third eigen value images ((E_2+E_3)/2). To calculate the mean FA, transversal and longitudinal diffusivity in the total brain, the procedure recently described by Benedict et al. (2007) was used. To remove skull and non-brain tissue from the images with b-value of 0 s/mm² a Brain Extraction Tool (BET) was used (Smith et al., 2002; Jenkinson, Pechaud, & Smith, 2005). The resulting brain image was segmented into cerebrospinal fluid (CSF) and parenchyma using FMRIB's Automated Segmentation Tool (FAST) (Smith et al., 2002). The obtained parenchymal map was eroded by one voxel with a 3x3x3, 6 connected kernel using Medical Image Processing, Analysis & Visualization (MIPAV) (McAulille et al., 2001). The eroded parenchymal map was used as mask for the FA, transverse and longitudinal diffusivity images in order to obtain the DTI measures within the parenchyma only. Mean FA, transverse and longitudinal diffusivity was defined in the whole brain.

Results

For the PASAT-3 test, there was a drop-out rate of two. The test was too frustrating for those two patients and was aborted. A mean score of 48.62 was observed (SD = 10.64). None of the patients fell out for the SDMT, with a mean score of 60.4 (14.52). A recent study by Parmenter et al. (2007) showed that for the SDMT a cut-off of 55 yields acceptable Bayesian probabilities for cognitive impairment screening in an MS population. When this cut-off was used, 7 patients for the investigated group could be classified as cognitively impaired against 8 patients classified as unimpaired. The mean SDMT score for the low performance group was 48.25 (SD=8.46), the high performance group had a mean score of 70.31 (SD=9.96). This is a good representation of the MS population in which about 50% of the patients are diagnosed with cognitive dysfunctions (Rao et al., 1991).

Mean total white matter lesion volume was 559.5 mm² (SD=476.28 mm²). The mean total FA in the parenchyma of the MS patients was 0.37 (SD=0.031), the longitudinal diffusivity in the parenchyma

was 1.27 x 10^{-3} mm²/s (SD=0.066 x 10^{-3}) and the mean transverse diffusivity 7.36 x 10^{-4} mm²/s (SD=0.612 x 10^{-4}).

Correlation analysis revealed that none of the correlations between performance on the PASAT-3 and the different cerebral damage measures (lesion volume, FA, longitudinal and transverse diffusivity) reached significance. A moderate correlation could be found between the SDMT score and parenchymal FA (R=0.53, p<0.05). This correlation was mainly induced by the correlation between SDMT performance and transverse diffusivity (R=-0.53; p<0.05), the correlation between SDMT and longitudinal diffusivity was not significant (R=-0.15; p=.60). Total lesion load did neither correlate with SDMT score (R=-0.15, p=0.61).

To further explore the relation between cognitive performance and the DTI derived measures in MS, an independent sample t-test was performed with the MS patients performing equal or under the cut-off of 55 on the SDMT and the patients performing above the cut-off. Both parenchymal FA and transverse diffusivity differed between both groups (t(13)=-2.23, p<0.05 for FA and t(13)=3.97, p<0.01 for transverse diffusivity). Longitudinal diffusivity did not differ for the low and high performers (t(13)=1.83, p=0.09). Mean DTI measures for both groups can be found in Table 1.

	SDMT high performers (score > 55)	SDMT low performers (score > 55)	Significance
FA	.39 (0.024)	.36 (0.031)	0.044
E_1 (x10^{-4} mm²/s)	1.24 (0.042)	1.30 (0.076)	0.090
$(E_2+E_3)/2$ (x10^{-3} mm²/s)	6.95 (0.43)	7.82 (0.42)	0.002
WMLV (mm³)	417.15 (345.49)	748.83 (589.41)	0.210

Table 1 The mean MRI measures for brain damage, more specific fractional anisotropy (FA), longitudinal diffusivity (E_1), transverse diffusivity [$(E_2+E_3)/2$] and white matter lesion volume (WMLV) for both the high and low performers on the SDMT. Standard deviations are between brackets.

Discussion

In the present study we investigated the relation between MS related cerebral damage and processing speed. In line with recent research that shows the importance of directional diffusion investigation in

MS (Oh et al., 2003; Lowe et al., 2006; Henry, Oh, Nelson & Pelletier, 2007), we investigated the correlation between processing speed as measured by the PASAT and the SDMT and directional diffusion, more specific diffusion along the principal diffusion direction, the longitudinal diffusivity, and diffusion along the non-principal directions, transverse diffusivity. Previous research showed that longitudinal diffusivity is much less affected in MS than transverse diffusivity (Lowe et al., 2006), and that this could be a specific marker for the demyelination and axonal loss associated with the MS pathology (Song et al., 2002; 2005).

To our knowledge, the only correlation study between directional diffusivity and disability measures in MS is the study by Lowe et al. (2006). In this study, the investigators focused on the directional diffusivity in one specific interhemispheric pathway, more specific the white matter pathway connecting bilateral SMA. They failed to find a direct correlation between PASAT performance and diffusion derived measures in the SMA pathway. This is not very surprising, as the involvement of the SMA to perform the PASAT is minimal and not essential. The PASAT recruits a broad set of cognitive functions and thus needs the involvement of several brain areas (Lazeron et al., 2003; Audoin et al., 2005).

