Functional and Structural imaging in Multiple Sclerosis patients

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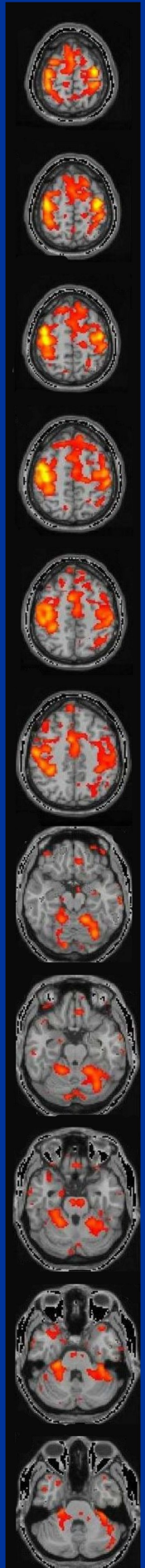
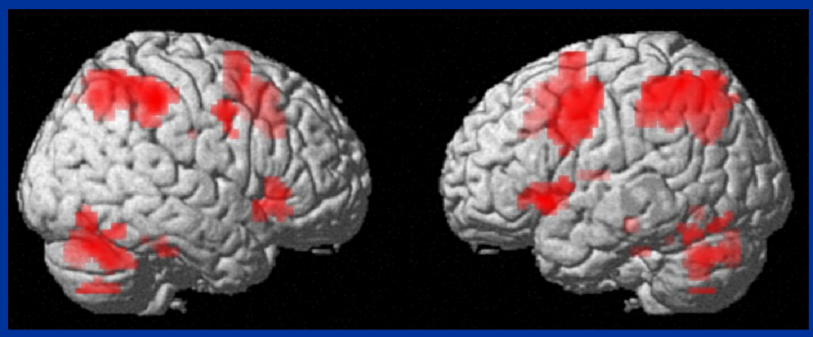
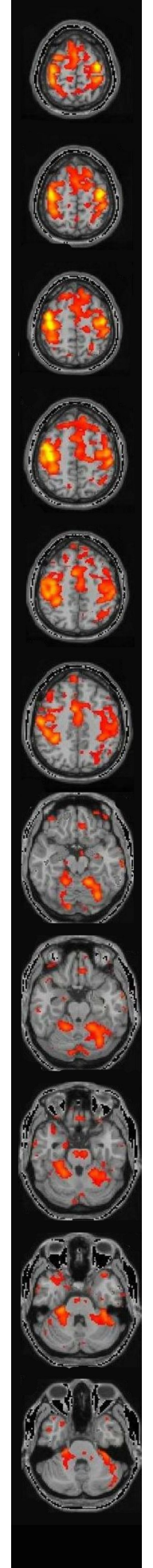


FUNCTIONAL AND STRUCTURAL IMAGING IN MULTIPLE SCLEROSIS PATIENTS

The relationships between selected cerebral functions and (functional and structural) M.R. parameters



Richard H.C. Lazeron



Functional and Structural imaging in Multiple Sclerosis patients.

The relationships between selected cerebral functions and (functional and structural) M.R. parameters.

Richard Hendrik Cornelis Lazeron

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VRIJE UNIVERSITEIT

FUNCTIONAL AND STRUCTURAL IMAGING IN MULTIPLE SCLEROSIS PATIENTS

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
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in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op maandag 3 juli 2006 om 15.45 uur
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De Boelelaan 1105

door

Richard Hendrik Cornelis Lazeron

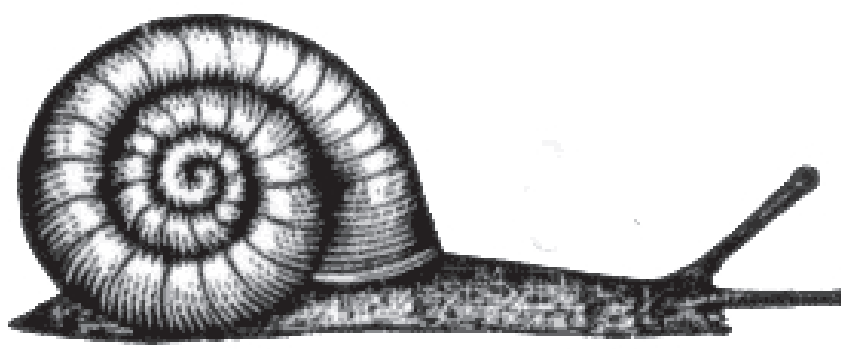
geboren te Amsterdam

promotoren:	prof.dr. F. Barkhof prof.dr. Ph. Scheltens
copromotor:	dr. S.A.R.B. Rombouts

"Als je eindelijk hebt bereikt wat je wilde bereiken, is het niet meer wat je wilde bereiken, maar eenvoudig datgene wat je hebt bereikt. Dan is het vanzelfsprekend geworden. Wat je wint verlies je eigenlijk, welbeschouwd.
Bovendien, als je ziet wat je hebt moeten aanrichten om het te bereiken, dan vergaat de bevrediging je wel. En uiteindelijk blijf je met meer vragen zitten dan er zijn beantwoord".

Uit: *De Ontdekking van de Hemel*, van Harry Mulisch

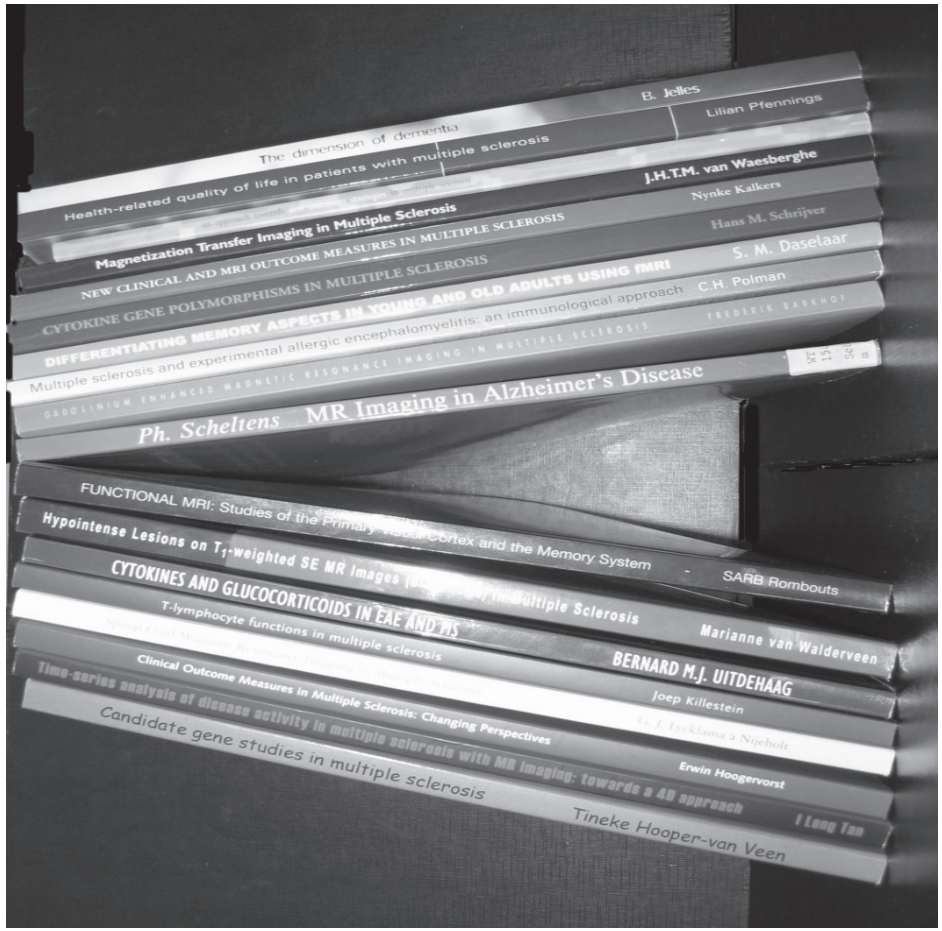
voor mijn ouders



Contents

CHAPTER 1

GENERAL INTRODUCTION


The dimension of dementia
B. Jelles
Health-related quality of life in patients with multiple sclerosis
Lilian Pfennings
Magnetization Transfer Imaging in Multiple Sclerosis
J.H.T.M. van Waesberghe
NEW CLINICAL AND MRI OUTCOME MEASURES IN MULTIPLE SCLEROSIS
Nynke Kalkers
CYTOKINE GENE POLYMORPHISMS IN MULTIPLE SCLEROSIS
Hans M. Schrijver
DIFFERENTIATING MEMORY ASPECTS IN YOUNG AND OLD ADULTS USING fMRI
S. M. Daselaar
Multiple sclerosis and experimental allergic encephalomyelitis: an immunological approach
C.H. Polman
GADOLINIUM ENHANCED MAGNETIC RESONANCE IMAGING IN MULTIPLE SCLEROSIS
FREDERIK BARKHOF
Ph. Scheltens MR Imaging in Alzheimer's Disease
FUNCTIONAL MRI: Studies of the Primary Visual Cortex and the Memory System
SARB Rombouts
Hypointense Lesions on T_1-weighted SE MR Images
Marianne van Walderveen
CYTOKINES AND GLUCOCORTICOIDS IN EAE AND MS
BERNARD M.J. UITDEHAAG
T-lymphocyte functions in multiple sclerosis
Joep Killestein
Clinical Outcome Measures in Multiple Sclerosis: Changing Perspectives
Erwin Hoogervorst
Time-series analysis of disease activity in multiple sclerosis with MR imaging: towards a 4D approach
J Long Tao
Candidate gene studies in multiple sclerosis
Tineke Hooper-van Veen

1.1 INTRODUCTION

(a thesis build on others)

In this thesis fMRI (functional magnetic resonance imaging) studies of cognition in multiple sclerosis (MS) patients are presented. Additionally, MRI techniques to evaluate structural pathology have been used to study the relationship between cognitive functioning and the presence of structural brain damage in MS patients. The relation between MR visible lesions, brain activity as depicted by fMRI, and neurological impairment, especially with regards to cognitive impairment, is not well understood. Better understanding and quantification of those relationships can hopefully lead to better understanding of symptoms, their mode of occurrence and perhaps even guide therapeutic strategies.

As an introduction to the studies described in this thesis a short description of the disease, cognitive impairment in MS and the fMRI technique are given. These themes have been the subject of many previous PhD theses from our Institute and reference will be made to them.

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system. In the second part of the 19th century it was clinically and pathologically described by Charcot[38]. MS is characterized histopathologically by multifocal lesions in the central nervous system, consisting of inflammation, demyelination, gliosis and degeneration of axons. In post-mortem studies, sclerotic plaques, that have given the disease its name, can be observed in many places throughout the central nervous system. The exact cause is unknown, but environmental factors (possibly including viral infection) and autoimmune processes (including reactions to unknown autoantigens) play an important role [*Polman thesis*[190], *Uitdehaag thesis*[259], *Killestein thesis*[118], *van Oosten thesis*[262]; *Schrijver thesis*[235]]; also a genetic component is suspected and some susceptible genes have been investigated [*Hooper - van Veen thesis*[263]].

MS mainly affects young adults (age of onset is 20 - 40 years of age) and is more prevalent in females than in males. In about two third of the cases MS starts with episodes of neurological problems, followed by intervals with complete or partial recovery. This is the so-called relapsing-remitting form of MS, which may be followed by a secondary

progressive course. In 10-15% of the cases the disease has a progressive course from onset on (primary progressive type).

Because MS lesions can develop throughout the whole CNS, both in brain and spinal cord [*Lycklama à Nijeholt thesis*[144]] a variety of symptoms can occur in MS, of which the most well known ones are sensory disturbances, visual problems and motor disturbances, as well as micturition and defecation problems and fatigue. The last two decades have witnessed a growing interest in cognitive disturbances associated with MS. Because MS affects such primary (neurological) functions necessary in daily living, it has a tremendous impact on social life [*Polman thesis*[190], *Pfennings thesis*[186]]. Cognitive impairment probably accounts for the most troublesome of all handicaps because it is more difficult to handle by the patient and his or her surroundings.

The diagnosis of MS remains a clinical diagnosis based on symptoms in different neurological systems and the time of appearance of these symptoms, but is greatly facilitated by ancillary techniques, notably MRI. The role of MRI in the diagnosis and especially the contribution of gadolinium has been reported many years ago [*Barkhof thesis*[13]]. Later, other characteristics like hypointense T1 lesions, or so called black-holes [*Van Walderveen thesis*[266]], and the role of MRI in disease severity (treatment trials) were described. Poser et al.[192] constructed diagnostic criteria in which MRI played a minor role, but recently the International Panel on MS Diagnosis presented revised diagnostic criteria in which MR parameters play a more important role[151]. In the McDonald criteria, the MR criteria described by Barkhof[14] have been included; one of the constituting elements is the presence of juxtacortical lesions.

MR imaging allows the possibility of quantifying atrophy and white matter changes, which can be correlated with clinical parameters. This validation process has been successfully completed for certain diseases, e.g. the relation between memory impairment and hippocampal atrophy in Alzheimer's disease [*Scheltens thesis*[231]]. For different reasons, the correlation of MRI and clinical findings has been proven more difficult in MS, the so-called the clinicoradiological paradox in MS.
The most important difficulty in this respect is probably the use of the expanded disability status scale (EDSS). This widely used clinical measurement takes into account especially motor, sensory and autonomic functions. Most likely

spinal cord lesions, rather than brain lesions, determine disturbances in those functions. Other scales, which take into account cognitive impairment have been proposed (the MS Functional Composite, and the Guy's Neurological Disability Scale) and show a better, though still not optimal correlation with MR parameters [*Kalkers thesis*[115], *Hoogervorst thesis*[98]].
Secondly, MR only shows the top of the iceberg of affected tissue. Tissue looking normal on standard MR images appear affected when quantitative MR techniques (Magnetic Transfer Ratio, T1 relaxation time measurements, spectroscopy, atrophy measurements, subtraction of images from different time points) are used [*Van Walderveen thesis*[266], *Van Waesberghe thesis*[264], *Lycklema thesis*[144], *Kalkers thesis*[115], *Tan thesis*[253]]. Another problem with lesion load measurement is the time consuming aspect of it. Pattern recognition systems can hopefully deal with this in the future, as is done in other brain research areas [for example *Jelles thesis*[107]].

Cognitive functions are the 'higher' functions of the brain. Examples of those functions are memory, language, calculation and executive functions (planning). Mental state (depression) and physical state (fatigue) strongly influence those functions. Charcot[38] already described cognitive impairment in MS patients. Later it was thought that chronic illness and fatigue were the main problems concerning cognitive difficulties. Some years before the studies described in this thesis started, cognitive impairment was reiterated as one of the main problems in MS patients, especially for functions of daily living. The contributing influence of depression, fatigue etc. was also observed [*Pfennings thesis*[186]].
Since MS lesions are usually widespread throughout the brain, it has been postulated that measures of cognitive functioning correlate better with brain MR parameters than for example motor functioning which is mostly dependent on spinal cord involvement.
A further introduction in cognitive impairment in MS is given in an introduction chapter (§ 2.1) preceding the studies on cognitive impairment and MR parameters in MS patients.

The study of impairment of cognitive functions regained new interest when a new MRI technique became available, termed functional MRI (fMRI)[20]. With this technique, the functional active brain parts can be examined non-invasively, and it was expected to find a better relation between

clinical and MR parameters in MS. Implementation of the technique and its post-processing is a necessary first step. In our institute this was performed by Rombouts and Hoogenraad [*Rombouts thesis*[224]*; Hoogenraad thesis*[97]]. To study a cognitive domain with fMRI, it is of the greatest importance to develop a suitable task, and test it in healthy controls. These steps are the first to be described in this thesis.

A further description of the fMRI technique and the paradigms used can be found in an introduction chapter (§3.1), preceding the fMRI related studies in MS patients.

1.2 OUTLINE OF THIS THESIS

The basic aim of the presented studies was to investigate the relation between cognitive functioning in MS and structural and functional MR parameters.

In *chapter TWO* the relation between structural lesions and cognitive impairment is studied. This was done in four different studies. The first study focussed on (juxta)cortical lesions, the second study focussed on brain atrophy and regional lesion loads. In the third and fourth study focussed on the attentional aspects of cognitive functioning in MS and the relation with structural MR parameters were analysed.

In *chapter THREE* two cognitive tasks, suitable for use with fMRI, are described. The Tower of London task, an executive functioning (planning) task, and the PASAT, an attentional task widely used in MS research, were transformed in an fMRI task. Brain activation during both tasks was analysed in healthy controls.

In *chapter FOUR* three studies of fMRI measured brain activation in patients are described. One study uses a light flash paradigm in optic neuritis patients, the second study used the fMRI Tower of London. Furthermore a small study evaluating Cannabis effects with fMRI was performed.

In *chapter FIVE* a review of the results and a discussion of the interpretation and significance of the observed findings is given, ending with ideas for future research.

CHAPTER 2

STRUCTURAL MRI AND COGNITION

2.1 INTRODUCTION COGNITIVE IMPAIRMENT IN MS

Charcot[38] already described cognitive impairment in MS patients. In many MS patients cognitive functions are affected, especially when the patients have a longer disease duration. In 1990 the cognitive function study group of the National Multiple Sclerosis society estimated the prevalence 54-65%[185]. The cognitive disability is very serious in 5 - 10 % of the patients[63,182]. With this knowledge it can be safely said that cognitive impairment, also because the impact in daily life, is a major problem in MS[18,83,202,260].

MS patients fail a significantly greater number of neuro-psychological tests than controls[202]. However, the cognitive impairment is not uniform in MS [15,106,184,195,279,280]. The heterogeneity of the affected cognitive domains is characteristic for MS. Because of this heterogeneity, different estimates of cognitive impairment have been observed, a further complicating factor is across studies different cognitive functions have been explored.
MS produces a cognitive impairment that resembles that of the a so-called subcortical dementia [52,281], characterized by specific deficits in recent memory, sustained attention, conceptual reasoning, visuo-spatial functions and information processing speed, with most of the times preserved language, gnosis, praxis [15,95,99,106, 140,195,199,202] and intellectual functions[195198]. The presence of this subcortical dementia can be explained by the involvement of the frontal lobe in MS, and therewith the impaired executive functions[44]; the pattern of cognitive decline seems to be the result of the lesion locations in the hemispheric white matter. It remains to be established whether cerebral demyelination disrupt a wide range of cognitive operations in a uniform manner or affects a specific subset of cognitive operations.

Some other characteristics of cognitive functioning (impairment) in MS patients exist.
Although cognitive functioning is in healthy individuals in general terms not dependent of the gender, it seems to be in MS[16]. Slower reaction times in MS patients have been frequently reported[64,108,112,126,140,204]. Increase of reaction time in MS patients with task complexity, suggesting a slowing of mental processing independent of motor slowing, has been observed[126,204], but others

failed to find such interactions[108,140]. Such inconsistencies might be explained by differences in applied tasks, severity of the disease, disease course, disease duration, and cognitive status of the MS patients[127].

The time of occurrence of cognitive impairment, starting either at the onset of MS or only in the later stages of the disease, has been studied also. Some studies found higher prevalence rates as well as severity of cognitive dysfunction in chronic progressive patients[2,41,83,95,128,159,201,202]. But cognitive impairment is also seen in patients with minimal physical disability (in RR patients)[194].

Studies failed to find substantial correlations between cognitive deficits and disease duration, and also correlations between the degree of physical disability as measured with the EDSS and severity of cognitive impairment in MS are weak[228] or virtually absent[104,105,128]. Most studies reported a relation between cognitive functioning and structural MR parameters. Many studies have reported a correlation between total brain lesion load and overall cognitive impairment[5,39,83,96,133,203,227,244,250], but not all studies did so (for example [99,146,177]). Several earlier studies did report a correlation between the total lesion load or total lesion score (defined in many different ways) and general cognitive impairment (scored as an index of more than one cognitive domain, evaluated with different tests, or as the score of one of the cognitive areas)[83,203,250]. In some studies the total lesion load or score showed a relation with the following cognitive domains: intelligence[5,203], attention[96,227], verbal and nonverbal memory[83,96,177,227], abstract and conceptual reasoning[83,203], recent memory[203], visuo-spatial problem solving[83,203] and linguistic problems[203]. In a few studies no correlation between cognitive impairment and lesion load was found[83,99,146,203,250]. The inconsistency of these findings probably relates in part to the marked differences in techniques and definitions.