Hence, in the present study we explored the relation between the score for the PASAT and the SDMT and directional diffusivity in the whole brain in MS patients. As the functional relevance of grey matter involvement in cognitive impairment in MS has been recently emphasised (Brass et al., 2006; Sanfilipo, Benedict, Weinstock-Guttman, Bakshi, 2006), diffusion derived parameters were defined in the whole brain. The results of this study, not only indicate significant negative correlations between the SDMT score and diffusion derived measures, the correlation was also mainly induced by transverse diffusivity, rather than by longitudinal diffusivity. This inverse correlation supports the hypothesis that increased transverse diffusivity reflects axonal damage, either from axonal loss, demyelination or both resulting in slower processing speed. The observation that the MS subgroup with slow processing speed did have decreased fractional anisotropy and increased transverse diffusivity, but no increased longitudinal diffusivity, compared to the MS subgroup with high SDMT performance, supports this hypothesis. Diffusion along the non-principal directions in the brain parenchyma thus seems to be a factor of impact in explaining information processing slowness in MS.

Although the PASAT is a frequently used neuropsychological test to measure processing speed in MS, no significant relationships were found between PASAT performance and diffusion weighted metrics. Earlier research consistently showed weaker correlation between brain damage in MS and PASAT performance than for SDMT performance (Benedict et al., 2004; Christodoulou et al., 2003). The absence of a significant correlation can be due to different factors. First of all, the PASAT has been criticised for being too frustrating with high dropout. Whereas all the patients in this study were able to perform the relatively easy SDMT, the PASAT (3 s version) was experienced as too frustrating for two patients resulting in a dropout rate of 13%. Second, earlier research indicated the use of different strategies while performing the PASAT (Coo et al., 2005). The patients in our sample could have used

different strategies leading to decreased validity of the PASAT. And, third, the psychometric characteristics for the SDMT are better than for the PASAT, with improved accuracy (72% against 69%) and sensitivity (.80 against .70) in predicting cognitive deficits in MS (Parmenter et al., 2007; Rosti, Hämäläinen, Koivisto, & Hokkanen, 2006). All of these aspects plus the fact that a relatively small group was tested are possible factors of not finding a significant correlation for the PASAT. Hence, research in a bigger cohort is warranted.

The results of this study show an association between processing speed and cerebral damage in MS as measured with diffusion tensor imaging, the only in vivo method to detect brain abnormalities related to MS in normal appearing brain matter. Moreover, the DTI measure most believed to be a possible signature of MS related white matter pathology, more specific, transverse diffusivity (Oh et al., 2003; Lowe et al., 2006; Henry et al., 2007) was related with processing speed as measured with the SDMT. This result makes a case for the clinical relevance of directional diffusivity in MS. A major weakness of this study is that only female MS patients were included. Further research using a more extensive cognitive battery, that for example includes memory tests, on larger cohorts is certainly necessary to further explore the relation between directional diffusivity measures and cognition in MS.

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Chapter 4

General Discussion and Conclusion

4.1 General Discussion

This thesis deals with callosal (dys)function in MS and investigates the relation between behavioural measures of callosal function and callosal lesion load as defined by diffusion derived measures. The relation between the cognitive measure processing speed and cerebral lesion was also explored.

4.1.1 The Redundancy gain paradigm: A behavioural measure for callosal function in MS

The results from the first two studies presented in this thesis indicate that the redundancy gain paradigm is a sensitive task to tap callosal function in MS. To the best of our knowledge the redundancy gain paradigm has not been tested before in a MS population, in which a large percentage of patients have corpus callosum damage (Simon et al., 1986; Dieteman et al., 1988; Rao et al., 1989). The advantage of this task is its simplicity in administration and analysis. Subjects have to respond as quickly as possible by pressing the response button whenever they see a flash of light that appears in the right, left or both visual hemifields simultaneously (detection task). The redundancy gain effect, or the effect that reaction times to bilateral stimuli are faster than to unilateral stimuli, is larger in patients with robust callosal damage (acallosal patients, patients with callosal section) compared to healthy controls (Reuter-Lorenz et al., 1995; Corballis, 1998; Iacoboni et al., 2000; Corballis et al., 2003). The results of the studies in this thesis show that the redundancy gain effect in MS patients, with more subtle and varying degrees of callosal damage, is enlarged compared to matched healthy controls. Hence, the redundancy gain paradigm is sensitive to pick up deficits in interhemispheric interaction in MS.

In a comprehensive study by Brown (2003), the sensitiveness of different callosal function measures was previously explored in different clinical populations with known callosal damage (commisurotomy, agenesis of the corpus callosum, dyslexia and MS). He found abnormal performance on the bimanual coordination task, the tactile maze and finger localisation task in MS, with greater deficits reported for all measures in the MS subgroup with abnormal cross-callosal evoked potentials. A concern about all behavioural tests in the study by Brown (2003) is that they all put high load on spatial processing and requires good motor control. In MS good motor control is a critical point as, due to MS related tremor good motor control in MS is not obvious. The redundancy gain paradigm puts minimal load on motor control and this task extends the series of tests useful in MS to assess callosal function. In contrast to other behavioural tasks that previously have shown to be able to pick up callosal damage, the emphasis of the redundancy gain task is not on spatial processing.

4.1.2 What about the crossed-uncrossed difference in MS

As described in the introduction, the CUD is a measure that is classically used to quantify the interhemispheric relay time. The overall rationale in this relay time difference is that contraleteral motor control is faster than any possible ipsilateral motor control, with crossed responses incorporating callosal relay. The assumption for the CUD in an MS population is that the CUD will be prolonged as slowed interhemispheric transfer is caused by MS related damage to the nerve tracts connecting both hemispheres. In contrast with this assumption, none of our results indicates a prolonged CUD for the investigated MS patients. These results are in line with the findings of Tomaiulo et al. (2003) who also failed to find a longer CUD in MS compared to controls. The fact that, in the same MS group, we could indicate an enlarged redundancy gain, but without evidence for a prolonged CUD, suggests that both effects rely on different mechanisms. Another possible explanation for the discrepant results is that the redundancy gain paradigm is a more sensitive measure than the CUD measure to pick up small callosal problems in an MS population with varying degrees of callosal involvement. According to this assumption, the redundancy gain paradigm has already proved to be a valuable measure to indicate subtle callosal problems in different populations like autism, schizophrenia, attention deficit disorder and children with developmental dyslexia. The results of this thesis extend this range of populations with MS-patients, another population in which the redundancy gain paradigm has proven its relevance.