Correlations with regional lesion load or score have been described for abstract reasoning[3,250] with the number of frontal lesions; for visuo-spatial problem solving, attention and verbal memory with the number of parietally localized lesions[250] and frontal lobe impairment with the frontal lobe lesion load[80,227]. Some studies described a relation between existence of periventricular lesion and different aspects of cognitive impairment[152,194].

The influence of regional lesion loads and brain atrophy on more specific cognitive problems is far less known, especially for the widely used Brief Repeatable Battery[5,21,42,80,96,165,227,250].

Sperling et al.[244] also found significant correlations between those test scores and regional lesion loads. The correlations they found were for all but one of the subtests always correlations with the same areas, namely total brain and the frontal and parietal lobes, representing almost the complete lesion load.

2.2 **MAGNIMS A1.2** study

Adapted from: Multiple sclerosis

Neuropsychological impairment in multiple sclerosis patients: the role of (juxta)cortical lesion on FLAIR.

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Multiple sclerosis, 2000 (6), 280-285

Abstract

OBJECTIVE

In this study we evaluated the correlation between neuropsychological impairment (measured with the Brief Repeatable Battery Neuropsychological Tests) and (juxta)cortical lesions detected with FLAIR and the relative sensitivity of the FLAIR sequence compared to spin-echo MRI sequences in detecting (juxta)cortical MS lesions.

METHODS

A total of 39 patients with definite MS were evaluated by MRI with a conventional and fast spin echo sequence and fast FLAIR sequence, and neuropsychological tests of the Brief Repeatable Battery Neuropsychological tests were performed. The Z score of all subtests were used to calculate a Cognitive Impairment Index.

RESULTS

The results show that a high number of (juxta)cortical lesions is detected with thin slice FLAIR (30% of all lesions seen). This percentage was not superior to spin-echo, reflecting the thin slice thickness (3 mm) we used. The lesions detected with FLAIR were to a certain degree different ones than the lesions detected with the other techniques. While the number of non-cortical lesions correlated with the expanded disability status scale ($r=0.32$, $p=0.045$), the number of (juxta)cortical lesions detected with the FLAIR showed a correlation ($r=0.34$, $P=0.035$) with the Cognitive Impairment Index.

CONCLUSION

Our study underlines the high number of (juxta)cortical lesions in MS and the value of thin slice FLAIR sequence to detect such lesions with MRI. It also stresses the importance of (juxta)cortical lesions on determining neuropsychological impairment.

INTRODUCTION

Multiple sclerosis (MS) is a multifocal demyelinating disease of the central nervous system. Magnetic Resonance Imaging (MRI) is very sensitive in showing cerebral lesions in MS[157], characteristically located in the periventricular region and corpus callosum. The pattern of cognitive impairment in MS is characterised by specific deficits in recent memory, sustained attention, conceptual reasoning and information processing speed, with preserved language and intellectual functions[1]. This so-called pattern of subcortical dementia[202,281] is usually attributed to the presence of extensive white matter involvement.

(Juxta)cortical lesions have long been under-recognized as part of MS, but pathological studies[31,143] have shown that gray matter is frequently affected. Using high resolution MRI (juxta)cortical lesions can be demonstrated, particularly with the use of gadolinium[117]; increased detection of (juxta)cortical lesions has also been reported using FLAIR (fluid attenuated inversion recovery sequences)[27,88,139,288]. This is perhaps due to the heavy T2-weighted contrast created with FLAIR, without partial volume effects due to CSF signal (which has been nulled out). While there have been reports about the frequency of (juxta)cortical lesions and epilepsy in MS, the clinical relevance of (juxta)cortical lesions in MS is largely unknown[117,156]; especially in relation to cognitive impairment.

The purpose of our study was to investigate the correlation between the amount of (juxta)cortical lesions detected with FLAIR and cognitive impairment, as measured by the Brief Repeatable Battery Neuropsychological Tests, a cognitive screening battery composed by Rao et al.[203]. In addition we wanted to reassure that the FLAIR sequence is more sensitive than spin-echo sequences in detecting (juxta)cortical lesions when thin (3 mm) slices are used, and especially whether lesions detected with FLAIR correlate better with the cognitive impairment.

MATERIALS AND METHODS

Subjects

We examined 39 patients (Amsterdam 19, London 10, Milan 10) with clinically definite MS according to the Poser criteria[192]; 24 patients had a relapsing remitting, 13 a secondary progressive and 2 a primary progressive course (according to the criteria of Lublin and Reingold[142]). MRI and clinical and neuropsychological evaluations were performed on separate days, but within a week of each other. The subjects had mild to moderate disability (EDSS range 0-6). Patients with clinically manifest dementia, speech disturbances, poor visual acuity or other physical symptoms interfering with the test performance were excluded. Patients characteristics are summarised in table I. The subjects of the control group (39 persons) were selected from a neuropsychologically evaluated group of healthy subjects and were matched as much as possible by age, sex and educational level. The educational level was scaled according to a ranging system in which 1 reflects no education and 7 education at university level.

Table I

Patient characteristics of MS patients (n = 39).

	Mean	*Standard deviation*	*Min*	*Max*
Age (yrs)	40	10.6	21	71
EDSS[1]	Median: 3	—	0	6
Educational level[2]	4.1	1.5	2	7
Disease duration (yrs)	10.3	8.7	2	43

1) EDSS: Expanded Disability Status Scale of Kurtzke[129].
2) The education level is a scale from 1 to 7; in which 1 reflects no education and 7 an education at university level.

MR Imaging

MR imaging included conventional (CSE) and fast (FSE) dual echo spin-echo, and a fast-FLAIR; the scanning parameters are summarized in table II. All the scans were performed on a 1.5T system and planned the same way. We used two interleaved sets of 23 slices, resulting in a contiguous data set of 46 slices with a thickness of 3 mm, and a 1 mm in-plane resolution. For analysis, the 3 types of scans were evaluated in a randomized fashion. Lesions were marked on hard copies by one experienced observer, and classified according to regions and relation with the cortex. A (juxta)cortical lesion was defined as a lesion in or in contact with the cortex.

Table II

Timing parameters of MR sequences per study site.

	Amsterdam (n = 19)			*London (n = 10)*			*Milan (n = 10)*		
	TR	*TE*	*TI*	*TR*	*TE*	*TI*	*TR*	*TE*	*TI*
CSE	2500	20-80	------	2000	20-90	-----	2500	20-80	-----
FSE	3300	16-98	------	3200	15-90	-----	3300	16-98	-----
FLAIR	9500	105	2000	11000	143	2200	9500	105	2200

Shown are the TR (repetition time), the TE (echo time) and the TI (inversion time) for conventional spin echo (CSE), fast spin echo (FSE) and fluid attenuated inversion recovery (FLAIR).

Neuropsychological tests

The neuropsychological tests were administered by a skilled psychologist, and consisted of the Brief Repeatable Battery developed by Rao et al.[202]. This battery consists of the Selective Reminding Task (remember and reproduce a list of items), the Spatial Recall Task (remember the position of 10 counters in a 6x6 grid), the Symbol Digit Modalities Test (matching numbers to symbols in 90 sec), the PASAT (listening to a tape, remembering the last number heard and summing it with the previous number heard, with two different presentation speeds) and the Word List Generation (a verbal fluency task). The test was

administered in the native language. For the first two tasks a delayed task is also part of the Brief Repeatable Battery.
From these tests, a Cognitive Impairment Index (= CII) was calculated by adding up the number of standard deviations the patient differed from the mean of the control group (Z-scores) on all subtests of the Brief Repeatable Battery; the method used is comparable with that used by Camp et al.[35]. Furthermore, we divided our group on the basis of the CII into a subgroup with minimal or no cognitive impairment (CII < 9) and a subgroup with mild to moderate cognitive impairment (CII $\geq$ 9). This cut-off was chosen to reflect the fact that on average the "impaired subgroup" scores were more than 2 standard deviations from the mean on an average of four of the five cognitive tests.

Statistics

Because this was an explorative study to detect possible relationships between MRI data and neuropsychological measures, we did not correct for multiple comparisons and the different MS types were not evaluated separately. Correlations between MRI data and clinical measures were calculated with the two-tailed Spearman's rank correlation coefficient (r), the comparison of the two cognitive subgroups was performed with the Mann-Whitney test, a non-parametric test for two groups with independent variables.

RESULTS

Neuropsychological research (table III)

The CII ranged from 1 to 22 (mean 6.18). The frequency distribution (figure 1) shows that the cut-off value of 9 separates a subgroup of 31 patients with no or minimal impairment from a subgroup of 8 (21%) patients with more severe cognitive impairment. All subtests were performed almost equally well, although the symbol digit modalities test revealed a slightly more abnormal pattern (mean Z-score 1.67 against all other Z-scores on average lower than 0.85).

Table III

Results of the Brief Repeatable Battery Neuropsychological Tests[198].

*Rao subtest**	*Highest possible score*	*Mean score patients*	*Minimum score patients*	*Maximum score patients*	*Standard deviation*	*Maximum score all*
SRT - ltr	72	42.9	5	64	13.7	69
SRT - cr	72	30.4	0	59	13.5	69
SPR	30	18.9	11	27	4.5	29
SDMT	110	44.9	10	81	14.4	81
PASAT (3" + 2")	120	72.3	7	111	27.2	118
Word fluency		24.5	13	43	6.1	44

* selective reminding task (SRT), long term retrieval (ltr) and consistent retrieval (cr); the 10/36 spatial recall test (SPR); the symbol digit modalities test (SDMT); the paced auditory serial addition task (PASAT), the 3 seconds and 2 seconds item interval together; verbal fluency (VF).

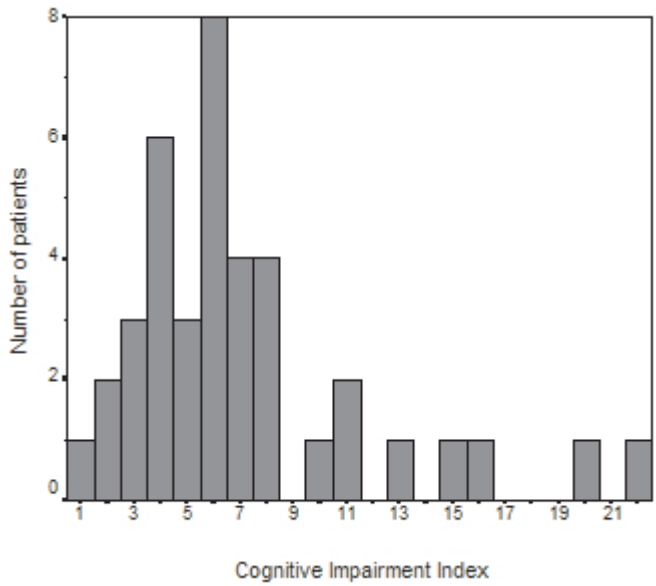
Table IV

Mean, minimum, and maximum number of lesions observed with the different sequences, according to location.

*Sequence**	*Total number of lesions*			*(Juxta)cortical lesions*			*Non-cortical lesions*		
	Mean	*Min*	*Max*	*Mean*	*Min*	*Max*	*Mean*	*Min*	*Max*
CSE	110	12	296	32	1	158	77	9	168
FSE	116	22	305	32	2	164	78	19	179
FLAIR	110	14	239	33	2	133	82	12	225

* conventional spin-echo (CSE), fast spin echo (FSE) and fluid attenuated inversion recovery (FLAIR). Note that the values for (juxta)cortical and non-cortical areas don't add up to the 'total' since they could occur in different patients.

Figure 1
Frequency table of the Cognitive Impairment Index scores.



The Cognitive Impairment Index was calculated by adding up the number of standard deviations the patient differed from the mean of a healthy control group (Z-scores) on all subtests of the Brief Repeatable Battery. The mean score is 6 with a standard deviation of 4.75. Note that eight patients (21%) had a score of 9 or more ("cognitive impaired").

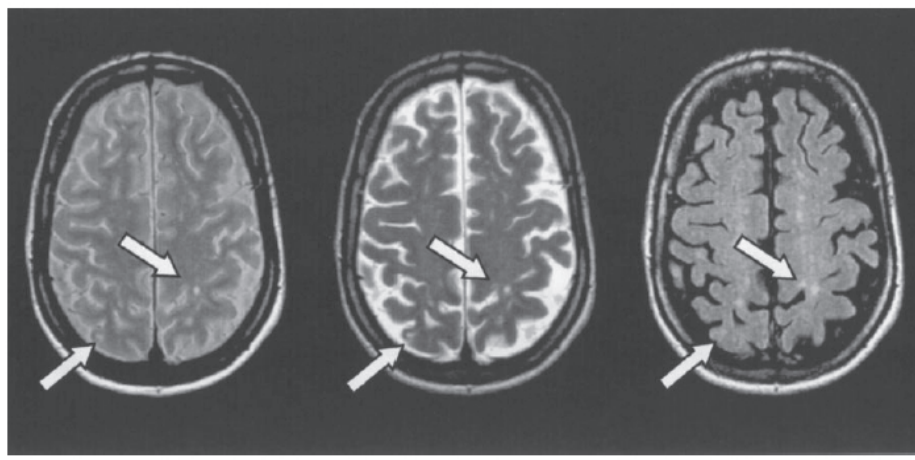
Detection of lesions using various techniques (see table IV)

All scans were of good quality. The total number of lesions we observed ranged from 12 to 305 per patient and the number of (juxta)cortical lesions from 1 to 164. The three different techniques showed no significant differences in detecting MS lesions. FSE showed slightly more, and fast-FLAIR slightly fewer lesions than CSE, but the differences were not significant ($p > 0.05$). Although most lesions could be seen on all three sequences, some lesions were only seen on one or two of the sequences (see for an example figure 2). There were minor differences with respect to the relative sensitivities across the three centres, but these differences were not statistically significant.

There were no differences between the three sequences in the amount of (juxta)cortical lesions detected (although not necessarily the same lesions). Lesions in the

Figure 2

An example of the difference between three MR sequences in detecting lesions.



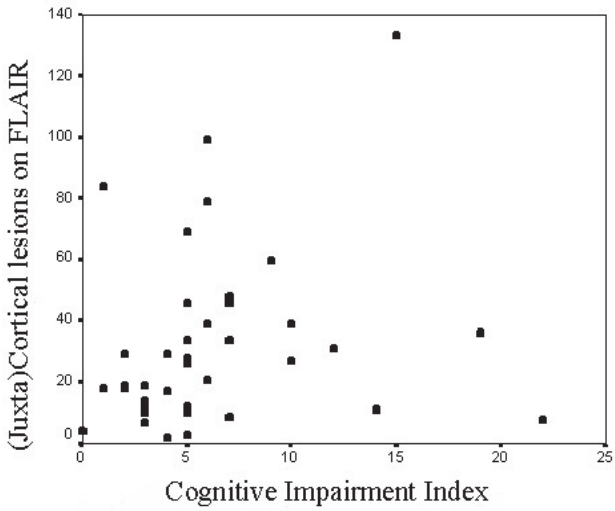
The same slice (proton density image on the left, T2 weighted image in the middle and FLAIR image on the right) is shown. Apart from several other (white matter) lesions, the lesion in the left hemisphere indicated by the arrow is well seen on the FLAIR image, but was not identified on the other sequences. The opposite is true for the lesion in the right hemisphere indicated by the arrow, which is not seen with FLAIR.

(juxta)cortical area were sometimes difficult to detect on CSE and FSE on the first echo, and frequently became more evident on the heavily T2-weighted images. In such cases, the proton density weighted images are important to exclude partial volume effects with CSF and in determining the position of the gray matter.

Most lesions were found in the frontal lobe, followed by the temporal and parietal lobes. This pattern was also seen for (juxta)cortical lesions. The total number of lesions measured with different sequences was highly correlated (all r values > 0.77). The percentage of (juxta)cortical lesions as a percentage of all lesions was 30% (6- 59%) for fast FLAIR, 29% (2 - 64%) for CSE and 28% (3 - 61%) for FSE.

Figure 3

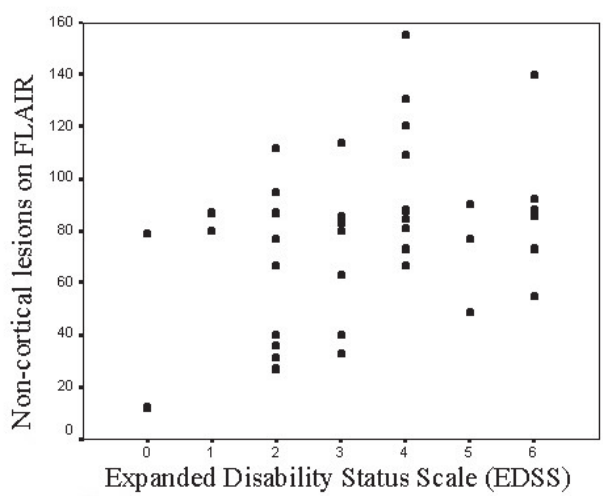
Scatter plot of the number of (juxta)cortical lesions detected with the FLAIR versus the Cognitive Impairment Index.



The correlation coefficient is 0.32 (p = 0.045). The number of non-cortical lesions did not correlate with the Cognitive Impairment Index.

Figure 4

Scatter plot of the number of non-cortical lesions detected with FLAIR versus the Expanded Disability Status Scale (= EDSS).



The correlation coefficient is 0.34 (p = 0.035). The number of (juxta)cortical lesions did not correlate with the Expanded Disability Status Scale (= EDSS).

Correlation of neuropsychological test results and clinical parameters with MR parameters

The CII is significantly correlated (figure 3) with the overall number of (juxta)cortical lesions on fast-FLAIR ($r = 0.34$; $p = 0.035$), and with the percentage of (juxta)cortical lesions on fast-FLAIR ($r = 0.36$; $p = 0.024$). However, the CII did not significantly correlate with the number of lesions measured by the other two techniques, nor with the non-cortical or the total number of lesions measured with any of the three techniques. None of the individual subtests of the Rao test battery correlated with the total number of ((juxta)cortical or non-cortical) lesions neither for the whole brain nor for any particular area. The EDSS correlated with the number of non-cortical lesions on fast-FLAIR ($r = 0.32$, $p = 0.045$) (figure 4), especially those in the basal ganglia ($r = 0.37$; $p = 0.02$).

No significant differences in contribution of the RR and SP patients was found for those results.

Compared to those with a score less than 10 on the CII, subjects who scored higher (eight patients) showed significantly higher scores on the EDSS ($p = 0.017$) and its Functional System Mental subscore ($p < 0.001$).

DISCUSSION

The goal of our study was to evaluate the correlation between the number of (juxta)cortical lesions as depicted by FLAIR and cognitive impairment. The CII, as indicator of cognitive dysfunctioning, showed a correlation with the number of (juxta)cortical lesions in the whole brain (FLAIR sequence), while the total number of lesions and the CII showed no correlation. Several earlier studies did report a correlation between the total lesion load or total lesion score (defined in many different ways) and general cognitive impairment (scored as an index of more than one cognitive domain, evaluated with different tests, or as the score of one of the cognitive areas)[83,203,250]. In some studies the total lesion load or score showed a relation with the following cognitive domains: intelligence[5,203], attention[96,227], verbal and nonverbal memory[83,96,177,227], abstract and conceptual reasoning[83,203], recent

memory[203], visuo-spatial problem solving[83,203] and linguistic problems[203]. In a few studies no correlation between cognitive impairment and lesion load was found[83,99,146,203,250]. The inconsistency of these findings probably relates in part to the marked differences in techniques and definitions; a fact that is well illustrated by the lack of a statistical significant correlation between the number of (juxta)cortical lesion and cognitive impairment using CSE or FSE. Our results indicates a possible role of (juxta)cortical lesions measured with FLAIR in determining cognitive dys-functioning; further research is needed to evaluate this possible relation in greater depth.