4.1.3 Brain lesion measures in MS

In the past, conventional brain imaging, *T2 and T1 weighted MR scans*, has been used to quantify the extent of brain tissue involved in the pathological process. The *fluid-attenuated inversion recovery* (FLAIR), a T2 based technique allows for higher levels of T2 weighting relative to other sequences and results in increased contrast between lesions and normal tissue in MS. One important drawback of these conventional MRI techniques is however the inability to characterize and quantify more subtle lesions, like normal appearing white and grey matter changes or tissue damage outside lesions. Different alternative quantitative magnetic resonance techniques may give complementary information to conventional MRI. *Magnetic resonance spectroscopy* (MRS) allows quantification of axonal pathology by measuring N-acetyl-aspartate levels in both lesions and normal appearing white matter. Hence, it may reveal on-going biochemical (active inflammation, demyelination and axonal injury) pathology that remains undetected by conventional MRI. Another alternative technique is *magnetization transfer imaging*. With this technique information about the interactions between free, very mobile and restricted (within structures such as myelin) hydrogen protons can be provided. The information about bound water associated with myelin sheets remains invisible with conventional MRI, but could be informative, especially in demyelination diseases like MS. The quantitative parameter related to the degree of exchange between free and restricted protons is called the

magnetization transfer ratio. A low ratio indicates axonal or myelin damage. A third recent technique is *diffusion tensor imaging* (DTI). This technique has made it possible to investigate white matter abnormalities in MS. Using DTI, the water diffusion process can be characterised on a pixel-by-pixel basis. Due to the highly ordered axonal tracts, water diffusion in human brain is highly directional or, so-called anisotropic. The measurement of anisotropic diffusion can provide in vivo detailed information on the white matter architectures, which cannot be obtained by any other radiologic tool (Guo et al., 2002; Vrenken et al., 2006). By this feature diffusion tensor imaging is a very promising technique in MS.

Fractional anisotropy is a commonly used diffusion derived measure of coherence of the orientation of white matter tracts in MS. The results of this thesis show a significant decrease of fractional anisotropy for the MS patients. This finding is in line with previous research indicating lower anisotropy in MS (Ge et a., 2004; Filippi et al., 2001; Werring et al., 1999). Furthermore, the present results indicate that the significant fractional anisotropy decrease was mainly induced by increased mean diffusivity along the non-principal directions, also referred to as transverse diffusivity. The longitudinal diffusivity, or the diffusivity along the principal direction appears to be much less affected than transverse diffusivity. These results are in line with previous studies (Oh et al., 2004, Lowe et al., 2006; Henry et al., 2003). In animal models of MS related demyelination and Wallerian degeneration increased transverse diffusivity was shown (Song et al., 2005). Increased transverse diffusivity is believed to be a specific and unique marker or MS related neuropathological changes in MS. The obtained findings in this thesis replicate these findings and confirm the importance of transverse diffusivity in MS. Given the recent emphasis on transverse diffusivity as being specific to MS related white matter disease, the results of this study are in the interest of matching these results to the recent literature. It also provides further evidence that transverse diffusivity is specific to axonal damage or demyelination.

4.1.4 Correlation between redundancy gain effect and diffusion derived brain lesion measures

Importantly, correlations were found for the redundancy gain effect with diffusion derived brain lesion measures in the investigated MS group. When the MS group was subdivided in a low and a high callosal damage group, based on diffusion tensor parameters, enlarged redundancy gain effect was only found for the highly damage subgroup. In the second study, it was shown that more callosal damage as defined by callosal fractional anisotropy (decreased anisotropy) was associated with a bigger redundancy gain. Behavioural performance on the redundancy gain effect thus reflects callosal damage. Or, the MS related callosal injuries, more specifically the increased transverse diffusivity, believed to be a unique marker of MS related pathology, contribute to behavioural interhemispheric problems is MS. Moreover, relative callosal lesion load nor longitudinal diffusivity were additional

factors in explaining the redundancy gain effect and transverse diffusivity was a predictor explaining 27% of the variance.

In vivo evidence for disruption of corpus callosum microstructure with functional ramifications for interhemispheric processing efficiency is also given by Schulte et al. (2005). In his study, a correlation was found between the redundancy gain effect and fractional anisotropy in genu and splenium of the corpus callosum and with diffusivity in the body of the corpus callosum of alcoholic patients with subtle but significant microstructural disruption of white fiber tracts linking the hemispheres. In a group of aged and alcoholic subjects, a marginal significant correlation was found between the redundancy gain effect and size of the corpus callosum (Schulte, Pfefferbaum and Sullivan, 2004). In this thesis, and in the study by Schulte et al. (2005), this weak effect could not be replicated. Diffusion tensor imaging thus seems to be more sensitive to pick up subtle white matter damage than callosal size reflecting callosal atrophy.

The results in this thesis stress the importance of transverse diffusivity. The observed changed diffusion along the non-principal directions in MS attributes to the behavioural measure of redundancy gain. Diffusion to the principal direction, also called the longitudinal diffusivity, does not contribute to this effect. These findings extend our insight into the pathological process of MS. It also broadens our understanding of the relation between the MS related pathological process and behavioural consequences.