We found a significant (but not very strong) correlation between the (juxta)cortical lesions detected with the thin slice FLAIR and cognitive impairment measured with the Brief Repeatable Battery. This is despite the fact that the Brief Repeatable Battery was developed as a cognitive screening tool. It is not especially suitable for assessing focal cognitive deficits and calculating correlations with regional lesion load. The Selective Reminding Task and the 10/36 Spatial Recall Test are verbal and visual memory tests respectively, the PASAT and the Symbol Digit Modalities Task are attentional tasks and Verbal Fluency tests executive skills. All of those functions are probably more spread throughout the brain, rather than being localised in a single region. The fact that the overall number of (juxta)cortical lesions is well correlated with the CII and none of the regional lesion loads did, underlines this hypothesis. Correlations with regional lesion load or score have been described for abstract reasoning[3,250] with the number of frontal lesions; for visuo-spatial problem solving, attention and verbal memory with the number of parietally localised lesions[250] and frontal lobe impairment with the frontal lobe lesion load[80,227]. Some studies described a relation between existence of periventricular lesion and different aspects of cognitive impairment[152,194]. In further research more specific tests should be used to evaluate correlations between number of (juxta)cortical lesions in a certain area and cognitive dysfunctioning in MS patients. Functional MRI, which can locate brain activity in stead of brain lesions can play a role in this research field.

Besides the correlation between the CII and the number of (juxta)cortical lesions, the number of non-cortical lesions showed a significant correlation with the EDSS. The latter phenomenon has been described a number of times [e.g. by Huber et al.[99]], although

there is no consensus about the relation between physical disability and cognitive impairment[3,76,146,176,182,200,249,260]. It thus seems that non-cortical lesions are more important for physical disability, while (juxta)cortical lesions have more impact on neuro-psychological functioning.
Our findings are in line with those recently reported by Miki et al.[156], where the presence of U-fibre involvement was found to be associated with cognitive impairment, regardless of physical disability.

Our study showed no significant differences between the number of lesions on FLAIR images compared with CSE or FSE. This was the case for both the (juxta)cortical and the non-cortical lesions. This is in contrast to most earlier work, which reported more (juxta)cortical lesions using the FLAIR sequence[75,88,139,248,288], although some studies[256] did not find more lesions on FLAIR than on spin echo images. We feel that the relatively high number (30% of all lesions seen on fast FLAIR) of (juxta)cortical lesions in our study relates to the use of thin slices (3 mm). This results in reduced partial volume averaging effects with sulcal CSF and favours the detection of typically smaller lesions in the cortical region[117]. Interestingly, many lesions detected by FLAIR were not seen with CSE and FSE, and vice versa. In the absence of a gold standard, it remains highly speculative what may have caused this discrepancy.

CONCLUSIONS

While MS is typically considered to be a pure white matter disease with a subcortical pattern of dementia[195], recent publications have renewed the interest of (juxta)cortical lesions. Our study suggests that such lesions may be important in determining cognitive decline in MS. The FLAIR sequences proved to be significant in detecting those (juxta)cortical lesions which correlated best with cognitive impairment.

2.3 THE PSYLIQ STUDY

Adapted from: Multiple sclerosis

Brain atrophy and lesion load as explaining parameters for cognitive impairment.

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Multiple sclerosis, 2005 (11), 524-531

Abstract

OBJECTIVE

Multiple sclerosis (MS) is a multifocal demyelinating disease of the central nervous system, with lesions widespread through the brain and spinal cord. An important manifestation is cognitive impairment, which, though difficult to measure, may have a major social impact.

METHODS

To better understand the relationship between structural tissue damage and cognitive impairment, we examined the extent and spatial distribution of brain lesions, as measured by magnetic resonance imaging (MRI), in relation to abnormal cognitive performance as measured by the Brief Repeatable Battery (BRB) in 82 MS patients. Possible confounders, like fatigue, pain and depression were also assessed. Brain MR image analysis included hyperintense T2 and hypointense T1 lesion load in the whole brain and the four lobes separately, as well as whole brain volume measurements.

RESULTS

Cognitive impairment (defined as more than two abnormal tests) was found in 67% of the patients. Moderately strong correlations were found between the subtests of the BRB and the lesion loads in the brain regions hypothesized to be associated with that cognitive test, although these correlations were in general not much stronger than those between the subtests and the overall lesion load (due to strong interrelationships). The Spatial Recall Test correlated best with parietal lesion load; the Symbol Digit Modalities Test, the Paced Auditory Serial Addition Task (PASAT) and the Word List Generation best with frontal, parietal and temporal lesion load, while the Verbal List Generation Test Index correlated only with atrophy.

CONCLUSION

Atrophy and lesion load were the main factors determining the test scores, explaining 10 to 25% of the variance in the test results, and were more important than fatigue, pain and depression; only depression had a minor, but significant, additional effect on the PASAT.

In conclusion, cognitive impairment in MS, is moderately dependent on amount (and distribution) of structural brain damage, especially in the more physically impaired patients group.

INTRODUCTION

Multiple sclerosis (MS) is a multifocal demyelinating disease of the central nervous system, that leads to cognitive dysfunctioning in many patients. The pattern of cognitive impairment in MS is characterized by deficits in recent memory, sustained attention, conceptual reasoning and information processing speed, with preserved language and intellectual functions[202].

To assess neuropsychological problems in MS, the Brief Repeatable Battery (BRB) was developed by the MS Cognitive Function Study Group[198] and is since then widely used[11,77,96,242,243,244].

Table I
The BRB test results

Test	Cognitive functions tested	Hypothesized localization brain areas
Selective Reminding Task (SRT)[33]	verbal memory and in particular wordspan	left temporal lobe[138] and both frontal lobes
10/36 Spatial Recall Task (SPR)[12,200]	visuospatial memory and delayed recall	parietal lobes[94,138], probably also temporal lobes
Symbol Digit Modalities Test (SDMT[241])	sustained attention and concentration	multiple areas, in literature especially caudate nucleus (in Huntington disease)[138].
Paced Auditory Serial Addition Test (PASAT[90])	sustained and divided attention and information processing speed	frontal and parietal lobes[47,285]
Word List Generation test (WLG)	verbal fluency test	frontal and temporal lobes for example[175]

The final BRB version consisted of five test [table I]. Those tests had the greatest power, of the 24 tests evaluated, in discriminating MS patients from healthy subjects. Hence the BRB allows the examination of (general) cognitive functioning in a comprehensive and time-efficient way, although not all domains are tested equally.

The purpose of our study was to investigate in a group of MS patients the relation between MR abnormalities (total extent as well as spatial distribution across the different brain regions) and the presence and pattern of neuropsychological impairment. For this study we analysed patients from two study samples, who underwent identical cognitive testing, except for the Selective Reminding Task (SRT), which was replaced by another verbal memory task in one of the samples.
While the brain regions subserving the functions necessary to perform these tests are not known in detail, we hypothesized some correlations between impaired cognitive function and location of lesions, based on the presumed active brain areas when performing the test [see table I].

MATERIAL AND METHODS

Study design

We evaluated 82 patients (33 men, 49 women) with definite MS according to the Poser criteria[192], they all were patients in our hospital at time of the study. Each patient underwent a clinical examination, followed by application of the BRB and finally an MRI scan. The clinical evaluation consisted of assessment of the type of MS, disease duration, level of education (in years) and a physical examination to determine the EDSS and the functional system scores[129]. Possible confounders included were pain, fatigue and depression. Pain was scored by means of a Visual Analogue Scale (rated by placing a point on a scale of 0 - 100 mm). Fatigue was measured by applying the fatigue severity scale[125] (FSS; a nine item questionnaire of fatigue related statements, every item scored 1 (full disagreement with the statement) to 7 (full agreement)), extended with a six item questionnaire of statements specifically related to fatigue in MS patients[236] (MS-FS; with the same scoring method). Depression was assessed through the Beck Depression Inventory[19] a self-rating depression scale.
The ethical review board the Vrije Universiteit Medical Center approved of the study and all patients gave informed consent.

Neuropsychological testing

As the current sample was drawn from two originally separate sources, to produce a large sample,

the SRT test[33] originally used in the BRB, was replaced, in the majority of patients (n = 56 (23 men, 33 women)), by the Dutch Verbal Learning and Memory Test (VLGT)[61], a comparable test for which normative scores were also available. Both tests are verbal memory tasks: they are item lists to measure wordspan. The outcome parameter of the VLGT is the global performance index (GPI), which is the total recall score; for the SRT the number of recalls is scored for each trial.

The Spatial Recall Task (SPRC) used is an adapted versions[200] of the original 7/24 Spatial Recall Test developed by Barbizet[12]. In the BRB version, the checkerboard is wider (6 x 6) and more checkers (ten) are used than in the original version. The SPRC score is the total number of correct responses for all three trials separately (SPRC1, SPRC2, SPRC3), their total (SPRC TOT) and a separate score for the delayed recall trial (SPRC DEL).

The Symbol Digit Modalities Test (SDMT) was developed by Smith in 1973[241]. It is a test measuring many cognitive domains, but especially sustained attention and concentration. The outcome parameter is the total number of correct substitutions.

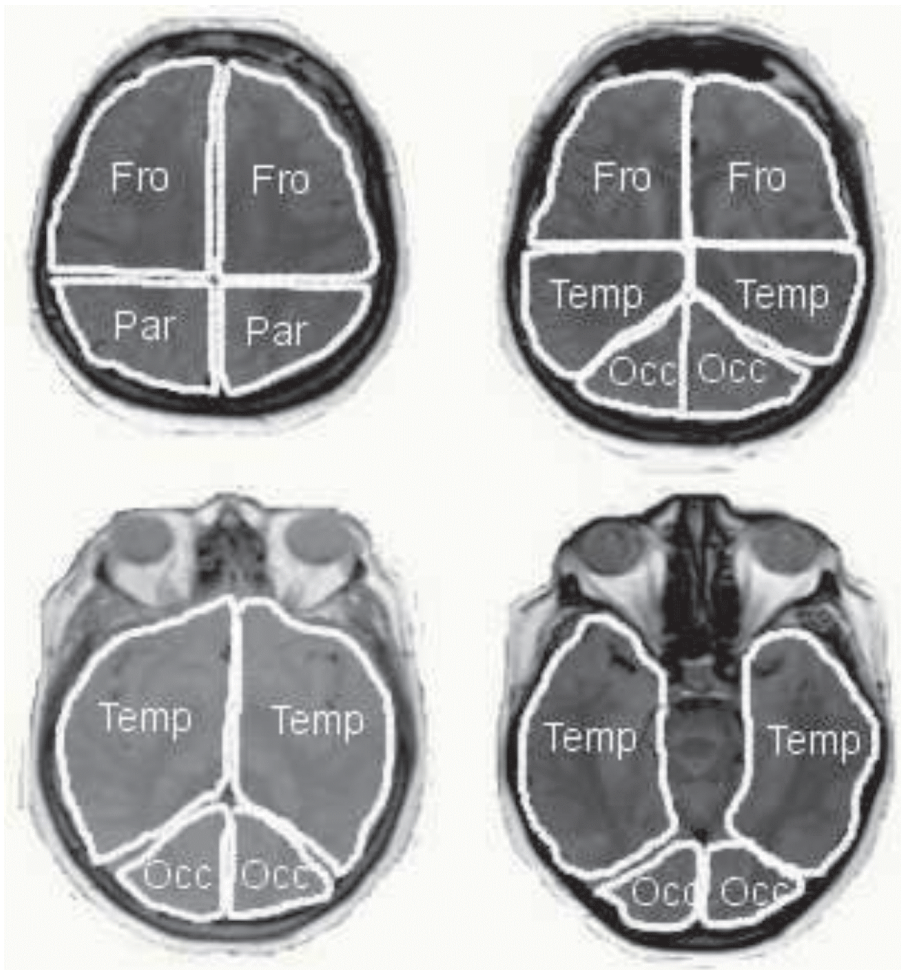
The Paced Auditory Serial Addition Task (PASAT) was developed by Gronwall[90] in 1977. It measures attention and concentration. The outcome score of the PASAT is the number of correct responses per trial (three seconds and two seconds number interval trial). The Word List Generation (WLG), also known as the Controlled Oral Word Association Task[245], is a semantic verbal fluency test to evaluate the spontaneous production. The score is the total number of correct responses.

MR imaging acquisition and analysis

MR imaging included T1 weighted (TR 620/ TE 15) and T2 weighted (TR 2500/ TE 45-90) sequences. Slice thickness was 3 mm with 1 mm in-plane resolution. Lesions were identified by visual inspection and were marked. Lesion load and brain volume measurements were performed on a workstation (Sun, Mountainview, California, USA) using home-developed semi-automated seed-growing software based on local thresholding (Show-Images), a method with high reproducibility, as described earlier by Van Walderveen et al.[267]. The total lesion load of hyperintense lesions as seen on the T2 images and of hypointense lesions on T1 weighted images were calculated, as were regional lesion loads in the four main brain areas (frontal, parietal, temporal and occipital; both left and right side; division

was performed by applying global landmarks by a trained and experienced operator) [figure 1].

Figure 1
The anatomical subdivision of the lobar regions as applied on this study.



On the highest slices a line halfway anterior and posterior was used to separate frontal and parietal. At the lower levels, once the splenium was visible, the posterior half was divided into occipital and temporal by use of a 90 angle, formed by the legs of the splenium.

Parenchymal and ventricular volumes were measured on T1-weighted images and intracranial volume was measured on the corresponding slices of the heavily T2-weighted images. Those volumes were used to calculate the relative brain volume (RBV = total parenchymal volume/ intracranial volume)[116].

Statistical analysis

Individual test results were considered abnormal when the score was more than 2 SD below the average score of a gender, age and education comparable control group[28]. To get a global index of neuropsychological performance, the Z-scores of all individual tests were, after signing them concordantly to cognitive performance, added to derive the Cognitive Index.

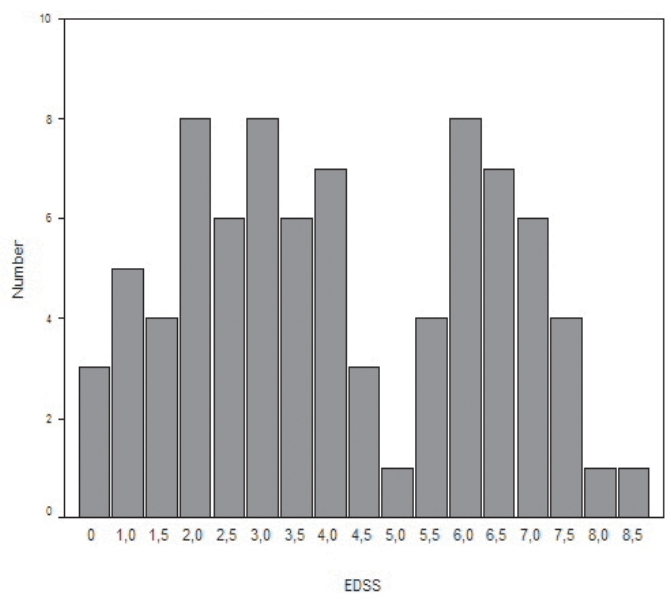
As MR data are typically not normally distributed, Spearmann's rank test was used to correlate (regional) lesion load and RBV with the test results. For none of the tests, with the exception of the SDMT, a significant correlation between the test score and the occipital lesion load was expected. Still the correlation between test score and occipital lesion load was calculated to reject the null-hypothesis that there is always a significant correlation between regional lesion load and cognitive test, because of the strong intercorrelations of tests and MR parameters.

For each neuropsychological test, a linear regression analysis was performed with the test score as the dependent variable. The independent variables were T2 lesion load, T1 lesion load and relative brain volume (as the MR parameters), EDSS, FSS, MS-FS, VAS pain and the Beck Depression Inventory (as the clinical scales), and years of education, age and gender (as possible confounders). To correct for skewness, the lesion load measurements were log-transformed before entering them in the model. A forward stepwise approach was chosen and the probability to enter the model was set at 0.05.

RESULTS

The patients had a mean age of 47.0 years (range 27 - 73); median level of the education was 11 years (range 4 - 20). Their EDSS scores ranged from 0 to 8.5, with a median of 4, and a typical bimodal distribution (figure 2)[275,276]. Of the 82 patients, 31 had a relapsing-remitting type of MS (mean age 42 years), 33 a secondary progressive form (mean age 47 years) and 18 a primary progressive form (mean age 55 years). Mean disease duration from the time of first symptoms was 15.3 years (range 3.3 - 35.0), and from the time of diagnosis 10.5 years (range 1 - 26.6).

Figure 2
Frequency distribution of the EDSS scores.



On the Beck Depression Index, the scores ranged from 1 to 26 (mean 10.6). The pain score on the Visual Analogue Scale ranged from 0 to 75 mm (mean 20 mm). The FSS scores ranged from 9 to 68 (mean 44.5) and the MS-FS from 6 to 39 (mean 23.3).

Results of the individual cognitive tests are represented in table II. Most test scores are, as the skewness shows, normally distributed. Each test of the BRB correlated significantly with most other tests (r from 0.32 to 0.87), with the exception of the PASAT and some of the subtests of the SPRC. The SRT was discarded for calculating correlations with specific brain regions, because too few people performed the SRT to have enough statistical power.

Table II

Neuropsychological test results.

Test	Mean	Min	Max	SD	skewness
SPRC1	5.42	1	9	1.81	-0.255
SPRC2	6.54	1	10	1.98	0.027
SPRC3	7.60	3	10	2.07	-0.431
SPRC TOT	19.56	7	29	4.86	-0.061
SPRC DEL	6.88	1	10	2.52	-0.480
SDMT	45.22	17	83	13.67	0.114
PASAT 3	39.70	0	60	18.93	-1.048
PASAT 2	29.44	0	55	15.36	-0.536
WLG	24.13	9	38	5.68	-0.056
GPI (n = 56)	47.50	22	66	11.20	-0.373
SRT (n = 26)	6.75	.83	11.0	3.04	-0.434

The mean, range, standard deviation (SD) and skewness of the test results of the Spatial Recall Test (three runs (SPRC1, SPRC2, SPRC3), together the SPRC TOT, and the delayed test (SPRC DEL)), the Symbol Digit Modalities Test (SDMT), the Paced Auditory Serial Addition Test (PASAT, the three seconds (PASAT 3) and two seconds version (PASAT 2)), the Word List Generation Task (WLG), the Global Performance Index of the VLGT (GPI) and the Selective Reminding Task (SRT).

In 6 - 44% of the patients, the individual test results were more than two SDs below the results of normal healthy controls; the SDMT was most often affected [table III]. For all tests, the group with an EDSS 4 had a greater percentage of patients with test results under the norm scores than the group with an EDSS < 4 [table III]. Cognitive impairment, defined as abnormal scores in two or more tests (or as a Cognitive Index below -2) was found in 67 % of the patients, only 18 (22%) patients scored less than 1 SD below the normative value.

No significant correlations were found between the possible confounders and the cognitive test results, except for the PASAT and the SDMT with the confounder MS-FS.

The MR parameters (RBV, total and regional lesion loads) are described in table IV. The greatest lesion load was found in the frontal lobes and smallest in the occipital lobes, both for the T2 and T1 lesion load. All regional lesion loads correlated well with each other (for T2 range 0.31 - 0.90; for T1 range 0.31 - 0.91) and with the total lesion load (for T2 range 0.66 - 0.90; for T1 range 0.61 - 0.91, all with a $p < 0.001$). The RBV ranged from 0.65 to 0.90 (mean 0.80). This RBV showed a correlation of -0.61 with the T2 total lesion load and -0.57 with the T1 total lesion load ($p < 0.001$).

Table III

Percentages of the patients which had a test result of more than 2 SDs below the mean scores in a healthy control group[28].

	> 2SD below mean			> 1 SD below mean
Test	Total group	EDSS < 4	EDSS >= 4	Total group
SPRC Total	12 %	10 %	14 %	33 %
SDMT	44 %	33 %	55 %	61 %
PASAT3	23 %	10 %	36 %	29 %
PASAT2	16 %	5 %	26 %	24 %
WLG	6 %	5 %	7 %	20 %
GPI and SRT	18 %	14 %	22 %	44 %

Table IV

Mean T2 and T1 lesion loads (SD) in total brain and different brain regions (in cm^3).

Lesion load (cm^3)		T2	T1
Total		11.40 (14.40)	3.10 (5.70)
Frontal lobe	right	2.24 (3.16)	0.65 (1.22)
	left	2.10 (3.17)	0.53 (0.97)
Parietal lobe	right	1.14 (1.61)	0.19 (0.34)
	left	1.08 (1.45)	0.16 (0.33)
Temporal lobe	right	1.03 (1.32)	0.35 (0.41)
	left	0.99 (1.29)	0.28 (0.46)
Occipital lobe	right	0.72 (0.81)	0.25 (0.33)
	left	0.66 (0.72)	0.24 (0.31)

The total T2 lesion load ranged from 0.11 to 93.05 cm^3 (mean 11.40 cm^3) and the total T1 lesion load ranged from 0 to 41.97 cm^3 (mean 3.10 cm^3).

MR lesion load measurements were correlated with the test scores [table V]. The Cognitive Index correlated with the lesion load of the total brain for both T2 (-0.418; $p < 0.001$) and T1 lesions (-0.389; $p < 0.001$), and with the RBV (+0.427; $p < 0.001$). When the group was dichotomized at a Cognitive Index of -2, the cognitively more impaired group showed a significantly greater lesion load on T2 and T1 images than the cognitively more intact group (for T2: 13.29 vs 7.19 cm^3, $p = 0.029$; T1: 3.83 vs 1.48 cm^3, $p = 0.020$); the RBV was lower (0.79 vs 0.82 ; $p = 0.012$) in the cognitively more impaired group. All tests correlated significantly with the RBV [table V].

In general terms it could be said that the correlations between the cognitive test and the areas hypothesized to be associated with that test were higher than with the other brain areas, although the differences are not very high. As hypothesized the lesion load in the occipital cortex did not correlate with any of the tests for the T2

Table V

Correlations of lesion loads and test scores.

	LL		SPRC tot	SDMT	PASAT3	PASAT2	WLG	GPI
T 2	total		-0.226 *	-0.503	-0.405	-0.374	-0.430	
	frontal	r		-0.459	-0.345	-0.297	-0.486	
		l		-0.558	-0.319	-0.311	-0.380	
	parietal	r		-0.403	-0.323	-0.330 *	-0.360	
		l	-0.269 *	-0.448	-0.335	-0.350	-0.421	
	temporal	r		-0.318	-0.294	-0.254 *	-0.298	
		l		-0.348	-0.231 *		-0.259 *	
	occipital	r						
		l						
T 1	total			-0.485	-0.312	-0.332	-0.347	
	frontal	r		-0.391	-0.382 *	-0.334 *	-0.353 *	
		l		-0.540		-0.339 *	-0.304 *	
	parietal	r		-0.388		-0.320 *	-0.449	
		l		-0.358 *	-0.400	-0.360 *	-0.482 *	
	temporal	r			-0.438	- 0.386 *	-0.403	
		l		-0.416			-0.336 *	
	occipital	r		-0.317 *				
		l						
Relative brain volume			0.247 *	0.537	0.339	0.360	0.272	0.409

Results of the correlations of lesion load and test scores. Non parametric (Spearman rank) results. For the occipital region lesion load correlations were calculated as a negative control.

empty fields p 0,05; * p < 0.05; p < 0.01; p < 0.001

Table VI

Regression analysis results for the neuropsychological tests.

Test	Main significant factor	Covariates (other significant)	adj. R^2
SPRC tot	T2 lesion load	-	0.110
SDMT	Rel. Brain Vol.	T2 lesion load	0.367
PASAT3	T2 lesion load	BDI	0.281
PASAT2	Rel. Brain Vol.	BDI	0.208
PASAT tot	T2 lesion load	BDI	0.270
WLG	Rel. Brain Vol.	-	0.490
GPI	Rel. Brain Vol.	-	0.237

Regression analysis was performed after a log transformation of the lesion load measurements. A forward stepwise model was used, with the test score as the dependent variable and MR parameters (RBV, log transformation of T2 lesion load, log transformation of T1 lesion load), clinical scales and other possible confounders (pain, FSS, MS-FS, depression (BDI), age, sex and education) as independent variables. The probability for a variable to enter the model was set to 0.05. The adjusted R^2 represents the explained variance of the total model.

lesions, while for the T1 lesions only the right side correlated significantly with the SDMT score; we thus feel right to reject the null-hypothesis that correlations of other regions with cognitive measures are due to chance.

The statistically significant correlations between MR lesion load measurements and test scores were mainly driven by the patients with a high EDSS score (> 3.5) who in general showed higher correlations than those with a low EDSS score.

Regression analysis [table VI] showed that for all individual tests the main significant factor, i.e. the factor that explained most of the variance in the test score, was always one of the MR parameters. T2 lesion load and RBV explained most of the variance, and addition of other explanatory variables only made small differences in the adjusted R^2 of the model. For the SDMT, both MR parameters independently explained variance. For the models of the PASAT, the depression rating was of minor

importance in explaining the test score variation. The other confounders considered in this study (age, sex, pain, fatigue, education) showed no independent contribution to any of the associations examined.

DISCUSSION

Cognitive impairment is a major problem in MS[18,83,202,260]. In our study, consisting of patients not selected for cognitive problems, 67% of the patients had a Cognitive Index below -2 (indicating cognitive impairment). For the individual tests, 6-44% of the patients scored 2 or more SDs below the normal mean score. When a less conservative threshold than two SD is used, even more MS patients could be considered cognitively impaired. Only 22% of the patients scored in the normal range for all tests.

Many studies have reported a correlation between total brain lesion load and cognitive impairment[39,83,133,203,244,250]. The influence of regional lesion loads and brain atrophy on more specific cognitive problems is far less known, especially for the widely used BRB[5,21,42,80,96,165,227,250]. Our main finding was that per test certain regions correlated significantly with the test score, roughly in keeping with the hypothesized regions based on (neuropsychological) literature. Although not very high differences were observed, those correlations do not represent an overall intercorrelation state, e.g. occipital lesion load did not significantly correlate with most test scores. Relative brain volume correlated well with lesion loads and with most of the test results. Moreover, it proved to explain a substantial part of the variance in test results.

We used the BRB as test instrument for cognitive functioning, with a small adaptation for the verbal memory task in part of the group. The BRB is a good instrument in discriminating MS patients from healthy subjects. The tests in this battery are selected for that purpose, not to investigate all cognitive domains equally well. This situation makes it harder to find a relation between cognitive test scores and regional MR parameters. Because we put together two data samples, to get a bigger sample volume, we had the disadvantage of two different verbal memory tests. Although

they are supposed to test the same cognitive domain, the differences makes it more difficult to interpret the results of those two tests together. The two cohorts did not differ in source or disease specific parameters.
The verbal memory tests probably need brain activity that has its main side of activity in the (left) temporal lobe and the frontal lobes. These hypothesized regions indeed showed a correlation with the VLGT test scores; however these were not stronger than for overall lesion load nor were there strong differences between left and right. The SPRC was expected to correlate with the (right) parietal lobe and the temporal lobes; however, correlations were only found with the left parietal lobe. The other areas did not reach significancy, as was the case for the overall lesion loads. The SDMT was expected to correlate with lesions in the whole brain and our results corroborated this notion, both for T2 and T1 lesions. Attention as is needed in the PASAT is believed to be located in the frontal and parietal lobes. A significant correlation of the test score with the lesion load in the frontal lobes, parietal lobes and whole brain was shown; in addition, a correlation with the temporal lobes was demonstrated. The WLG was also hypothesized to be a 'whole brain test', which was substantiated by our results, again with exception for the occipital lobes.

Sperling et al.[244] also found significant correlations between the BRB test scores and regional lesion loads. The correlations they found were for all but one test (the WLG) always with the same areas, namely total brain and the frontal and parietal lobes. The WLG did not correlate with the total lesion load, nor with any regional lesion load in their study[244]. Because in their study the frontal and parietal regional lesion loads formed almost the complete total lesion load, and (therefore) correlated very strongly with the total lesion load ($r > 0.97$), we feel that the anatomical definitions or the MR imaging technique and analysis used in that study, may have precluded a more differentiated result.

Our main issue in this study, establishing the relation between (regional) lesion load and test scores, was as hypothesized for most tests. However, the correlations were not very strong, indicating other contributing factors. The strength of the correlations was comparable to a previously published study[244], although some small differences existed. We observed the greatest lesion load in the frontal lobes, but

all regional lesion loads and the total brain lesion load had strong intrinsic correlations, as was found by others[244,250]. That not all areas are, at least on a functional level, equally involved, is reflected in the cognitive dysfunction profile in MS patients. Language disorders, for example, are rare, while attention and recent memory are often affected.

Establishing the impact of regional lesion load on test scores depends a great deal on the specificity of the tests used. All tests of the BRB are selected on the basis of a high incidence of abnormal scores in a MS group[202], and the tests used are tests in which more than one brain area is involved. That more or less the whole brain is involved in those tests is partly represented by the presence of strong correlations with the RBV. However, for most tests one or a few brain areas can be identified that are thought to be more involved in the tasks needed to perform the test than other brain areas. The regional analysis, as defined in this study, may not have been precise enough to reveal more specific spatial relations. However, in the absence of well defined functions and spatial restrictions, it is practically impossible to address these in more detail.

The third major factor that could have influenced the observed correlations, are other parameters, like pain, fatigue, depression, age, sex and education, that might have an impact on cognition. In our data set, regression analysis revealed that those parameters were of marginal importance [table IV]. The regression analysis also showed that even the main factors (RBV, lesion load measurement) only predicted at best 25% of the variance in test score.

In our study we put together the results of all MS subtypes, although there is more and more evidence that PP type patients have a distinct cognitive impairment pattern (for example [17,58,101,290]). In this study we were unable to find differences between subtypes, probably because the subgroups were too small to reliably detect differences.

CONCLUSIONS

In conclusion, our study confirms the frequent occurrence of cognitive dysfunctions in MS patients, as well as the moderately strong relation with structural brain damage (atrophy and regional lesion load), across the disease subtypes. The regional relationships with each test score reflect the fact that certain brain areas are more involved in one test than other areas. Nevertheless, strong intercorrelations were found, illustrating the widespread distribution of the disease and the (resulting) general cognitive dysfunctioning as captured by the BRB. However, even though in this study cognitive impairment in MS is dependent on amount (and distribution) of MR abnormalities, structural brain damage explains only about 25% of the variance in the cognitive test results.

2.4 THE ANT TASK IN MS

Adapted from: Neuropsychologia

Information processing characteristics in subtypes of multiple sclerosis.

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Abstract

OBJECTIVE

The purpose of this study was to evaluate information processing characteristics in patients with multiple sclerosis (MS).

METHODS

We selected 53 patients with MS and 58 matched healthy controls. Using computerized tests, we investigated focussed, divided, sustained attention, and executive function, and attempted to pinpoint deficits in attentional control to peripheral or central processing stages.

RESULTS

The results substantiate the hypothesis that cognitive slowing attention-demanding (controlled) information processing underlying more complex cognitive skills is general, i.e. irrespective of type of controlled processing, with MS patients being 40% slower than controls. MS patients may suffer from focussed, divided and sustained attention deficits, as well as from compromised central processing stages, with secondary progressive (SP) patients showing the most extensive range of deficits, closely followed by primary progressive (PP) patients, while relapsing–remitting (RR) patients appear to be much less affected. General slowing appears to be highest in PP and SP type MS patients (50% slower) versus relapsing–remitting MS (24% slower). In contrast to most previous results, (complex) processing speed appeared to be robustly correlated with severity of MS as measured by the expanded disability status scale and with disease duration.

CONCLUSION

Patients did much less differ in accuracy of processing from controls, suggesting the importance of using time strategies in planning everyday life and job activities to compensate for or alleviate MS-related speed handicaps.

INTRODUCTION

Several reviews of neuropsychological studies in multiple sclerosis (MS) indicate the frequent occurrence of deficits in various domains of cognitive function such as recent memory, attention, information processing speed, executive function and visuospatial perception, whereas general intelligence, language, and short-term memory seem to be preserved[183,195,196]. However, a recent meta-analysis of 36 studies focussing on performance differences between MS patients and healthy controls showed that general cognitive ability, in particular performance IQ, discriminates between MS patients and healthy controls, and that language and verbal intellectual ability may be affected by MS[284]. A significant effect of rapid processing demands was seen across neuropsychological tests, suggesting the importance of processing speed and working memory demands in neuropsychological investigations with patients with MS. Vulnerability to increased demands for speed and working memory might be manifestations of a reduced processing capacity. MS patients therefore seem to suffer from deficits in controlled information processing which is serial, attention-demanding, and limited by the capacity of the working memory[233,240] MS results in multiple focal areas of axonal demyelination with lesions[54,274], occurring especially in the white matter surrounding the ventricles, within the deep white matter of the frontal lobes, and within the corpus callosum[31]. In the neural efficiency model of intelligence, differences in performance on intelligence tests are attributed to differences in the speed and efficiency with which acquired neurophysiological processes are executed[269]. There are several theories suggesting a relation between intelligence level and central nerve conduction speed[211,212]. Miller postulated the hypothesis that nerves with thicker myelin sheaths are faster and more accurate in signal processing[158] and Peters suggested that myelin breakdown slows neural conduction along an axon and may influence problem solving speed[181]. If the slower information processing in patients with MS is indeed associated with neural demyelination, it appears likely that the slowing would be global rather than restricted to a few tasks.

Data on the generality of cognitive slowing are still scarce as, to date, only three relevant studies have

been published. Kujala et al.[126] reported widespread slowing on speeded tasks in patients with MS with mildly deteriorated cognitive functioning. Kail and Salthouse[113], using Brinley plots[29] as a method to study cognitive aging[37,230], examined the extent of cognitive slowing in MS by fitting reaction time (RT) data of MS patients and healthy controls to the regression equation $RT_{MS} = a + b\ RT_C$ which states that the mean RT of a group of MS patients will increase linearly as a function of the mean RT of a group of healthy controls. Kail et al.[111,112] confirmed this hypothesis in a meta-analysis of archival data from 12 studies and another study in which original data were collected. Meta-analyses, however, are flawed by the use of archival data from different studies, which implies that regression equations might be confounded by sample characteristics, and limitations in sample size (11 female MS patients) and data set (only 15 data points from three tasks). As argued by Kail et al.[112], firmer conclusions about the general slowing associated with MS will require a larger and more representative sample of MS patients and a wider range of cognitive tasks.

We performed a study to compare the speed and accuracy of performance on a comprehensive set of information processing tasks designed to evaluate basic processes underlying more complex cognitive skills, i.e. attention-demanding (controlled) information processing, in MS patients and healthy volunteers. Further, we explored whether the rate of slowing varies as a function of subtype of MS, i.e. relapsing-remitting (RR), secondary progressive (SP), and primary progressive (PP). Following the assumption that cognitive slowing is general, we expected this slowing to be reflected in a fit of the data to the regression equation of the above formulated type.

METHODS

Subjects

Patients with clinically definite multiple sclerosis according to the criteria of Poser et al.[192] were randomly selected at the secondary/tertiary referral centre for MS of the Vrije Universiteit Medical Center, and SP, PP, and RR MS subtypes were classified according to the criteria of Lublin and Reingold[142]. Patients with any other CNS disorder, or metabolic, psychiatric, learning disorders or a condition other than MS that

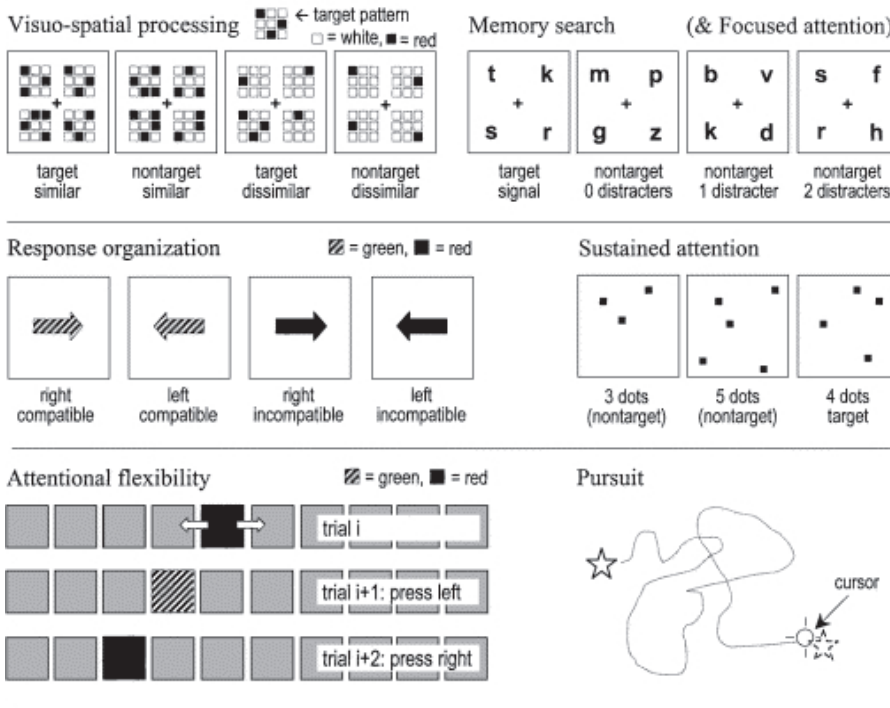
might have interfered with tests were excluded. The recruitment procedure resulted in a population that is quite typical for a hospital-based series, which is of course different from a population-based series. Healthy controls were chosen from the community to match the patient group according to age, gender, and level of education. Age at testing and at diagnosis, disease duration (years passed since diagnosis and years passed since occurrence of first subjective symptoms), and education level derived from a three-point scale in which 80, 100, and 120 denoted 8, 9 - 10, or > 10 years of education, respectively, were recorded. The Extended Disability Status Score (EDSS)[129], used to estimate severity of MS, was obtained by a physician, according to standardized procedures, who was blind to the test performances and had received special training for this purpose. All patients were tested when they were clinically stable and had a level of visual acuity that would not interfere with task performance. The Medical Ethics Committee of the Vrije Universiteit Medical Centre Amsterdam, approved the research protocol, and informed consent was obtained from all participants.

Tasks

Eight tasks from the Amsterdam Neuropsychological Tasks program[56] were administered in approximately 1h 10 minutes in a fixed order as indicated below. The paradigms, designed to tap skills ranging from basic reaction speed and simple perceptual-motor processes to neuropsychological functions underlying the more complex cognitive processes, have been used extensively in patient populations and have proven to be sensitive to the effect of medical treatment programs that are well known to influence brain function[32,60,188,232].

The reaction time paradigms are modelled according to the attention theory of Shiffrin and Schneider[233,240] who postulated attention as a limitation in the rate at which information can be processed in the working memory. The tasks also allow the application of the additive factor method of Sternberg[247] who defined cognitive processing as a set of independent component mental processing stages that represent the subsequent transitions from stimulus input to response output, e.g. encoding, memory search, decision, and response organisation. Through manipulation of appropriate task variables, the duration of the information processing stages can be influenced. Deficits associated with these stages can be identified by showing that task effects are

Figure 1
Examples of the signal types in the neuropsychological tasks.