4.1.5 Correlations between processing speed and brain lesion measures

Over the past two decades the relation between cognitive impairment and lesion load in MS has received great interest. Although there is good agreement on the nature of cognitive dysfunction in MS, the relation with pathological cerebral damage remains unclear. On the neuropsychological side, information processing speed appears to be most consistently impaired irrespective of specific clinical features of the disease. The SDMT and PASAT, two speed-related cognitive tests appear to be most appropriate to screen overall cognitive impairment. On the brain imaging side, diffusion tensor imaging proved to be a sensitive technique to quantify MS related cerebral damage. As described above, transverse diffusivity is of particular interest in MS. Given the unique information provided by transverse diffusivity, is it surprising that very few studies focused on the relation between directional diffusion and cognition in MS. To the best of our knowledge the only study investigating such a correlation is the study by Lowe et al. (2006). The Lowe study is quite limited in the sense that directional diffusion was only quantified in a specific pathway, the supplementary motor pathway. It is not very surprising that significant correlations between cognitive tests and directional diffusion measures in this pathway were only found for cognitive tests recruiting motor areas.

In this thesis we wanted to explore the relation between overall brain damage in MS as quantified by directional diffusivity and processing speed. MS has long been considered as a focal inflammatory

disorder. Many studies have consequently focused on the relation between cognitive parameters and the extent of damage as detected with conventional magnetic resonance with emphasis on the overall relationship (Rovaris al., 1998; Nocentini et al., 2001; Benedict et al., 2004; Benedict et al., 2006), or on the relationship between lesion location and specific cognitive changes (Anzola, et al., 1990; Miki et al., 1998; Comi et al., 1999; Sperling et al., 2001). At present, due to the mounting evidence of substantial grey matter involvement in MS (Davies et al., 2004; Kutzelnigg, et al., 2005; Oreja-Guevara, et al., 2005; Rovaris, et al., 2005), the contribution of grey matter damage to cognitive impairment has been highlighted (Kutzelnigg and Lassmann, 2006; Amato et al., 2004; Morgen et al., 2005; Brass et al., 2006; Portaccio et al., 2006; Sanfilipo et al., 2006). A second trend is the application of quantitative MRI techniques that have the potential to provide robust estimates of irreversible tissue damage in lesions as well as in normal-appearing brain tissue. The evidence that normal-appearing white matter is far from normal remains central for understanding the mechanisms of tissue damage in MS. It has clearly been shown that the extent and severity of normal-appearing brain tissue alteration is more strikingly associated with cognitive impairment than the extent of focal pathology (Filippi et al., 2000; Deloire et al., 2005; Rovaris et al., 2002).

In this thesis we take advantage of both trends by using diffusion tensor imaging in brain parenchyma (whole brain white and grey matter). Thorough investigation of the effect of grey matter tissue loss caused by axonal damage can however not be accomplished by DTI. For this aim the amount of brain atrophy has to be defined. This is a limitation of this study. Previous research indicate that the impact of brain atrophy depends on the duration of the disease, with a larger impact as the disease progresses. In our MS group mean disease duration was relatively short (5,13 years) and it could be assumed that brain atrophy could have a minor impact in this stage of the disease. Nevertheless, we believe that cognitive (dys)function in all phases of MS involves a combination of different components including the extent of lesion load and brain atrophy, but also the location of lesions, the connectivity efficiency between distant brain functional areas and cortical reorganization (Ranjeva et al., 2006). In this work we focused on the unique impact of lesion load as defined by diffusion tensor imaging techniques. Therefore, we used directional diffusion measures, believed to be specific indicators of MS related demyelination pathology, and correlated these measures for cerebral brain damage with information processing speed as assessed by the PASAT and the SDMT. A significant correlation between these measures was found for the SDMT. Transverse diffusivity in the whole brain parenchyma correlated with SDMT performance, indicating that the unique MS related brain pathology is associated with slower information processing. The PASAT score was not correlated with diffusion derived measures. The absence of this correlation could be due to the weaker psychometric qualities of the PASAT (Diehr et al., 2003; Coo et al., 2005).

It is believed and supported by the findings in this thesis that diffusion derived measures should be quantified in the whole brain, including grey matter, to assess overall cerebral damage in MS. The subtle white matter damage that seems normal on conventional MR imaging, referred to as normal

appearing white matter, is an important factor in explaining the correlation between pathological brain damage and processing speed in MS. Overall, these findings once again make a case for the clinical relevance of directional diffusivity in MS research. To the best of our knowledge, this study for the first time shows a relation between directional diffusivity parameters in the whole brain and neuropsychological measures. Although this study is done in a rather small amount of patients, we were able to indicate a significant correlation. In light of the previously found small, or in best cases modest correlations between classic psychometric measures and cognition in MS, the results in this thesis are of great interest. It illustrates the importance of further exploration of directional diffusion parameters in MS, and the correlation with a broad range of cognitive performances. Certainly as directional diffusion showed to be a unique and specific parameter of MS related demyelination pathology.

4.1.6 Recommendations for future research

- In future studies the variable condition of cerebral and more specific callosal damage cannot be ignored when investigating the relation between cognitive performance and lesion load as defined by different MR techniques.
- Future research should further investigate interhemispheric function in male MS patients to generalise the findings in this thesis.
- To get a profound insight in the MS pathology it would be very interesting to evaluate directional diffusivity in the early stage of MS. This could be an important issue in regard to the justification of early disease modifying therapy.
- The correlation between different cognitive paradigms (for instance tactile performance test, finger localization test,…) that tap callosal function and diffusion derived measures in MS should further be explored so a battery of tests evaluating callosal function in MS can be constructed. The corpus callosum should be subdivided in different regions and cognitive tests assessing the function of these regions should be used to evaluate the impact of regional lesions on behavioural performance.
- The relation between different cognitive measures assessing the complete range of cognitive problems in MS (memory, higher order visual perception, attention and executive function,…) and MS related brain damage as defined by the sensitive diffusion tensor technique, should be investigated to get a profound insight in the relation between brain damage and cognition. Transverse diffusivity in special should be used as brain lesion measure.
- Cognitive (dys)function differs between the subtypes of MS (Huijbregts et al., 2006). Future research should explore diffusion tensor imaging in those subtypes and explore the relation with cognition in each subtype.