The panels in depict examples of the signal types in: the visuo-spatial task (upper left) and part 3 of the memory search task (upper right), the response organisation task (centre left) and the sustained attention task (centre right), an example of three consecutive trials in part 3 of the attentional flexibility task (lower left), and the pursuit task (lower right).

larger in the experimental group(s) than in a control group, i.e. testing the task effect x group interaction. Processing deficits can thus be pinpointed to limitations in peripheral stages (perceptual and response processes) and central stages (memory and decision processes) of information processing.

All test stimuli were presented on a computer screen and subjects were required to respond by pressing a mouse key, or to use the mouse as tracking device. 'Yes' and 'no' answers were assigned to the right and left mouse keys, respectively, for right-handed subjects, and the other way around for left-handed subjects. Practice runs were given

prior to each test, and subjects were instructed verbally in combination with a display of probes and stimulus types on the screen before practising. The same trained instructor tested all subjects. In all reaction time (RT) tasks the evaluation parameters were speed and accuracy of responses per signal type, the employed post-response interval (PRI: period between response and next stimulus onset) was 1200 ms unless indicated otherwise, and signals were presented in pseudo-random order.

Baseline Speed

In the baseline speed task, subjects have to press a key with the index finger whenever a square appears in the centre of the screen (32 trials for each hand). The PRI randomly varies between 500 and 2500 ms to prevent anticipatory strategies. As cognitive demands are restricted to the mere detection of a stimulus, this task measures simple response speed.

Divided attention: visuo-spatial processing (encoding)

After memorization of a predefined target pattern (see figure 1, upper left panel) subjects have to detect this target pattern in a signal consisting of four patterns. Half the signals contain this target pattern (target signals) requiring the subject to press the 'yes'-key, the other half do not (non-target signals) in which case the 'no'-key should be pressed. For 50% of the target signals the other three patterns look very similar to the target, and in the other 50% the other patterns are very dissimilar to the target. Likewise, 50% of the non-target signals consist of four patterns that look similar or dissimilar to the target pattern. The similarity manipulation in this pattern recognition task affects the duration of the encoding stage of processing. The task consists of $4 \times 20 = 80$ trials.

Divided attention: Memory search

The memory search task employs a display load of four letters (see figure 1, upper right panel) and consists of three parts in which target set size (memory load) is increased from one to three target letters: k (part 1), k+r (part 2), and k+r+s (part 3). Signals that contain the complete target set require a 'yes'-response. All other signals, also those containing an incomplete target set, require a 'no'-response. RT to target signals is predicted to increase linearly with memory load, reflecting the prolongation of the memory search stage, with the slope of RT denoting the rate of memory search. In part 3, the presence of an insufficient number of target letters in non-target signal affects response time in that RT will

increase with the number of these 'distracters' (0 or 1 in part 2, and 0, 1, or 2 in part 3). Each part consists of 50% target and 50% non-target signals with 40, 72, and 96 trials in parts 1–3 respectively, with non-target trials evenly divided across distracter type.

Response-organisation

A left- or right-pointing arrow is presented in the centre of the screen (see figure 1, centre left panel). When the arrow is green, it requires a compatible response (arrow to the left: press left; arrow to the right: press right) and when it is red an incompatible response (arrow to the left: press right; arrow to the right: press left). Stimulus-response (SR) mapping is assumed to affect the duration of the response organization stage. The task consists of 4 x 15 = 60 trials.

Focussed attention

This task employs a similar four-letter display load as in the memory search task, but now only two diagonal locations are relevant (known in advance to the subjects) and subjects should attend to those positions only. A target signal is defined as a signal that contains a target letter on the relevant diagonal. Upon its presentation the 'yes'-key should be pressed. Irrelevant target signals, i.e. with a target letter on the irrelevant diagonal, and non-target signals (target letter absent) require the subject to press the 'no'-key. It is expected that the processing of an irrelevant target signal takes longest, or causes more errors, than of other signals. The task consists of two parts with a memory load of one and three target letters, respectively. Each task part consists of 40 target trials, 20 irrelevant target trials and 20 non-target trials.

Sustained attention

In this task, 50 series x 12 patterns (600 signals) are presented in a continuous fashion with a PRI of 250 ms. Each series contains an equal number of signals consisting of three, four or five dots (see figure 1, centre right panel), presented in random order. On four dots (target signal) subjects should press the 'yes'-key, on three and five dots (non-targets) they should press the 'no'-key. Main parameters are tempo (mean completion time per series), fluctuation in tempo and the change (deterioration) of performance level with time-on-task. During performance, subjects were informed about errors by a beep signal. Correct responses following an error were separately registered enabling the measurement of the effect of feedback, which is defined as the difference RT after feedback - RT regular.

Attentional flexibility

The signal consists of a horizontal bar that is permanently present (see figure 1, lower left panel). On this bar, a coloured square jumps randomly from left to right or vice versa. Depending on the colour of the square after the jump, the subject should copy the movement, i.e. press right (left) when the square jumped to the right (left), or is required to 'mirror' the movement, i.e. press left (right) at a right (left) movement. The task consists of three parts. In part 1 the subject is required to copy the movements, in part 2 only trials that require 'mirror' responses are presented, but in part 3 the square may change colour upon each jump in random fashion which forces the subject to adjust his response behaviour.

Parts 1 and 2 consist of 40 trials characterised by a fixed SR-mapping condition, either compatible (part 1) or incompatible (part 2), that does not require attentional flexibility. The 80 trials of part 3, with a random mix of the SR-mapping types, do require attentional flexibility. It is expected that the 'mirror' responses in part 2 are executed slower than the responses in part 1, and that those in part 3 are slower than those in part 1 and 2 because shifting attentional set takes its toll in terms of processing speed. In all parts a PRI of 250 ms is used.

Pursuit

This task assesses the quality of eye–hand co-ordination and fine motor control, constituting a measure of psychomotor speed. The subject has to track a small star, which moves continuously in a random fashion across the screen, by trying to position the mouse cursor as closely as possible on the moving star (see figure 1, lower right panel). Subjects have to constantly adjust their movements, as future movements of the star cannot be anticipated. The task time is 60 s. During task performance the mean distance between the moving target and mouse cursor per second task time is registered. The outcome measures are the percent of time-on-task that the subject satisfies the accuracy criterion, i.e. stays within 3, 6, and 12 screen units from the star, the mean distance to the moving target and the within-subject S.D. of this distance during time-on-task.

Disease severity

Neurological impairment was measured using the Extended Disability Status Score (EDSS), the most commonly used marker of severity of MS[129]. The evaluation of seven functional systems (pyramidal, cerebral (or mental),

brainstem, sensory, bowel and bladder, optic, and "other") and ambulation contribute to the total EDSS score.

Data analyses

Results were evaluated per task by analysis of variance with group (controls, RR, PP, SP) as between-subjects factor using the SPSS 10 statistical program. Helmert contrasts were chosen to compare controls with the total MS group (first contrast), RR with the PP + SP group (second contrast), and PP with SP patients (third contrast). The logic of these contrasts lies in our aim to (1) determine the existence of processing differences between controls and MS patients, (2) to investigate whether the RR patients meet our expectation that they are relatively better off than PP and SP patients, and (3) to test differences between the latter two groups. The various task manipulations were used as levels of within-subject factors in a repeated measures design and are indicated per task: Visuo-spatial analysis: stimulus type ('similars', 'dissimilars') and signal type (target, non-target); memory search: memory load (parts 1–3), distraction within part 3 (0–2 distracters); response organization: SR-mapping (compatible, incompatible); sustained attention: feedback (regular, after feedback); focussed attention: signal type (target, irrelevant target, non-target); attentional flexibility: attentional flexibility (not-required, required) and SR-mapping (compatible, incompatible); pursuit: accuracy criterion (level 3, 6, 12). Separate runs were made with reaction time and with accuracy (error percent) as dependent variable. As reaction time is correlated with age, and the RR group is younger than all other groups (including the controls, see table I), this variable was entered as a covariate in the reaction time analyses. Mean tempo and fluctuation in tempo in the sustained attention task, respectively mean distance and fluctuation in distance from target in the Pursuit task were entered in a multivariate analyses of covariance as the respective sets of variables are correlated. Subjects were excluded from task analysis when their error rate was >50% or in case of extreme mean RT values (>3× the interquartile range). The number of excluded subjects in the control group and MS group varied between zero and four per task (in total 15 exclusions across all eight tasks in the control and in the MS sample). The association of severity of MS and disease duration with task performance was investigated by performing multiple regression analyses. Because age, disease duration and neurologic disability are all

correlated with one another the EDSS total score, disease duration, age, and education level were used as predictors. For disease duration we entered two variables: years passed since diagnosis and years passed since occurrence of first MS symptoms as the former parameter is a conservative and the latter a probably more accurate measure of this predictor. The chosen method was backward in which all predictors were entered and then removed successively in case the removal criterion was met.

Table I

Group	Test age	EDSS	Education	Age at diagn.	Years since diagn.	Years since first sympt.	n
CTRL	47.3 ± 11.2		101.4 ± 14.4				58
PP	53.1 ± 13.9	5.4 ± 2.1	100.0 ± 11.8	45.9 ± 13.9	7.7 ± 6.3	13.3 ± 7.5	19
SP	50.6 ± 9.8	5.3 ± 1.6	108.2 ± 12.2	39.0 ± 7.7	11.6 ± 10.2	16.5 ± 10.7	18
RR	39.0 ± 8.9	3.0 ± 1.2	112.5 ± 17.7	33.2 ± 7.8	6.0 ± 5.1	8.0 ± 5.7	16
MS total	48.2 ± 12.6	4.7 ± 2.0	106.4 ± 14.6	39.5 ± 11.3	8.6 ± 7.8	12.8 ± 8.9	53

Test age, age at diagnosis (years), years since diagnosis, years since 1st symptoms, score on the Kurtzke expanded disability status scale (EDSS), level of education, for controls and MS groups

RESULTS

Subjects [table I]
Fifty-three patients with clinically definite multiple sclerosis were selected, comprising 18 SP (11 women, 7 men), 19 PP (12 women, 7 men), and 16 RR patients (11 women, 5 men). Age at testing and at diagnosis, EDSS scores, years

passed since occurrence of first subjective symptoms and years passed since diagnosis, and education level are summarised in table I.

The controls did not differ in age from the total MS group ($p = 0.94$). The RR patients were younger than the SP and PP patients ($p < 0.001$) who did not differ significantly from each other ($p = 0.46$). Education level of the controls was lower compared to the total MS group ($p = 0.046$). Differences in education levels between MS subgroups were marginally significant with the RR patients having the highest scores and PP patients the lowest scores ($0.06 < p < 0.09$). The RR patients had a lower EDSS total score compared to the other groups ($p < 0.001$) while the PP and SP groups did not differ ($p = 0.92$). Time passed between occurrence of first MS symptoms diagnosis and assessment was lower in RR patients compared to the other groups ($p = 0.015$) while the latter two groups did not differ on this measure ($p = 0.17$). A similar outcome was obtained as regards time passed since diagnosis ($p = 0.014$, $p = 0.07$).

Baseline speed

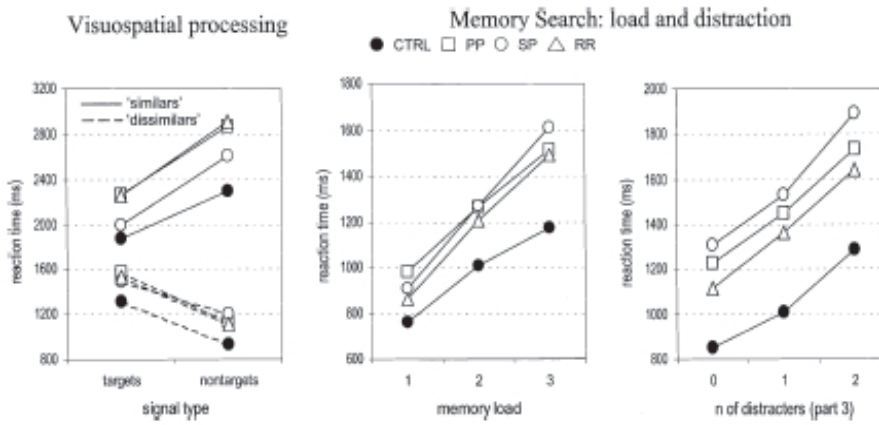
Mean reaction speed was 282 ± 37 ms for the controls and 361 ± 74 ms for the MS patients. The groups differed in speed ($F(3, 104) = 18.90$, $p < 0.001$], with controls faster than the total MS group ($p < 0.001$) and faster than the RR group ($p < 0.001$). The SP patients were marginally slower than the PP patients ($p = 0.079$).

Processing stages

Encoding (visuo-spatial task)

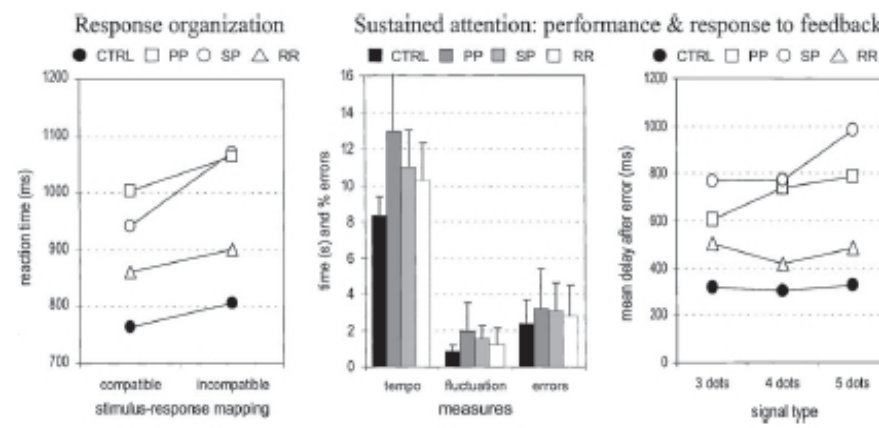
Figure 2 (left panel) shows that processing of 'similars' was much slower than of 'dissimilars' ($F(1, 91) = 12.30$, $p = 0.001$). Furthermore, stimulus type interacted with signal type: responses to non-targets were slower than to target signals in case of 'similars', while the opposite was true in case of 'dissimilars' ($F(1, 91) = 7.88$, $p = 0.006$). Groups differed in speed of processing ($F(3, 91) = 4.74$, $p = 0.004$) with total MS group ($p < 0.001$) with differences between MS subgroups being absent. Group interacted with stimulus type ($F(1, 91) = 3.33$, $p = 0.023$): differences in speed between groups were larger for 'similars' than for 'dissimilars'. Post-hoc analyses, comparing the separate MS subgroups with controls, confirmed this effect in the RR ($p = 0.011$) and PP ($p = 0.021$) groups. Accuracy of processing depended on signal and stimulus type. Error rates were larger for 'similars' than for 'dissimilars' ($F(1, 92) = 62.19$, $p < 0.001$), and differences were larger for target signals compared with

Figure 2



Performance on visuo-spatial processing and memory search tasks: left panel, RT as a function of signal type (target, non-target) and stimulus type ("similars", "dissimilars"); centre and right panel, RT as a function of function of memory load, respectively as a function of distraction.

Figure 3



Performance on response organisation and sustained attention tasks: left panel, RT as a function of stimulus-response mapping; centre panel, tempo (mean completion time per series), fluctuation in tempo, and error rate on the sustained attention task; right panel, increase in RT following feedback on errors as a function of signal type.

non-target signals ($F(1, 92) = 65.03$, $p < 0.001$), with error rates of 4.7 and 0.5% for 'dissimilar' targets and non-targets, and 15.4 and 3.6% for 'similar' target and non-targets respectively. Differences in accuracy between groups were absent ($F(3, 92) = 0.68$, $p = 0.57$).

Response organization

Figure 3 (left panel) shows that SR-mapping affected reaction time in that compatible responses were faster than incompatible responses ($F(1, 101) = 31.63$, $p < 0.001$). Groups differed in speed ($F(3, 101) = 8.43$, $p < 0.001$), with MS patients being slower than controls ($p < 0.001$), and PP + SP patients slower than RR patients ($p = 0.044$) who were not slower than controls ($p = 0.12$). Group interacted with SR-mapping ($F(3, 101) = 3.3$, $p = 0.024$), indicating that speed differences between MS patients and controls increase under incompatible SR-mapping conditions. This effect must be attributed to the SP group as was confirmed in a post-hoc analysis ($p = 0.004$). Mean error rate varied between 1.7 and 3.0% for all response types. There were no significant differences in accuracy between MS patients and controls ($0.31 < p < 0.82$).

Memory search

Figure 2 (centre panel) depicts the response latency to target signals as a function of memory load as imposed in part 1, 2 and 3 respectively, and the response latency to non-target signals in part 3 as a function of the presence of distracters (right panel). Both manipulations imposed high demands on the working memory system. Reaction time increased linearly with load ($F(2, 204) = 247.8$, $p < 0.001$). Groups differed in speed ($F(3, 101) = 11.32$, $p < 0.001$) with total MS group being slower than controls ($p < 0.001$) but differences between MS subgroups were not significant. Group interacted with memory load ($F(6, 202) = 4.64$, $p < 0.001$), reflecting that differences in speed between MS patients and controls increased with load. Post-hoc analyses confirmed this interaction effect in all MS subgroups separately (P 0.007). Mean error rates across response types varied between 3.0 and 7.0%. Overall group differences in accuracy were marginally significant ($F(3, 102) = 2.21$, $p = 0.092$) but the contrast analyses indicated that MS patients (total group) were less accurate than controls ($p = 0.022$). Differences in accuracy between MS subgroups were not significant. The analysis of the data of task part 3 shows that reaction time increased with distraction ($F(2, 204) = 439.7$, $p < 0.001$). Groups differed in speed ($F(3, 101) =$

13.33, $p < 0.001$] with MS total group ($p < 0.001$) but differences between MS subgroups were not significant. Group interacted with distraction ($F(6, 202) = 2.78$, $p = 0.013$) indicating that differences between MS patients and controls became larger with increasing distraction. Post-hoc analyses confirmed this interaction effect for the RR and SP groups (P 0.035). Mean error rates across response types were low and varied between 0.2 and 2.5%. Accuracy decreased with distraction ($F(2, 204) = 9.93$, $p < 0.001$), but differences in accuracy between groups were absent.

Decision

The difference between responses to target and non-target signals in part 1 of the memory search task was taken as an index of decision speed. 'No'-responses took longer than 'yes'-responses ($F(1, 102) = 174.66$, $p < 0.001$), Groups differed in speed ($F(3, 101) = 15.05$, $p < 0.001$), with MS total group being slower than controls ($p < 0.001$). The RR patients were also slower than the controls ($p = 0.012$) but faster than the PP + SP patients ($p = 0.027$). Signal type interacted with group classification ($F(3, 101) = 8.19$, $p < 0.001$) reflecting that decision speed was slower in MS patients. This interaction was significant for the comparison of PP patients ($p = 0.025$) and of SP patients ($p < 0.001$) with controls.

Sustained attention

Tempo and fluctuation in tempo varied significantly between groups ($F(6, 196) = 6.88$, $p < 0.001$). Contrast analyses showed that MS patients were slower and had a higher fluctuation in tempo ($p < 0.001$) (see figure 3, centre panel) than controls, RR patients were slower than controls ($p = 0.009$) but faster than the PP + SP patients ($p = 0.029$), and PP patients were slower than SP patients ($p = 0.024$). As regards fluctuation in tempo, contrast analyses revealed a higher fluctuation in MS patients compared to controls ($p < 0.001$), RR patients were more stable than PP + SP patients ($p = 0.05$) but did hardly differ from controls ($p = 0.073$). Accuracy was high, error rate varied between 0.7 and 3.8% only. Differences between groups in accuracy approached significance when the MS total group was contrasted with the controls ($p = 0.053$), showing lower accuracy in MS patients. Figure 3 (right panel) shows the mean delay following feedback on errors, calculated as the within-subject difference between RTs following error responses and RTs of similar responses following correct responses. This measure was taken to reflect the adequacy

of behavioural adjustment, i.e. taking more time after an error to process the next signal. Feedback caused a significant drop in response speed ($F(1, 92) = 8.61$, $p = 0.004$), and this delay varied between groups ($F(3, 92) = 13.15$, $p < 0.001$), with MS patients slowing down much more than controls ($p < 0.001$), RR patients did not differ from controls in this regard but RR patients slowed down less than PP + SP patients ($p = 0.008$).

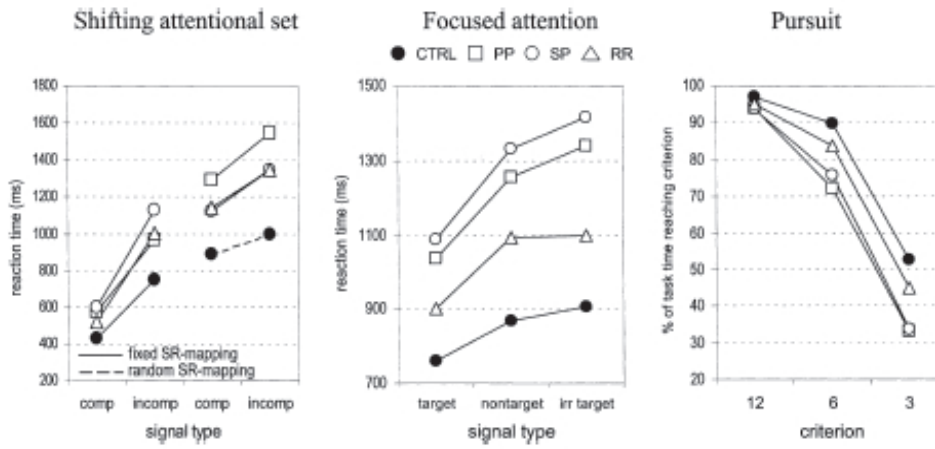
Attentional flexibility

Figure 4 (left panel) shows that compatible responses were faster than incompatible responses ($F(1, 95) = 127.44$, $p < 0.001$), and that reaction time of both type of responses increased further under random SR-mapping conditions (part 3) ($F(1, 95) = 263.31$, $p < 0.001$). Group differences in speed were significant ($F(3, 94) = 10.73$, $p < 0.001$), with total MS group ($p < 0.001$) but differences between MS subtypes were not significant. Differences in speed between groups were relatively larger for incompatible responses ($F(3, 94) = 3.36$, $p = 0.022$), and when attentional flexibility was required ($F(3, 94) = 6.98$, $p < 0.001$). Subsequent analyses indicated that the group × compatibility interaction was significant when contrasting SP patients and controls ($p = 0.003$) and the group×flexibility interaction was significant when contrasting PP patients with controls $p < 0.001$). Groups differed in accuracy ($F(3, 95) = 2.61$, $p = 0.051$) with total MS group ($p = 0.012$) being less accurate than controls ($p = 0.012$, mean error rate across task parts was 4.5% versus 2.8%) and RR patients being less accurate than controls ($p = 0.026$), while differences between MS subgroups were not significant.

Focussed attention

Figure 4 (centre panel) shows that reaction time depended on signal type ($F(2, 208) = 196.58$, $p < 0.001$), i.e. non-target signals take longer than target signals, reflecting the cost of exhaustive search, and the rejection of irrelevant target signals is slower compared to non-target signals which reflects the impact of the presence of the irrelevant target breaking through the process of focussed attending. Groups differed in speed ($F(3, 103) = 14.39$, $p < 0.001$), with MS total group slower than controls ($p < 0.001$) and RR patients faster than PP+SP subtypes ($p = 0.021$). Differences in speed between groups depended on signal type ($F(6, 103) = 9.98$, $p < 0.001$), with largest differences for the irrelevant target signals. Contrasting PP and SP patients with controls, these interactions were confirmed for the groups

Figure 4



Performance on attentional flexibility task, focussed attention task, and pursuit: left panel, RT as a function of attentional flexibility requirements (1, 2: fixed SR-mapping vs. 3: random SR-mapping) and type of SR-mapping (c: compatible SR-mapping, i: incompatible SR-mapping). Centre panel: RT as a function of signal type; right panel, accuracy as a function of criterion (staying <12, 6 or 3 screen distance units from the target).

separately ($p < 0.001$). Groups differed in accuracy ($F(3, 104) = 3.43$, $p = 0.02$) with overall mean error rates varied between 0.8 and 4.5%. Controls were more accurate compared to the MS total group ($p = 0.025$) and RR patients were more accurate than the SP + PP patients ($p = 0.039$) but they did not differ in accuracy from controls.

Pursuit (Eye-hand co-ordination)

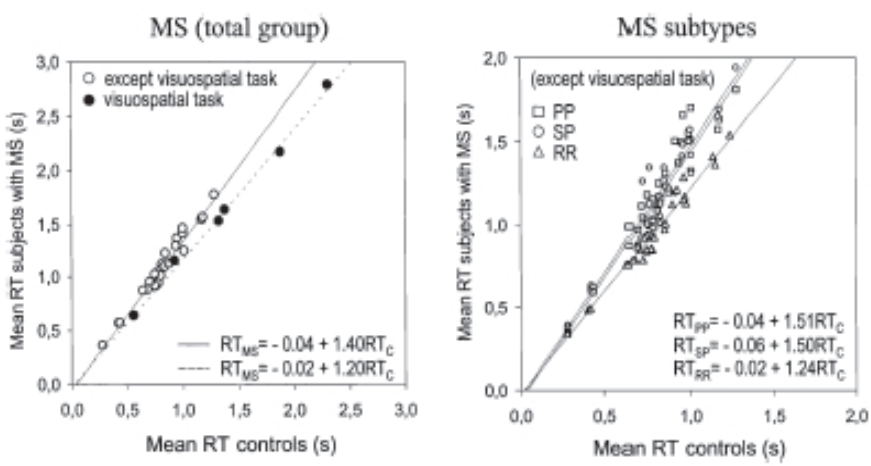
Groups differed in accuracy ($F(3, 96) = 9.71$, $p < 0.001$). The MS total group was less accurate in meeting the criterion than controls ($p < 0.001$), SP + PP patients were less accurate than RR patients ($p = 0.035$) and RR patients were marginally less accurate than controls ($p = 0.09$). Differences between groups increased when the criterion was set at a stricter level ($F(6, 192) = 8.38$, $p < 0.001$) [figure 4, left panel]. This interaction was confirmed when contrasting PP and SP patients with controls separately ($p < 0.001$). Multivariate analysis of mean distance and fluctuation of distance with time-on-task revealed significant differences between groups ($F(6, 192) = 3.93$, $p = 0.001$) [see figure 5, right panel]. Subgroup analyses confirmed these

differences for the PP ($p < 0.001$, $p = 0.003$) and SP groups ($p < 0.001$, $p = 0.05$) separately. The RR group did not differ significantly from the controls on all measures (P 0.13).

Regression analysis of cognitive slowing

The administered tasks provided 37 pairs of mean reaction times with values ranging from 0.35 to 2.80 s. Initial analysis made clear that more optimal solutions would be reached when the data from the visuo-spatial task (six pairs) would be fitted separately (see also discussion). This meant that two regression equations were fitted, one for the 31 pairs representing the data from all tasks except the visuo-spatial task and one for the six pairs from that task. This was done for the total MS group and per subtype. With R^2 varying between 0.96 and 0.99, there was a strong fit of the linear models. The values of the linear regression coefficient imply that MS patients take about 40% more time to respond than controls [figure 5, left panel]. For the MS subtypes these values were 51% (PP), 50% (SP) and 24% (RR), respectively [figure 5, right panel]. The slowing rate for the visuo-spatial task was much less with values of 20% (MS) [figure 5, left panel], 26% (PP), 15% (SP) and 21% (RR).

Figure 5



General slowing in (subtypes of) MS. Mean RT for subjects with MS as a function of mean RTs for controls, along with the line depicting the equation $RT_{MS} = a + b\ RT_C$, for all RT data without the visuo-spatial task (left and centre panel), and for the RT data of the visuo-spatial task, respectively (right panel). CTRL: control group.

Severity of MS (EDSS) and disease duration

The multiple regression analyses with the EDSS score, disease duration, age, and education level as potential predictors of task performance [see table II] show that disease duration and severity of MS (EDSS score) are substantially associated (on their own, or in combination with each other - memory search, response organisation, shifting attentional set) with speed of processing (0.30 r 0.66). The highest values are found for visuo-motor coordination pursuit: 0.56 r 0.75). Age in itself plays a minor role as this parameter was removed in 24 out of the 27 analyses, and it occurs only in combination with disease duration. Level of education plays a role, in combination with severity of MS or disease duration, only as regards the sustained attention task. The number of significant outcomes is much greater for reaction time measures than for accuracy measures (as regards the pursuit task, it is noted that the four outcome measures concerns parameters in which accuracy is a 'distance-from-target' parameter instead of error percentage).

DISCUSSION

Processing deficits

The present study shows that there are deficits in various attentional domains, i.e. divided, focussed and sustained attention, in patients with MS. They demonstrated a slower response speed compared to controls when they simply had to detect the mere presence of a stimulus. When higher cognitive demands were imposed in the more complex tasks, differences in speed between controls and MS patients increased dramatically. It was clearly shown that MS patients were slower in processing visually presented information. Significant task x group interactions revealed that differences between groups increased under more complex task conditions, indicating deficits in the two central processing stages "memory search" and "decision". Deficits in the peripheral processing stages were also present as indicated by the group x stimulus type (visuo-spatial task) and the group x SR-mapping (response organisation task) interactions.

Table II

Summary of regression analyses (backward method) for variables predicting outcome on the primary task performance indices

Task	Variable/index	Predictors	B	S.E. B	β	P	R
Baseline speed	RT	Yrs 1st symptoms	3.04	1.18	0.358	0.013	0,36
	Fluctuation	Yrs 1st symptoms	5.47	1.83	0.407	0.004	0,41
Visuo-spatial processing	RT	Yrs 1st symptoms	26.55	8.57	0.440	0.004	0,44
	Errors	EDSS	0.69	0.33	0.320	0.042	0,32
	Similarity effect (RT)	Yrs 1st symptoms	18.38	8.48	0.328	0.036	0,33
	Similarity effect (errors)	Yrs 1st symptoms	0.27	0.14	0.295	0.061	0,30
Memory search	RT	EDSS	59.32	22.09	0.350	0.010	0,59
		Yrs 1st symptoms	14.55	5.06	0.375	0.007	
	Errors	Yrs diagnosis	0.07	0.04	0.267	0.073	0,28
	Effect load (RT)	Yrs diagnosis	16.89	5.75	0.396	0.005	0,49
		EDSS	38.23	21.83	0.236	0.087	
	Effect distraction (RT)	Yrs 1st symptoms	9.44	2.93	0.437	0.002	0,44
	Decision (RT)	Yrs 1st symptoms	8.09	2.11	0.501	< 0.001	0,50
Response organization	RT	EDSS	50.06	17.17	0.395	0.006	0,55
		Yrs 1st symptoms	7.71	3.85	0.271	0.052	
	Errors	Yrs diagnosis	0.17	0.05	0.479	0.001	0,48
	Effect SR-mapping (RT)	Yrs diagnosis	6.52	2.01	0.441	0.002	0,44
Focused attention	RT	EDSS	96.63	22.12	0.546	< 0.001	0,55
	Errors	Yrs 1st symptoms	0.07	0.03	0.305	0.037	0,31
Shifting attentional set	RT	EDSS	47.22	20.83	0.285	0.029	0,66
		Yrs 1st symptoms	17.91	4.48	0.502	< 0.001	
	Effect flexibility (RT)	Yrs 1st symptoms	24.45	6.67	0.803	0.001	0,50
		Yrs diagnosis	−21.11	7.62	−0.607	0.008	
	Effect SR-mapping (RT)	Yrs 1st symptoms	12.83	3.97	0.451	0.002	0,45
Sustained attention	RT	EDSS	0.72	0.25	0.388	0.007	0,48
		Education	−0.06	0.03	−0.241	0.085	
	Fluctuation	Yrs diagnosis	0.02	0.02	0.318	0.031	0,32
	Errors	Yrs diagnosis	0.05	0.03	0.260	0.073	0,41
		Education	−0.03	0.02	−0.292	0.045	
	Delay after feedback	EDSS	85.56	31.81	0.387	0.010	0,39
Pursuit	Mean accuracy	Yrs diagnosis	0.15	0.04	0.512	< 0.001	0,74
		EDSS	0.51	0.14	0.432	0.001	
	Fluctuation	Yrs diagnosis	0.14	0.03	0.468	< 0.001	0,72
		EDSS	0.51	0.13	0.454	< 0.001	
	Criterion	Yrs 1st symptoms	−0.63	0.25	−0.301	0.016	0,70
		EDSS	−4.88	1.11	−0.528	< 0.001	
	High–low criterion	EDSS	4.36	0.99	0.561	< 0.001	0,56

Predictor variables entered: age at testing, education level, EDSS total score, and two disease duration indices: years since occurrence of first symptoms of MS (yrs 1st symptoms) and years since diagnosis of MS (yrs diagnosis). RT: reaction time.

MS patients were more susceptible to distraction than controls: speed of performance deteriorated disproportionately in the presence of distracters (memory search task) and irrelevant targets (focussed attention task), both results reflecting a focussed attention deficit. Inordinate slowing in response speed when switching between two attentional sets was required (attentional flexibility task) strongly suggests executive function deficits that have been found on earlier occasions[6,80]. Fluctuation in performance level, i.e. the S.D. of tempo during sustained attention task performance, was almost twice as high in MS patients, which is indicative of a sustained attention deficit. The MS patients slowed down much more after making an error than controls, the extent of this delay suggesting an interruption of the ongoing process rather than an adequate adjustment, underscoring the existence of executive control weaknesses. This behavioural response to feedback has been studied with the same task paradigm in children with minor neurological dysfunction and children with ADHD. It is interesting to note that the MS patients in their response resemble children with minor neurological dysfunction who showed a similar type of behavioural adaptation on the same task[59] and strongly deviate from subjects with ADHD who hardly adjusted their processing speed following feedback on errors[60].

Slower reaction times in MS patients have been frequently reported[62,64,108,112,126,131,140,204]. Inordinate increase of reaction time in MS patients with task complexity, suggesting a slowing of mental processing independent of motor slowing, has been observed elsewhere[4,126,204], but others failed to find such interactions[109,131,140]. Such inconsistencies might be explained by differences in tasks, severity of the disease, disease course, disease duration, and cognitive status of MS patients[127], or a different statistical approach[131]. In the eye–hand co-ordination task (pursuit) MS patients were less successful in staying close to the moving target and showed larger variation in distance from the target, both results being indicative of poorer fine motor control and psychomotor speed.

The analyses of error rates in the reaction time tasks clearly indicate that differences in accuracy between MS patients and controls are much smaller and less widespread than differences in speed. MS patients were as accurate as controls on tasks assessing peripheral processing stages (visuo-spatial task and

response organisation task), but less accurate on tasks assessing aspects of central processing stages, focussed and sustained attention and attentional flexibility. Overall differences in accuracy on the latter tasks were significant but the accuracy itself was high with a mean error rate varying between less than 4.5 (most tasks) and 7% (memory search task). The results are important in two ways: they suggest that not-timed tasks are far less sensitive to pick up functional decline, and secondly, they suggest the importance of using time strategies in planning daily life and job activities to compensate for or alleviate MS-related cognitive limitations. It is, however, conceivable that under too much time pressure MS patients might only be able to complete tasks by trading accuracy for speed, i.e. at the cost of a high error rate. It would of course be an oversimplification to attribute the cognitive deficits in MS solely to slowing as this would not explain e.g. the highly prevalent failures on measures of free recall from long-term memory in this patient group[124,255,290]. As regards the issue of counselling and rehabilitation, the above results stress the importance of developing and improving suitable attentional strategies in patients with MS to cope with daily life requirements and task or job demands. We found support for this notion in a study by Demaree et al.[62] who recently demonstrated improvement in performance accuracy in MS patients when they were given more time to process information, and in a treatment study by Jonsson et al.[110] who found similar results after manipulating time pressure.

General slowness

The regression analyses unequivocally substantiate the hypothesis that in MS patients the slowing of attention-demanding (controlled) information processing underlying more complex cognition is general (irrespective of type of controlled processing). The use of this regression technique has not been without criticism[78,180], but others have convincingly disputed these claims[36,164]. As Myerson et al.[163] recently argued that these techniques are neither flawed nor inappropriate as long as outliers in the dispersion of data and residuals are absent, it appears reasonable to use the regression analyses to determine the degree to which the effects of multiple sclerosis on processing speed is task-independent as well as to assess the magnitude of general slowing. Using a wider range of tasks in a larger and more representative sample of MS patients and controls, the results of the present

study confirm those of the study by Kail[112].

Irrespective of type of required behaviour in all but the visuo-spatial task, the equation $RT_{MS} = -0.04 + 1.40\ RT_C$ implies that MS patients are 40% slower than controls. This slowing rate is very close to the figure (46%) found by Kail et al. when his data were fit to a linear function through the origin $RT_{MS} = 1.46\ RT_C$). The slowing rate in the visuo-spatial task was "only" 20%, indicating that speed of processing of visuo-spatial information was relatively less affected in MS patients. An explanation might possibly be found in that stimulus encoding, the prime assessment focus of the employed visuo-spatial task, is associated with automatic processing rather than with controlled or effortful information processing[161]. Automatic processing is fast, runs in parallel, and requires a limited amount of mental effort. It is speculated that this type of processing is less susceptible to MS related changes in the brain. This suggestion is consistent with previous[89,93] and recent investigations[124] that showed preservation of implicit (or automatic) processing in patients with MS as opposed to explicit (or controlled) processing.

Whereas the slope of the regression line provides an estimate of the cognitive slowing factor, the intercept reflects the difference between sensorimotor and cognitive slowing factors[162,278]. The intercept is positive when sensorimotor processes are slowed more than cognitive processes, it is negative when cognitive processes are slowed more than sensorimotor processes, and zero when both types of processes are equally slowed. In all our equations, the intercepts are very close to zero (constant 0.06), thus indicating that cognitive and sensorimotor processes are equally slowed in our MS sample. Together with the evidence of deteriorating performance under more complex task conditions, we take the position, unlike Jennekens-Schinkel et al.[108] and Laatu et al.[131] that patients with MS not only exhibit motor or perceptual slowness but also cognitive slowness, such as also demonstrated by others[4,126,204]. A word of caution regarding the interpretation of general slowing phenomena in MS patients is appropriate. The extent of this slowing, at the group level, is surely considerable. At the individual level, however, these unfavourable conditions may work out differently, in particular on the various (higher) cognitive skills, also in relation to the strategies the patient is able to develop to cope with the problems.

Speed accuracy trade-off

Comparisons of performance between groups can be impeded by the "speed versus accuracy confound"[62]. This holds in particular for speeded tasks, such as e.g. the traditional paced auditory serial addition task (PASAT) in which faster presentation rate results in decreased accuracy. Demaree et al.[62] demonstrated that when patients with multiple sclerosis are provided additional time to process information they perform as accurately as healthy controls. In the ANT task paradigms, the stimulus remains on the screen until a response has been given and the next stimulus follows a fixed interval thereafter. The self-paced character of the tasks might explain the fact that accuracy differences between groups are less frequent. Differences in processing strategies between groups may also confound group comparisons. Trading accuracy for speed results in fast but relatively inaccurate performance whereas the opposite strategy would result in accurate but rather slow performance. Correlations between mean reaction time and mean error rate per task were found to be not significant in controls and in patients with multiple sclerosis they were positive ($0.30 < r < 0.47$, $0.036 < p < 0.004$), indicating that both groups did not trade accuracy for speed (reflected in negative correlations). The positive correlations in the MS group suggest that the slowest patients are also the ones that are least accurate, obviously reflecting more extreme levels of impairment associated with MS.