4.2 Conclusion

The main conclusion of this thesis can be summarized as follows:

- The redundancy gain paradigm is a detection task in which subjects has to respond as quickly as possible whenever they detect a flash of light that can be presented in the left, right or both visual hemifields simultaneously. This task is a useful paradigm to evaluate callosal function is MS.
- Moreover the redundancy gain paradigm is a simple task to administer, but also to analyse.
- Diffusion tensor imaging is a promising technique to evaluate cerebral brain damage in MS. Typical, fractional anisotropy, a diffusion derived measure reflecting inter- and intravoxel fiber coherence, is decreased in MS.
- This decrease is mainly induced by increased diffusivity along the non-principal directions, also called the transverse diffusivity. The longitudinal diffusivity, or diffusivity along the principal direction, is not as much increased in MS.
- Increased transverse diffusivity is a unique marker to the MS related pathology of demyelination and axonal loss.
- The redundancy gain effect correlates with callosal damage as defined by diffusion tensor imaging.
- Moreover, this correlation was primarily defined by transverse diffusivity, and neither the longitudinal diffusivity nor lesion load were additional factors in explaining this correlation.
- Information processing speed is slowed in MS.
- Information processing speed, as defined by the SDMT is correlated with cerebral brain damage as defined by the diffusion derived measure transverse diffusivity.
- This correlation was not found for information processing speed as defined by the PASAT. A possible reason for this discrepancy is the weaker psychometric qualities of the PASAT.

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Summary

Multiple sclerosis (MS) is a chronic neurological disease of the central nerve system that affects young adults with a higher prevalence in women (ratio 3:2). The neuropathology of the disease is characterised by demyelination of the white matter in the brain and central cord. MS may involve degeneration of white matter throughout the nervous system, with a predilection for specific target zones that includes the corpus callosum. The pathologic process may lead to motor problems, but halve of the patients has cognitive problems associated with MS. In this thesis, we focus on the cognitive problems and the relation with neuropathological brain damage.

One of the brain areas preferentially involved in MS, is the corpus callosum. This brain structure is the largest white matter tract connecting both hemispheres. Research in callosotomy patients, acallosal patients and callosal section patients indicates that robust callosal damage may lead to interhemispheric transfer dysfunctions. In the first part of this thesis callosal problems in MS are explored. Damage to the corpus callosum in this patient group is subtler than in callosotomy patients. Moreover, the callosal damage strongly varies from patient to patient.

In this thesis the redundancy gain paradigm, a behavioural measure to investigate interhemispheric communication is used. In this task, flashes of light are presented to the left, right or bilateral (left and right simultaneously) visual hemifield while the subject fixates to the middle of the screen. As soon as the subject detects a flash, he presses the response button with the left or right hand (detection task). An effect that is typically observed in healthy subjects is that reaction times to bilateral stimuli are faster than to unilateral stimuli. This effect is referred to as the redundancy gain effect. Previous research shows that the redundancy gain effect is enlarged in patients with callosal problems (acallosal patients or patients with callosal section). The results in this thesis show, in analogy with the results in patients with robust callosal damage, an enlarged redundancy gain effect for MS patients. These results demonstrate the sensitiveness of the redundancy gain paradigm to investigate callosal problems in MS.

To explore the effect of the amount of callosal brain damage on the redundancy gain effect, the callosal damage needs to be quantified. For this purpose diffusion tensor imaging was used. With this technique, water diffusion in the white matter can be investigated. Water in the brain spreads preferentially along the direction of the axonal fibers. Intact myelin sheets are effective barriers for the water. Demyelination, an important pathological aspect of MS, leads to decreased delineation of the tracts along which the water spreads. This results in changed diffusion derived measures. Fractional anisotropy is an important diffusion derived measure for inter- and intravoxel fiber coherence. Previous research shows that fractional anisotropy is decreased in MS patients compared to healthy controls. To calculate the fractional anisotropy, diffusion measures along three directions are defined, more specific along the principal direction, along the direction of minimal diffusion and along a third

direction that is orthogonal to the previous two. With this information, the longitudinal and transverse diffusivity can be calculated. Longitudinal diffusivity is the diffusion eigenvalue along the principal direction, whereas the transverse diffusivity is the mean of the eigenvalues along the other two directions. Recent research shows that demyelination and axonal loss, specific for MS pathology, is characterised by increased transverse diffusivity. Hence, transverse diffusivity is a unique marker for MS. The results of this thesis confirm this and show that transverse diffusivity is significantly more increased than longitudinal diffusivity in MS patients compared to healthy matched controls.
Thirdly, a correlation between the behavioural results, the redundancy gain effect, and the brain imaging measures, the diffusion derived measures, was found: the larger the transverse diffusivity, or in other words, the MS related callosal damage, the larger the redundancy gain effect in MS patients. Moreover, neither longitudinal diffusivity, nor callosal lesion load as defined on conventional T2 images were additional factors in explaining this correlation.
The results of the first part of this thesis show a) that the redundancy gain paradigm is a sensitive measure to investigate callosal brain damage in MS, b) that diffusion derived parameters are subtle measures to indicate MS related brain damage and c) that a significant correlation between callosal brain damage and the redundancy gain effect could be found in MS patients.

In the second part of this thesis the focus was on the relation between cerebral brain damage as defined by diffusion derived measures and information processing speed in MS. Information processing speed is a cognitive measure tested by the Paced Serial Addition Test (PASAT) and the Symbol Digit Modalities Test (SDMT), two commonly used neuropsychological tests in MS. A significant correlation between the performance on the SDMT and transverse diffusivity in the whole brain was found in MS patients, indicating that demyelination and axonal damage, characteristic for MS pathology, are important factors for explaining the slowed information processing speed in MS. No correlation was found with the performance on the PASAT, which can be explained by the weaker psychometric qualities of the PASAT compared to the SDMT.

First of all, the results of this thesis corroborate the heterogeneous pathological condition in MS. Research on callosal problems in MS can not be done without considering these individual differences. Based on our results, diffusion weighted imaging seems to offer a promising technique to determine cerebral damage in MS. Transverse diffusivity, considered to be a unique benchmark of white matter demyelination as seen in MS, is of special interest. Moreover, this diffusion derived measures correlate with cognitive (dys)function in MS, a correlation not consistently found for conventional imaging (lesion load on T2 of T1 images).

Samenvatting

Multiple sclerose (MS) is een chronische neurologische aandoening van het centrale zenuwstelsel die jonge mensen en dan vooral vrouwen treft (verhouding 3:2). De neuropathologie van de ziekte wordt gekenmerkt door demyelinisatie van de witte stof in de hersenen en het ruggenmerg. Hoewel dit proces op meerdere plaatsen in het centrale zenuwstelsel kan plaatsvinden, zijn er gebieden die vaker getroffen worden, zoals het corpus callosum. Dit ziekteproces kan leiden tot motorische problemen, maar ongeveer de helft van de MS patiënten heeft ook cognitieve problemen geassocieerd met MS. In dit proefschrift focussen we ons op die cognitieve problemen en de relatie met de neuropathologische hersenschade.

Eén van de gebieden waar MS gerelateerde hersenschade vaker gevonden wordt, is het corpus callosum. Dit is de grootste witte stof baan in de hersenen en deze anatomische structuur verbindt beide hersenhelften met elkaar. Uit onderzoek bij corpus callosum patiënten, acallosale patiënten en patiënten met callosale sectie blijkt dat robuste callosale schade kan leiden tot problemen bij transfer tussen beide hemisferen. In het eerste luik van dit proefschrift gaan we dan ook dieper in op de callosale problematiek bij MS. De schade in het corpus callosum van deze patiëntengroep is vaak subtieler dan bij callosotomie patiënten en daarenboven kan callosale schade sterk variëren van patiënt tot patiënt.

Het gedragsmatig paradigma dat in dit proefschrift wordt gebruikt om interhemisferische communicatie in MS te onderzoeken is het redundancy gain paradigma. Bij deze taak worden lichtflitsen rechts, links of bilateraal (links en rechts tegelijkertijd) aangeboden terwijl de proefpersonen naar het midden van het scherm naar een fixatiekruis kijken. Zodra de proefpersoon een flits ziet, drukt hij zo snel mogelijk met de linker- of rechterhand op een responsknop (detectietaak). Bij gezonde volwassenen wordt typisch gevonden dat de reactiesnelheid op bilaterale stimuli sneller is dan op unilaterale stimuli. Dit effect wordt ook wel het redundancy gain effect genoemd. Eerder onderzoek toont aan dat dit effect groter is bij patiënten met een callosale problematiek (acallosale patiënten of patiënten met callosale sectie). In dit proefschrift wordt er bij MS patiënten, in analogie met de bevindingen bij patiënten met een meer robuste callosale problematiek, een verhoogd redundancy gain effect gevonden. Deze resultaten tonen aan dat het redundancy gain paradigma een sensitieve maat is om callosale problemen bij MS te onderzoeken.

Om het effect van de grootte van callosale hersenschade op het redundancy gain effect te onderzoeken, dient eerst de callosale hersenschade gekwantificeerd te worden aan de hand van beeldvormingsmaten. Daartoe werd de diffusie gewogen beeldvorming gebruikt. Met deze techniek is het mogelijk om de waterdiffusie in de witte stof in vivo te bestuderen. Water in de hersenen verspreidt zich bij voorkeur in de richting van de axonale vezels. Een intacte myeline schede vormt een effectieve barrière voor het water. Demyelinisatie, een belangrijk pathologisch aspect van MS,

leidt tot verminderde afbakening van de banen waarlangs het water zich verspreidt en resulteert in veranderde diffusie afgeleide maten. Fractionele anisotropie is een belangrijke uit diffusie afgeleide maat voor inter- en intravoxel vezel coherentie. Eerder onderzoek toont aan dat bij MS patiënten de fractionele anisotropie verlaagd is in vergelijking met gezonde controle personen. Om de fractionele anisotropie te berekenen wordt de diffusie maat berekend in drie richtingen, namelijk langs de hoofdrichting, langs de richting van de minimale diffusie en langs een derde richting die orthogonaal staat op de vorige twee. Op basis van deze gegevens, kan fractionele anisotropie uitgesplitst worden in longitudinale en transversale diffusie. Longitudinale diffusie is de belangrijkste diffusie eigenwaarde langs de hoofdrichting, terwijl de transversale diffusie het gemiddelde is van de eigenwaardes langs de andere twee richtingen. Uit recent onderzoek blijkt dat de specifieke MS gerelateerde pathologie van demyelinisatie en axonale schade gekenmerkt wordt door verhoogde transversale diffusie. Transversale diffusie is dus een unieke marker voor MS. De resultaten van dit proefschrift bevestigen dit en tonen aan dat de transversale diffusie sterker verhoogd is dan de longitudinale diffusie in het corpus callosum van MS patiënten in vergelijking met gezonde gematchte controles.
Vervolgens worden in dit proefschrift de gedragsresultaten, meer bepaald het redundancy gain effect, gecorreleerd met de diffusie gewogen beeldvormingsmaten. Een significant verband wordt gevonden: hoe hoger de transversale diffusie, of met andere woorden, hoe groter de MS gerelateerde callosale schade, hoe groter het redundancy gain effect voor de MS patiënten. Daarenboven zijn noch de longitudinale noch callosale lesievolume zoals bepaald op basis van een conventioneel T2 beeld aanvullende factoren voor de gevonden correlatie.
De resultaten van het eerste luik van dit proefschrift tonen aan dat a) het redundancy gain paradigma een efficiënte methode is om callosale hersenschade in MS te onderzoeken, b) diffusie gewogen parameters subtiele maten zijn om hersenschade in MS in kaart te brengen en c) er een correlatie bestaat tussen callosale hersenschade zoals bepaald aan de hand van diffusie gewogen beeldvorming en het redundancy gain effect.