MS disease subtypes

The results of this study suggest that subtype of MS disease is associated with severity of attention and information processing deficits. Whenever MS patients were less accurate than controls, between the MS subgroups differences in accuracy were absent, except on the focussed attention task in which RR patients were less accurate than the other patients. As regards speed of processing, differences between MS subgroups were absent on baseline speed, memory search, and attentional flexibility. Response organisation and visuo-motor coordination seem to be unaffected only in RR patients. SP +PP patients were, compared to RR patients, slower on response organisation, sustained attention, and focussed attention, showed more fluctuation (instability) during sustained attention, slowed down more after making an error, and performed less well on visuo-motor coordination. Between PP and SP patients significant differences in speed of

processing were restricted to tempo on the sustained attention task, to the disadvantage of the PP patients.

In RR patients, increased processing demands associated with the presentation of irrelevant targets, attentional flexibility requirements, and incompatible stimulus-response mapping did not result in an inordinate RT increase while memory load, distraction, and stimulus similarity did. In the other MS subgroups all task manipulations did result in over additive effects on RT except for stimulus similarity and attentional set shifting (SP patients), respectively distraction and stimulus-response mapping (PP patients). The PP and SP patients thus stand out as the most seriously compromised groups, which corroborates with earlier observations[4,64,95].

As regards general slowing similar conclusions can be drawn. The linear function coefficients support the notion that general slowing occurred in all MS subtypes with higher slowing rates for the SP and PP subtypes. Judging from the regression coefficients (1.50 versus 1.24), the RR patients seem to hold a position halfway between the controls and the PP/SP group. Overall, RR patients are relatively better off, which is not surprising as they are, on the average, characterised by a younger age and shorter disease duration. Multiple sclerosis may start with a relapsing–remitting phase RR), which is followed by a transition to the secondary progressive phase (SP), and as a consequence SP patients are in general older and have been ill longer. Alternatively, the disease may take a primary progressive (PP) form from the start. To date, see review by Hämäläinen and Ruutiainen[92] , there have been surprisingly few studies focussing on the role of disease subtype or course with regard to cognitive decline, but from these studies it is clear that RR patients are relatively spared (for example. [91,95,127,209]). In our study, PP patients equal at least the cognitive decline found in SP patients. This result contrasts that of Comi et al. who reported significantly greater cognitive impairment in SP patients[41]. Recent comparative studies of neuropsychological task performance suggest only few and subtle differences to the disadvantage of the SP patients[79,251]. Brain magnetic resonance imaging (MRI) metrics have been found to be associated with cognitive findings[92,96,227], but others could not confirm this association[79]. A recent MRI and magnetisation transfer (MT) study focussing on the pathology of the three clinical phenotypes, showed that all subtypes of MS patients

had lower MT metrics than controls, with SP patients showing the lowest MT measures and highest lesion loads[92]. The PP patients showed in addition microscopic damage in normal appearing white matter, which may be a major contributor to disability in PP MS. It is perhaps in light of this finding, that we may understand that information processing of PP patients appears to be at least as compromised as in the SP patients, even though their disease duration (since occurrence of first symptoms) was almost 4 years less.

Disease duration and severity of MS

Previous studies failed to find substantial correlations between cognitive deficits and disease duration[4,17,185,202] and also correlations between the degree of physical disability as measured with the EDSS and severity of cognitive impairment in MS are weak[17,68,202,228,270] or virtually absent[4,79,92,105,128]. These negative results are explicable in that a long duration of symptoms is not necessarily synonymous with brain pathology while physical disability may relate to spinal as opposed to cerebral lesions, the former sparing cognition. The results of the multiple regression analyses, dealing with the existence of substantial reciprocal correlations between age, disease duration and physical disability, show that disease duration and severity of MD (EDSS score) are suitable and sometimes strong predictors, on their own or in combination, of task performance. It goes without saying, however, that even more convincing evidence for a continuous deterioration of functions with age might emerge from longitudinal studies that allow for within-subject comparisons of disease-related functional decline[96,128]. As regards speed of processing it is interesting to note that lowest values of R are found in relation to tasks with a low cognitive load (baseline speed and visuo-spatial perception), moderate values in relation to focussed and sustained attention tasks, and highest values for RT tasks that are characterised by high working memory demands or requiring executive function skills. Highest R-values (0.70) are found for visuo-motor performance, which of course was to be expected as performance on this particular task depends not only on visual processing speed but also on motor (hand) dexterity. Although differences in accuracy between MS patients and controls appeared to be limited and less widespread than differences in speed, the analyses demonstrate that accuracy of processing in all RT tasks is unfavourably influenced by disease

duration with R-values varying between 0.28 (memory search task) and 0.48 (response organisation task). At first sight it might look odd that the effect of flexibility requirements (shifting attentional set task) are best predicted by both disease duration parameters with beta being positive for "yrs since 1st symptom" and negative for "yrs since diagnosis". The former parameter has an unfavourable effect on speed while the latter seems to have a favourable effect. This inconsistency is clarified when the difference score yrs since 1st symptom - yrs since diagnosis is entered in the regression equation. This score might be considered to reflect a "delay" in treatment (larger difference then later treatment onset). The new analysis resulted in a solution with this parameter (beta = 0.373) and age of subject (beta = 0.260) as predictors with r = 0.55. Later treatment, as calculated since occurrence of 1st subjective symptoms, and older age are thus associated with a larger effect of flexibility requirements, i.e. unfavourable affects aspects of executive function. As this outcome suggests that early treatment may postpone or attenuate unfavourable effects of the disease, we have redone the regression analyses with inclusion of this difference score but the final models did not deviate from the ones found earlier.

Cognitive deterioration and physical disability may develop in parallel. To the extent that multiple sclerosis associated pathology in our patients also extends to the cerebral hemisphere areas, and the premise that attentional deficits are sensitive indicators of cognitive dysfunction, it does explain our findings quite well. In patients with optic neuritis, representing early demyelinating disease, significant correlations between total lesion area in the brain and some tests of attention were found[66]. A recent study[273] revealed total lesion load to be positively correlated with impairment in attention, memory and executive functioning in RR patients. Hohol et al.[96] studying the relation between disease burden and cognitive dysfunction, found that patients who demonstrated cognitive decline did so primarily on tests of attention and information processing speed, and those tests showed the most robust correlation with baseline MRI parameters and worsening atrophy. Probably, the accumulation of demyelinating changes in wide areas of the cerebrum interferes with the function of distributed neural networks in deep cortical and subcortical structures. In a disease that can be as widespread in the brain as MS, attentional functions that rely on the integrity of complex neural

formations are thus extremely vulnerable to the impact of MS pathology.

Caveats

Individuals with psychiatric disorders that might have interfered with tests were excluded. As depression scores were only scarcely available we could not directly control our data for the possible influence of depression or depressive symptoms on speed of processing. MS-related fatigue might also have a systematic effect on task results in that it could manifest itself relatively more in later tasks as compared to earlier tasks. A fixed task order was chosen above a counterbalance procedure because we prefer to deal with a systematic rather than with an unsystematic source of variation, such as may be caused by the occurrence of crossover effects from one task to another and not vice versa. Furthermore, counterbalancing would be hardly practical with the number of tasks and participants per group in the study and would not remediate such crossover effects. Following the data collection phase we found no relation between task order and relative differences in speed between MS group and controls as the task presentation order, ranked from lowest to highest difference appeared to be 1st, 2nd, 6th, 3rd, 7th, 5th, and 4th. Furthermore, we would like to refer to a recent study[4] in which covariate effects of fatigue and depression on speed of processing were reported to be absent.

One might wonder whether the evidence for cognitive deficits in patients with multiple sclerosis in this study is confounded with the influence of their physical disability as it is well known that patients with MS may suffer from impaired vision, slowing of eye movement, sensory motor slowing and hand dexterity problems. The baseline speed task demonstrated that MS patients are about 80 ms slower compared to controls. Assuming that slowness of the peripheral response system (from motor cortex to index finger) is the major contributor to this difference, it cannot explain why differences in speed between groups increase 5–20-fold in the other RT tasks, in which the required response is a similarly simple key press. Likewise, slowing of eye movements can not explain the observed slowing as substantial differences in speed between controls and MS patients are also present in tasks, which do not or minimally require eye movements. On the response organisation task, the MS patients are much slower than controls, in comparison to the difference in speed on the baseline speed task, suggesting that this is the influence of a higher cognitive load in the

former task. In the shifting attentional set task the visual scanning requirements for parts 1–3 are absolutely identical. Nevertheless, the differences between MS and controls in speed increase significantly from part 1 to 3. This can only be attributed to the cognitive requirements (spatial incompatibility and imposed switching between response sets). The regression coefficient for the task with probably the highest visual scanning requirements (visuo-spatial task) was the lowest, in other words: the relative speed differences between controls and MS patients were smallest on this task. Finally, we would also like to refer to a study that used a comprehensive set of 31 binocular spatial and non-spatial visual tasks of which only four tasks yielded significant rates of impairment in only 26% of a representative sample of patients with MS[270]. None of these four tasks resembled our tasks as regards the required demands, with the possible exception of the FM-100 Test[65] that demonstrated that those patients had impaired colour discrimination, particularly in the blue-green spectrum. Impaired colour discrimination, we have no data on this of our patients, is possibly relevant for the response organisation and the attentional flexibility task that use red and green stimuli. The task effects, associated with the colour manipulation was significant in controls but also in our MS patients, which adequately demonstrates that our MS patients can discriminate between red and green in these tasks.

Taken together, the present study has elucidated manifold information processing deficits in patients with MS. Firstly, it confirms the hypothesis that the slowing in MS patients of attention-demanding (controlled) information processing is general. Secondly, we have demonstrated that MS patients may suffer from deficits in divided, focussed and sustained attention and executive functioning. Thirdly, processing speed appears to be compromised most in PP and SP patients, in particular under more complex task conditions. Fourthly, processing speed is substantially correlated with disease duration and disability, suggesting cerebral pathology in our patients. It is further noted that the magnitude of these correlations is much stronger than reported in previous investigations. Fifthly, accuracy of processing in MS patients in self-paced tasks is much less compromised compared with speed, suggesting the importance of using time strategies in counselling and rehabilitation programs.

2.5 THE ANT IN RELATION WITH MRI

Adapted from: Multiple Sclerosis

Cognitive slowing in multiple sclerosis is strongly associated with brain volume reduction.

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Abstract

OBJECTIVE

In this study we investigated the influence of in vivo disease pathology (measured as MRI lesion load and brain volume reduction) on cognitive functioning, especially the speed of processing, in multiple sclerosis (MS) patients. Since MS is characterized by cognitive slowing, rather than impaired accuracy, we used the Amsterdam Neuropsychological Tasks (ANT) program, a computerized test proven to be very sensitive to cognitive slowing in MS patients.

METHODS

Thirty-two patients performed the ANT and underwent MRI scanning. Using the ANT computerized tests , we investigated focussed, divided, sustained attention, executive function and psychomotor function, and examined associations of speed, speed fluctuation and accuracy of performance of these tests with MRI lesion load and brain volume parameters.

RESULTS

A decrease in speed of processing and response speed stability, and a decrease in psychomotor accuracy and stability were clearly associated with less brain volume, and with higher lesion loads, in particular at frontal and occipital areas. Correlations with brain volume reduction were found for all domains, except for visuo-spatial processing. In particular speed and speed fluctuation scores correlated with brain volume reduction, while accuracy of performance, in general, did not correlate. Only some test speed and speed fluctuation scores correlated with lesion load measurements.

CONCLUSION

This study shows that in MS patients accuracy of processing is not compromised unless high working memory demands are involved. Problems in neurocognitive functioning in MS are mainly modulated by speed and stability of speed processing, in particular when attention-demanding controlled information processing is required. Abnormalities in these domains are most strongly associated with brain volume loss, confirming that pathology beyond focal lesions is important in MS.

INTRODUCTION

Multiple sclerosis (MS) can cause deficits in all neurological systems, including those subserving cognitive functions. Not all neuropsychological functions are affected equally. Working memory, attention, information processing speed and executive functions are more often disturbed than language functions and general intelligence[15,195,202,284]. Many studies have shown the impact of the disease on processing speed and working memory, including a recent study[58] which focussed on those functions, using a set of tasks from the Amsterdam Neuropsychological Tasks program (ANT)[56,57]. Studies by Kujala et al.[126], Kail et al.[111,112] and our group[58] have clearly demonstrated that cognitive slowing in MS patients is general, i.e. various attentional domains (divided, focussed, sustained attention) all show deficits. The ANT computer test battery[56] is a comprehensive set of information processing tasks, designed to evaluate basic processes underlying more complex cognitive skills, i.e. attention-demanding controlled information processing. One of the major advantages of the ANT is that it allows for a quantitative assessment of slowing in a variety of cognitive processes. It has been shown in MS patients that, even though cognitive slowing is general, the amount of slowing is especially remarkable for tasks with higher cognitive demands, where MS patients were found to be 40-50% slower than healthy controls[58]. The slowing of the processing speed in MS is believed to result from fiber disconnection and myelin breakdown. MS is characterized by multiple focal areas of axonal demyelination [43,54,111], especially in the periventricular white matter, the corpus callosum and the temporal lobes. In areas of demyelination conduction speed is diminished; conduction can even be blocked completely.

Magnetic resonance imaging (MRI) is a highly accurate technique to visualize MS lesions. In this study we investigated the relation between in-vivo disease pathology (expressed as lesion load and brain volume reduction on MRI) and cognitive slowing as tested with the ANT program.

We hypothesized that structural brain abnormalities, both brain volume reduction and lesion loads, are the reason for cognitive slowing, while accuracy of performance is less affected.

METHODS

Subjects:
Thirty-two randomly selected MS patients performed the ANT and underwent MRI scanning. Both investigations were performed within one week, in most cases on the same day. The MS patients were diagnosed as relapsing remitting (RR, 11 patients), secondary progressive (SP, 13 patients) or primary progressive (PP, 8 patients). The patient characteristics are summarized in table I.
The mean age was 48.2 (27.9 - 72.3) years and the median EDSS was 4.0 (1.5 - 7.5). The mean disease duration was 12.2 (5.0 - 33.0) years.

Table I
Patient characteristics

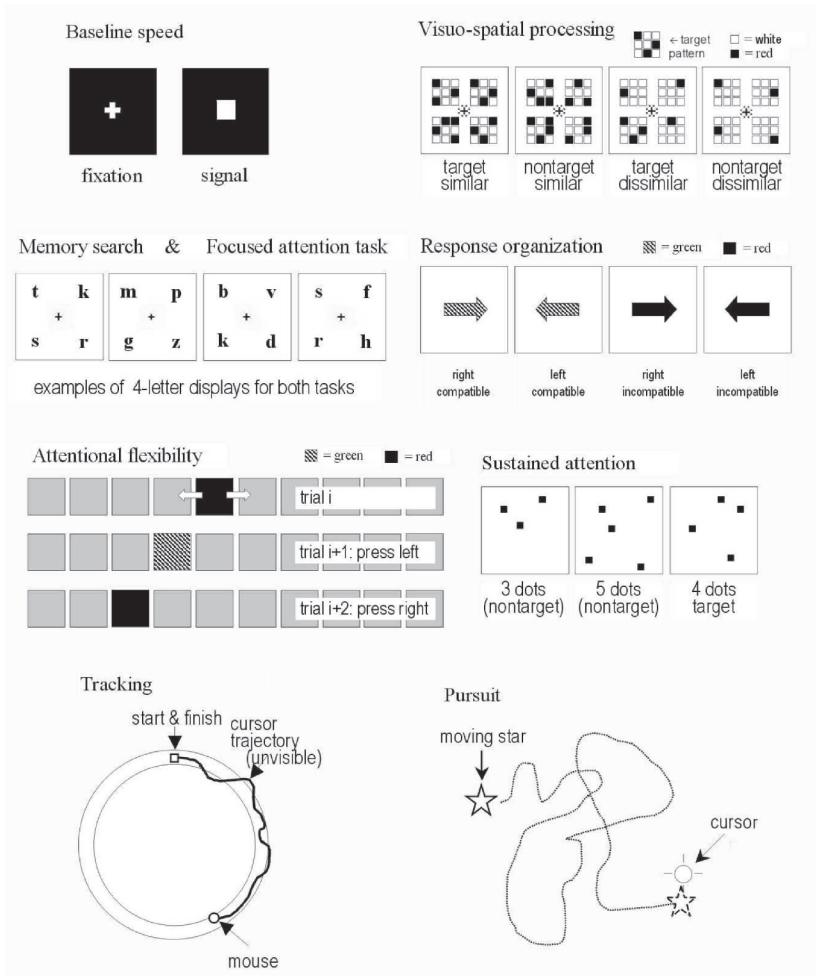
Variable	Mean	Median	SD
Age (yrs)	48.20	49	12.37
EDSS	n.a.	4	1.80
Disease duration (yrs)	12.20	12	6.30
T2 Lesion Load (ml)	3.61	2.3	3.58
T1 Lesion Load (ml)	0.97	0.42	1.42
Relative Brain Volume	0.78	0.79	0.06

The ANT tasks:
Eight tasks from the ANT program[56] were administered to assess speed and accuracy of baseline speed, focussed, sustained and divided attention, visuo-spatial processing, response organization, attentional flexibility (executive function), and psychomotor function. The test stimuli were presented on a computer screen, and the subjects were required to press a mouse key or use the mouse as a tracking device. The right key was the 'yes' key and the left key the 'no' key for patients in which the right hand is the dominant hand; and vice versa for left dominant hand patients. A short description of the tests used in this study follows (see figure 1). The ANT tasks were described in more detail elsewhere[56,100,114].

Baseline Speed:
This task measures simple visuomotor reaction time, involving minimal cognitive effort. The subject has to push the 'yes' key whenever a square appears in

Figure 1

ANT screens



Examples of stimuli and signal types of the selected tasks from the ANT program. In the visuo-spatial processing task, the distractors (non-target patterns) resemble the target quite well (similar condition) or look very different (dissimilar condition). In the focussed attention task, a letter of the memory set is only target letter when it is presented on the relevant diagonal. The diagram of the attentional flexibility task displays two trials of part 3 with indication of correct responses.

the center of the screen. The post-response interval (PRI), the time between response execution and next stimulus onset, is set randomly between 500 and 2500 ms.

Sustained attention:
A continuous performance test, requiring the subject to discriminate between signals containing 3, 4 or 5 dots, presented in 50 series of 12 signals each. The PRI is 250 ms. Fluctuation in speed of processing during time on the task is considered the most important outcome measure.

Memory Search:
A divided attention (letter detection) task that assesses working memory capacity. It employs a 4-letter display load. The memory load is increased across task parts by increasing the number of letters to be detected in the presented signals from 1 to 3 in part 1, 2 and 3 respectively. The task parts consists of 40, 72 and 96 trials respectively, each with 50% target trials ('yes' key) and 50% non-target trials ('no' key).

Focussed attention:
This task uses a similar 4-letter display load as the memory search task, but now only two diagonal locations are relevant (known in advance to the subjects) and subjects should attend to those positions only. This test consists of two parts, with a working load of one and three target letters, respectively. Both parts consist of 80 trials, 40 of which require a 'yes' response, 20 trials have the target letter at the wrong location (irrelevant target signals) and 20 trials contain no target letters.

Response organization:
This test requires the subject to take two assignments into account. A left- or right-pointing arrow is presented in the center of the screen. When the arrow is green, it requires a compatible response (left arrow - press left button, right arrow - press right button) and when it is red an incompatible response (left arrow - press right button, right arrow - press left button). The task consists of 60 trials.

Shifting attentional set:
This task assesses attentional flexibility, an aspect of executive functioning. A coloured square jumps randomly on a horizontal bar to the right or left. Depending on the colour of the square right after the jump, the subject has to execute a compatible response (press the key towards which the jump was directed) or an incompatible response ('mirror' movement; press the right key when the jump was to the left and vice versa). This test consists of

three parts. During the first two parts of the task the colour is constant (fixed stimulus response mapping), but in the third part the colour varies, requiring attentional flexibility by continuously having to adjust response type. The PRI is 250 ms in all parts of the test. The first two parts consist of 40 trials, the third part consist of 80 trials.