In het tweede luik van dit proefschrift wordt er gefocust op de relatie tussen cerebrale hersenschade zoals bepaald aan de hand van diffusie gewogen beeldvorming en informatieverwerkingssnelheid bij MS. Deze cognitieve maat wordt bepaald aan de hand van de Paced Serial Addition Test (PASAT) en de Symbol Digit Modalities Test (SDMT), twee veelgebruikte neuropsychologische tests bij MS. Er werd een significante correlatie gevonden tussen de prestatie op de SDMT en de transversale diffusie in de hele hersenen. Dit wijst erop dat demyelinisatie en axonale schade karakteristiek voor MS pathologie een belangrijke factor zijn in het verklaren van de vertraagde informatie verwerkingssnelheid bij MS patiënten. Er wordt geen correlatie gevonden met de prestatie op de PASAT. Dit kan verklaard worden door de zwakkere psychometrische kwaliteiten van de PASAT in vergelijking met de SDMT.

Allereerst bevestigen de resultaten beschreven in dit proefschrift de heterogeniteit van cerebrale (callosale) pathologie in MS patiënten. Bij de studie naar cognitieve (callosale) problemen is het bijgevolg noodzakelijk om deze individuele verschillen in rekening te brengen. Diffusie gewogen beeldvorming blijkt op basis van de resultaten een veelbelovende techniek om hersenschade in MS te kwantificeren. De transversale diffusie, die beschouwd wordt als een unieke parameter voor MS pathologie, is uitermate interessant. Bovendien correleren deze uit diffusie gewogen beeldvorming afgeleide maten met cognitief (dys)functioneren in MS, een correlatie die niet consequent gevonden wordt met conventionele beeldvormingsmaten (lesievolume op basis van T2 of T1 gewogen beelden).

Résumé

La sclérose en plaques (SEP) est une affection neurologique chronique du système nerveux central qui touche des jeunes adultes et en majorité des femmes (ratio 3:2). La neuropathologie de la maladie est caractérisée par la démyélinisation de la substance blanche dans le cerveau et la moelle épinière. Bien que ce processus puisse se situer dans plusieurs zones du système nerveux central, il y en a qui sont touchées plus fréquemment, comme le corps calleux. Ce processus pathologique peut mener à des problèmes moteurs, mais environ la moitié des patients souffre également des problèmes mentaux liés à la SEP. Dans cette thèse nous nous intéressons aux problèmes mentaux et à la relation aux lésions cérébrales neuropathologiques.

Une des zones où l'on retrouve plus fréquemment des lésions cérébrales liées à la SEP, c'est le corps calleux. C'est le plus grand faisceau de substance blanche dans le cerveau. Cette structure anatomique relie les deux hémisphères. Des études chez des patients ayant des lésions du corps calleux, des patients acalleux et des patients ayant subi une section du corps calleux, ont montré qu'une grosse lésion calleuse peut mener à des problèmes de transfert entre les deux hémisphères. Dans la première partie de cette thèse nous étudions plus à fond la problématique calleuse de la SEP. Les lésions du corps calleux de ces patients sont souvent plus subtiles que chez les patients ayant subi une callosotomie. En plus les lésions calleuses peuvent varier considérablement d'un patient à l'autre. La pathologie fait que nous pouvons examiner l'effet du volume des lésions.

Dans cette thèse, nous utilisons le paradigme du gain de redondance, un paradigme comportemental pour examiner la communication interhemisphérique chez les patients SEP. Pendant cette tâche, des éclairs de lumière sont présentés à droite, à gauche ou bilatéralement (en même temps à gauche et à droite) pendant que les sujets regardent une croix de fixation au centre de l'écran. Dès que le sujet perçoit un éclair, il doit appuyer le plus vite possible sur un bouton de réponse avec la main gauche ou la main droite (tâche de détection). Chez les adultes sains il est typique que la vitesse de réaction aux stimuli bilatéraux soit plus grande qu'aux stimuli unilatéraux. Cet effet est appelé l'effet du gain de redondance. Des études ont montré que cet effet est plus grand chez les patients ayant des problèmes calleux (des patients acalleux ou des patients ayant subi une section calleuse). Les résultats présentés dans cette thèse montrent que le paradigme du gain de redondance est une mesure sensitive pour étudier les problèmes calleux chez la SEP. Les patients SEP ont un effet de gain de redondance plus haut, par analogie avec les résultats d'autres patients calleux.

Pour étudier les effets du volume des lésions calleuses sur l'effet du gain de redondance, il faut quantifier les lésions cérébrales calleuses. A cet effet l'imagerie pondérée en diffusion est utilisée. Grâce à cette technique prometteuse il est possible d'étudier la diffusion de l'eau dans la substance blanche in vivo. L'eau dans le cerveau a tendance à diffuser dans la direction des fibres axonales. Une gaine de myéline intacte forme une barrière effective contre l'eau. La démyélinisation, un aspect

pathologique important de la SEP, entraîne une barrière moins résistante des voies par lesquelles l'eau se diffuse. Cela résulte en des altérations des mesures de diffusion. L'anisotropie fractionnelle est une mesure de diffusion importante pour la cohérence de la fibre intra- et entre-voxel. Des études ont montré une diminution de l'anisotropie fractionnelle chez les patients SEP en comparaison avec les sujets sains. Pour calculer l'anisotropie fractionnelle la mesure de diffusion est définie dans 3 directions, à savoir la direction principale, la direction de la diffusion minimale et une troisième direction qui se trouve orthogonalement aux directions antérieures. Sur la base de ces données, l'anisotropie fractionnelle peut être dérivée en diffusion longitudinale et diffusion transversale. La diffusion longitudinale est la plus importante valeur propre de diffusion le long de la direction principale, pendant que la diffusion transversale est la moyenne des valeurs propres le long des 2 autres directions. Des études récentes ont montré que la démyélinisation et les lésions axonales, des caractéristiques de la SEP, sont caractérisées par une plus grande diffusion transversale. La diffusion transversale constitue ainsi une caractéristique unique de la SEP. Les résultats de cette thèse confirment cela et montrent que la diffusion transversale est plus grande que la diffusion longitudinale dans le corps calleux des patients SEP en comparaison avec des sujets sains comparables.
Finalement les résultats comportementaux, à savoir l'effet du gain de redondance, sont corrélés dans cette thèse avec les mesures de l'imagerie, à savoir les mesures pondérées en diffusion. Une corrélation significative est observée: plus élevée la diffusion transversale, ou en d'autres mots plus grandes les lésions calleuses liées à la SEP, plus élevé l'effet du gain de redondance pour les patients SEP. En plus, ni la diffusion longitudinale, ni le volume de lésions calleuses comme défini sur la base d'une image T2 conventionnelle, sont des facteurs complémentaires pour expliquer cette corrélation.
Les résultats de la première partie de cette thèse montrent que a) le paradigme du gain de redondance est une méthode efficace d'étudier les lésions calleuses chez la SEP, b) les paramètres de diffusion sont des mesures subtiles pour montrer les lésions cérébrales calleuses chez la SEP et c) il existe une corrélation entre les lésions cérébrales calleuses comme défini par l'imagerie en diffusion et l'effet du gain de redondance.

Dans la deuxième partie de cette thèse nous nous intéressons à la relation des lésions cérébrales comme définie par l'imagerie en diffusion et la vitesse de traitement de l'information chez les patients SEP. Cette mesure cognitive est déterminée par le test «Paced Serial Addition Test» (PASAT) et le test «Single Digit Modalities Test» (SDMT), 2 tests neuropsychologiques couramment utilisés chez les patients SEP. Une corrélation significative entre les résultats obtenus au test SDMT et la diffusion transversale dans le cerveau entier a été observée chez les patients SEP. Cela signifie que la démyélinisation et les lésions axonales, caractéristiques pour la pathologie SEP, sont des facteurs importants pour expliquer la vitesse de traitement de l'information plus lente chez les patients SEP. Une corrélation avec les résultats obtenus au test PASAT n'a pas été observée, ce qui peut être

expliquée par les qualités psychométriques plus faibles du test PASAT en comparaison avec le test SDMT.

D'abord les résultats dans cette thèse confirment l'hétérogénéité de la pathologie cérébrale (calleuse) chez les patients SEP. Lors de l'étude des problèmes cognitifs (calleux) il est par conséquent nécessaire de prendre en compte ces différences individuelles. Sur la base de ces résultats, l'imagerie pondérée en diffusion est une technique prometteuse pour quantifier les lésions cérébrales chez les patients SEP. La diffusion transversale, considérée comme paramètre unique de la pathologie SEP, est particulièrement intéressante. En plus ces mesures de l'imagerie en diffusion ont une corrélation avec le (dys)fonctionnement cognitif chez les patients SEP, une corrélation qui n'est pas toujours observée conséquemment avec des mesures d'imagerie conventionnelles (volume des lésions sur la base des images pondérées en T2 ou T1).

Appendix

Appendix 1

Errata

Chapter 2.1.

The headings of the two tables in this article as published in Brain Research have changed places. The correct heading of the first table is ‘Mean values (standard deviations between brackets) for chronological age (in years), years of education, fractional anisotropy and mean diffusivity (10^{-3} mm^2/s) for the MS and control group’. For the second table, the correct heading is ‘Characteristics of the high and low FA subgroup’.

The formula given in part 4.2.2 line 20 is not correct. The correct formula is $P_{ic} – (P_i + P_C)$.

Although both corrections were reported in the proof correction process before publication, unfortunately, they were not corrected in the published article.

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Een doctoraat is een werk van lange adem, met als typisch kenmerk de vele ups en downs. De down van een mislukte experimentopzet, een niet geslaagde scanpoging, bijtende kritiek op een geweigerd artikel,... Maar dan ook de eerste afname die lukt of, eindelijk, het eerste aanvaarde artikel. Dat laatste zorgt ervoor dat je, met de woorden van Guy '*een week op wolkskes loopt*'. Doorheen dit hele, nogal bergachtige proces had ik meer dan eens het gevoel dat ik vanuit mijn ivoren toren onderzoek verrichtte. Maar, nadien, als je durft terug te blikken, zie je dat vele mensen je gesteund hebben.

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