Visuo-spatial processing:
Divided attention and encoding aspects of cognitive functioning are tested. After memorization of a visuo-spatial pattern (a 3x3 matrix containing 6 white and 3 red squares), subjects have to detect this pattern in signals containing four patterns. When the target pattern is present, a 'yes' response is required, otherwise a 'no' response. The test consists of 80 trials of which 50% are target trials. Of the other 40 trials of non-target patterns, the half look very similar to the target pattern, the other half look very dissimilar to the target pattern.

Pursuit:
This task measures visuo-motor control by requiring the participant to continuously track a target moving randomly on the screen. As the trajectory of the target is unpredictable, this task demands the concurrent planning and execution of movements, i.e. executive function. During task performance the distance between the mouse cursor and the moving target is continuously registered, resulting in 60 distance (deviation) scores.

Tracking:
A similar eye-hand coordination task as the pursuit task, but requiring less control as the subject has to draw a circle by moving the mouse cursor in-between two concentric circles. During task performance the distance between the mouse cursor and the ideal track line is continuously registered, resulting in 60 distance (deviation) scores.

MR parameters:
Imaging was performed on a Siemens 1.5 T scanner. For identification of lesions a T2 weighted (TR 2500/ TE 45-90/ 1 excitation) spin-echo sequence was used. The slice thickness was 3 mm with a 1 mm in-plane resolution; in total 42 contiguous slices were scanned to cover the whole brain. Lesions were identified by visual inspection and marked. Lesion load measurements were performed on a workstation (Sun, Mountainview, California, USA) using in-house-developed semi-automated seed-growing software based on local thresholding differences (Show-Images), as described earlier[267]. The total volume of hyperintense lesions

seen on the T2-weighted images was calculated, as were regional lesion loads in the four main brain areas (frontal, parietal, temporal and occipital) as was described earlier[132]. On a T1-weighted (TR 620/ TE 15/ 2 excitations) scan after gadolinium, in the same manner the T1 hypointense lesion load (total and regional) was calculated.

Parenchymal volumes were measured on T1-weighted images (TR 620/ TE 15/ 2 excitations) and intracranial volume was measured on the corresponding slices of the heavily T2-weighted images with the same software package. Those volumes were used to calculate the relative brain volume (RBV = total parenchymal volume/ intracranial volume) as a measure of atrophy[116].

Data analysis:

The ANT tasks each provide a speed score, a speed fluctuation score and an accuracy of performance (% errors) score. On the basis of normative data, obtained in various studies[58,232,258] from healthy subjects and stratified by age (mean age 30, 40, 50, 60 years old), the scores were transformed into z-scores for each response variable. In the pursuit and tracking tasks the mean distance and distance fluctuation variables were subjected to a similar Z-score transformation. These distance scores were related to speed and accuracy of eye-hand coordination. Test-retest reliability for the tasks used in this study ranges between $0.75 < r < 0.95$, and sensitivity, expressed as the effect size (partial eta squared, ^{2}) of group differences, ranges between $0.11 < {}^2 < 0.45$ [57].

The ANT Z-scores and the EDSS were correlated, using Spearman's rank correlation, with the MR parameters for brain volume, T2 lesion load (total and per region) and T1 lesion load (total and per region). For the four main cerebral regions the left and right area were correlated separately as well as both sides together.

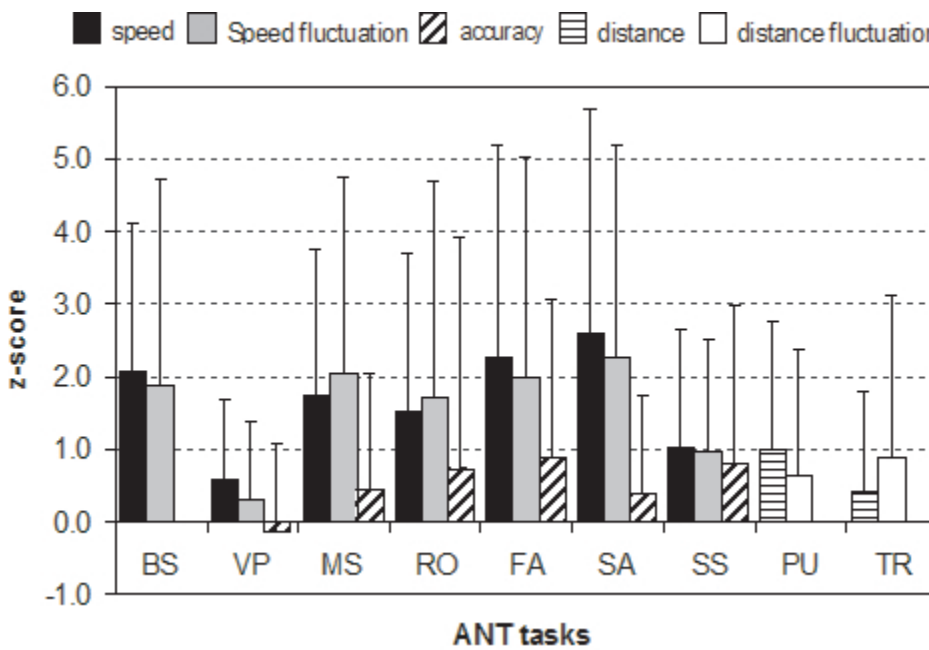
To determine the relative strength of the correlations, multiple linear regression analysis was used, with the ANT results as the dependent variable, and brain volume, T2 and T1 lesion load, EDSS, sex and disease duration as the independent variables. Since previous studies on healthy controls[56] found no association with age in adults, age was not included as a predictor in these models (certainly since it correlated with disease duration). A forward stepwise model was used with a probability of F to enter of 0.05.

RESULTS

The mean speed and speed stability of the MS patients was at least one standard deviation below the norm on all reaction time (RT) tasks except for visuo-spatial processing (see figure 2). By contrast, all accuracy scores differ less than one standard deviation from the norm.

Figure 2

ANT test Z-scores of speed, speed fluctuation and accuracy of performance



The results from 32 MS patients on the ANT tests, represented as Z-scores (difference of the result in SDs from mean of control group). From baseline speed (BS) the Z-scores for speed and speed fluctuation are given. For this task no accuracy of performance exists. For visuo-spatial processing (VP), memory search (MS), response organization (RO), focussed attention (FA), sustained attention (SA) and shifting attention (SS) Z-scores of speed, speed fluctuation and accuracy of performance are given. For the pursuit task (PU) and tracking (TR) the distance (comparable with sum of speed and accuracy of performance) and fluctuation (comparable with speed fluctuation) are given. Speed and speed fluctuation show higher Z-scores than accuracy of performance, which tends to be in the more normal range.

Table II
Correlations.

		T2 lesion load	T1 lesion load	RBV
Baseline speed	speed	.46 **		
	fluctuation			
Focussed attention	speed	.38 *		-.68 ***
	fluctuation	.39 *		-.41 *
	accuracy			-.38 *
Visuo-spatial processing	speed			
	fluctuation			
	accuracy			
Memory search	speed	.50 **	.43 *	-.63 ***
	fluctuation	.44 *	.41 *	-.59 ***
	accuracy		.48 **	
Response organization	speed			-.61 ***
	fluctuation			-.49 **
	accuracy			
Sustained attention	speed	.37 *	.46 *	-.45 *
	fluctuation			
	accuracy			
Shifting attention	speed			-.53 **
	fluctuation			-.39 *
	accuracy			
Pursuit	distance	.41 *		-.68 ***
	fluctuation	.42 *		-.63 ***
Tracking	distance			
	fluctuation			-.45 *

Correlations between the ANT tests and MR parameters are shown.
* indicates $0.01 < p < 0.05$, ** indicates $0.001 < p < 0.01$, *** indicates $p < 0.001$, blank if not significant.; RBV = total parenchymal volume / intracranial volume.

The mean T2 lesion load was 3.61 ml (range 0.19 - 14.30), the mean T1 lesion load was 0.97 ml (range 0.00 - 7.12). The mean RBV was 0.78 (range 0.65 - 0.88). In this sample of patients, the EDSS showed a significant correlation with RBV as a measure of atrophy ($r = -0.61$; $p = 0.001$), but not with T2 or T1 lesion load. We did not find significant differences between RR, SP and PP patients with respect to ANT scores for speed, speed fluctuation and accuracy.
All correlations between ANT indices and MRI parameters are given in table II.

ANT versus T2 lesion load.
Total T2 lesion load correlated with baseline speed, speed of the focussed attention, the memory search and the sustained attention tasks, with speed fluctuation of the focussed attention and the memory search task and with the pursuit task scores. It did not significantly correlate with any of the accuracy scores ($0.37 \leq r \leq 0.50$, see table II).
The correlation analyses per region showed that the overall T2 lesion load was mainly driven by the frontal lesion load, which also had the highest correlations (regional details not reported in table).

ANT versus T1 hypointense lesion load
Total T1 lesion load only showed significant correlations with all scores of the memory search task and the speed score of the sustained attention task. ($0.41 \leq r \leq 0.48$, see table II). The analyses per region resulted in correlations for all main brain regions of similar magnitude as the overall T1 lesion load correlations, and showed significant correlations of frontal and occipital lesion load with speed in the focussed attention task.

ANT versus brain volume
Relative brain volume reduction (RBV) showed significant correlations with most of the speed and speed fluctuation scores of the different tasks ($-0.38 < r < -0.68$). Not only were a higher number of significant correlations found for ANT versus brain volume compared to ANT versus lesion loads, correlations typically were also stronger.

Multiple linear regression analysis
Multiple linear regression analysis was used to further investigate the relative strength of various relations (table III). Among the MR parameters examined, brain volume was the strongest predictor in the model for most of the test speed and test fluctuation scores. None of the parameters was significant in explaining (part of) the ANT test accuracy of performance in our model. Besides the MR parameters, disease duration was the other strong

explanatory variable for the other tests. Sex was a significant independent variable in explaining the visuo-spatial processing fluctuations score. When performing the same regression analysis without EDSS and sex, no different explaining variables were found.

Table III

Regression analysis, stepwise forward regression.

		Variable	R	Adjusted R square	F	Signif.
Baseline speed	speed	-				
	fluctuation	-				
Focussed attention	speed	RBV	.533	.252	8.74	.007
	fluctuation	Disease duration	.566	.289	10.36	.004
	accuracy	-				
Visuo-spatial processing	speed	-				
	fluctuation	Sex	.532	.248	8.27	.009
	accuracy	-				
Memory search	speed	RBV	.614	.351	13.95	.001
	fluctuation	RBV	.667	.421	18.46	< .001
	accuracy	-				
Response organization	speed	RBV	.536	.255	8.88	.007
	fluctuation	-				
	accuracy	-				
Sustained attention	speed	T1 Lesion load	.501	.217	7.39	.013
	fluctuation	Disease duration	.567	.290	10.41	.004
	accuracy	-				
Shifting attention	speed	RBV	.698	.464	20.49	< .001
	fluctuation	RBV	.576	.302	10.94	.003
	accuracy	-				
Pursuit	distance	RBV	.717	.468	11.11	.001
	fluctuation	Disease duration	.684	.443	19.30	< .001
Tracking	distance	-				
	fluctuation	-				

Multiple linear regression analysis was performed. The ANT score was set as the dependent variable, the MR parameters for brain volume, T2 lesion load and T1 lesion load, sex, age and disease duration as the independent variables. The model used was a forward stepwise model with a probability of F to enter of 0.05.

DISCUSSION

In this study we found strong correlations between ANT scores and MR measures. In general, higher lesion load, but especially progressive brain volume reduction, was associated with slower speed of processing and larger fluctuations in response speed in the choice reaction time tasks, and with an poorer performance on the visuomotor control tasks, in particular on the pursuit task. With the exception of the memory search task and focussed attention task, choice reaction time accuracy did not correlate with MR measures.
Correlations were strongest as well as most frequent for brain volume. Moreover, T2 lesion load was found to correlate more often with task performance than T1 lesion load. The memory search task, the sustained attention task and the focussed attention task all depend on more than one MR parameter, probably because all are highly dependent on controlled processing.

In a recent study applying the ANT, a test that probes various attentional domains in a quantitative fashion, we demonstrated that MS patients have a slower speed of cognitive functioning than healthy controls, with a largely maintained accuracy[58]. This was especially true for more complex tasks, in line with previous studies[108,109,112,126,204]. Cognitive slowing was found in many studies, including our previous study, to be more than only motor slowing[58,126,204]. We speculate how much of this cognitive slowing in MS patients could be explained by the structural lesions and brain volume reduction seen on MRI.
Previous studies on correlations between cognitive functioning and brain lesion loads show markedly different results. Most studies reported a relation between cognitive functioning and MR measurements (for example [5,83,96,133,203,227,250]), but not all studies did (for example [99,146,177]). These discrepancies can partly be explained by differences in cognitive tasks administered and by the fact that some studies focussed on accuracy of performance without taking into account the time needed to complete tasks. Previous studies have clearly shown that if test time is not restricted, MS patients probably can perform almost equally well as healthy subjects on most cognitive tasks[22,58,62,110]. In a previous study by our group we found correlations between MR

parameters (brain atrophy and lesion load parameters) and a screening test battery often used in MS research, the Brief Repeatable Battery[132]. The focus on attention and processing speed shows that those functions, essential for good cognitive functioning, are impaired. The present study also shows, in this relatively small population, that accuracy is less (or not) compromised in comparison with other aspects of cognitive functioning (given a sufficient amount of time).

In progressive stages of the disease or under too much time pressure, a decline in performance can be expected to occur in MS patients. In our current small sample, meaningful differences between MS subgroups could not be evaluated. We did not find a correlation between visuo-spatial processing and brain volume reduction or lesion load. The reason for not finding such a correlation, might be that automatic processing activity, associated with tasks involving low processing loads, is less vulnerable to consecutive MS lesions than controlled processing, which is required in tasks involving high working memory load demands.

The ANT scores show better correlations with brain volume reduction than with lesion load measures. The cognitive functions tested by the ANT require the co-operation between brain areas located diffusely through the brain rather than more localized areas. This is also shown by our results that regional brain lesion loads are equally well correlated with MR parameters as the overall lesion load. The relation with brain volume proved to be stronger than with lesion load, suggesting that abnormalities beyond the resolution of the scanner (in the normal appearing white or gray matter) are important predictors of worse test results in MS patients[72,265].

Performances on tasks as used in the ANT, require the integrity of functional networks for communication between different brain areas. Lesions in MS lead to slowing of transportation of information and, therefore, we had expected lesion loads to show better correlations. Absence of correlations with lesion loads might be related to subtle, but extensive, abnormalities in normal appearing white matter, which was not quantitatively interrogated in this study. If connections between brain areas are still intact, then besides cognitive slowing, accuracy should not necessarily be affected. This might explain the relations found for ANT scores on speed, but not for accuracy. It also might explain that whenever a correlation was found, this was seen in all four main brain regions most of the

times, an observation also induced by the fact that lesion loads in these areas are highly interrelated (results not shown). We found correlations to be the highest for the frontal regions, which is in line with observations by Swirsky-Sacchetti et al., who also described that frontal lesions correlate best with cognitive impairment[250]. In another study in MS patients, Benedict et al. also found correlations between brain volume reduction, even in regional areas, and some cognitive tasks[21]. The importance of atrophy, compared to lesion loads, in relation to clinical disability in MS was also emphasized by Kalkers et al.[116], who found that brain atrophy cannot simply be explained by lesions alone.

With this study we further refined the cognitive problems in MS in relation to underlying structural abnormalities (lesion load, brain volume reduction) on MR. Our observations convincingly show that speed of cognitive functioning is the main problem, and not performance. Based on the correlation analysis, we suggest that such impairment is driven by diffuse cerebral damage, beyond focal lesions, and cerebral volume loss.

CHAPTER 3

FUNCTIONAL MRI TESTS

3.1 INTRODUCTION fMRI

MRI is a non-invasive method using magnetic fields to image tissue, making use of the natural properties of hydrogen protons. When a magnetic field is applied to a body, the (hydrogen) protons align with the field lines; when the magnetic field is turned off, the protons redirect themselves and transfer energy to their surroundings. Each tissue responds differently, because of the different amount of protons and the chemical state of the protons in that tissue. Thereby the different tissues give another signal, with contrast in the image as a result. Normal brain tissue gives therefore another signal than an MS lesion, which can be detected in this way.

fMRI TECHNICAL ASPECTS

Functional MRI (fMRI) was first described in a study of brain activation in humans in 1989 by the group of Belliveau and Rosen[20]. This first study made use of a exogenous contrast agent. A few years later fMRI studies without exogenous contrast agents were performed[130,167]. The basis of this fMRI method is the difference in magnetic characteristics of oxygenated haemoglobin and haemoglobin without oxygen (deoxyhaemoglobin). Increased neuronal activity increases oxygen consumption. Blood flow is increased to deliver the extra oxygen, however to a higher extent than the extra oxygen extracted (overcompensation)[187]. Hence paradoxically, neuronal activation is associated with increased concentrations of oxygenated haemoglobin (and therefore a decrease in deoxyhaemoglobin) in the region of activation. This increases phase coherence of protons in the activated region, increasing T2*, and therefore increasing signal on T2* weighted images. This is the so-called blood oxygenation level dependent (BOLD) effect[167]. The main determinant of the signal is the increased metabolic rate in and around the synapse, rather than the neuronal firing rate perse[141,150].

This BOLD signal difference is very small and much smaller than that of the differences between normal tissues. Many samples

(images) have to be acquired to get a sufficient signal-to-noise ratio to statistically detect brain activation. This can be achieved by using fast sequences which image the whole brain in only a few seconds, at the cost of spatial less resolution. The technique mostly used is the echo planar imaging (EPI) sequence. A further description of the technical aspects of fMRI is beyond the scope of this thesis.

FMRI PRACTICAL ASPECTS

In the MR room, a test is applied to the subject by a beamer (outside the room) projecting images on a screen in the MR room, viewed by the subject through a mirror placed above the subject's head in the MR bore. If needed, the subject can respond during the task by pushing buttons. Speaking is problematic, because it causes movement artifacts and because of the noise of the scanner.
Usually the images acquired during two or more conditions are compared statistically. It is important that the difference between conditions isolates the function of interest. The difference in the signal then represents a difference in brain activation, associated with the cerebral function of interest. Practically, problems are the small differences in the signal and a good task construction with two or more conditions which differ in the desired cerebral function only.

FMRI STATISTICAL ANALYSIS

Because of the many data samples, adequate statistical methods are needed, compensating for coincidences. SPM [www.fil.ion.ucl.ac.uk/spm][86] and AFNI [afni.nimh.nih.gov/afni][50] are the software packages used to analyse the data of the studies described in this thesis. These software packages offer methods of image registration (realigning the image differences caused by (small) head movements during the experiment), and preprocessing tools such as (temporal and spatial) filtering, and statistics.
First for each individual voxel (volume pixel) the signal changes

are tested against a null hypothesis ("no brain activation") constructed from the test characteristics and the thereby expected signal (activity) changes (a general linear model of the expected signal). The second step is a statistically compensation for the many comparisons (many voxels) and thereby possible many false positive test results. This step can be performed with statistical tests compensating for multiple comparisons.

To study a cognitive domain, it is of importance to develop a suitable task, testing it in healthy controls to see whether the results meet the expectations. For the MS fMRI studies in this thesis, this step had to be performed first because no ready-to-use tasks were available. For the fMRI part of this thesis, this first hurdle was taken. Also some implementation studies of the fMRI tasks were performed.

3.2 fMRI ADAPTED TOWER OF LONDON TEST

Adapted from: American Journal of Neuroradiology

Visualising brain activation during planning: The Tower of London test adapted for fMRI.

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Abstract

Objective
Recent positron emission tomography and single-photon emission CT studies using the Tower of London test have shown that brain activation during planning activities primarily resides in the prefrontal cortex. In this study, we adapted the Tower of London test for functional MR imaging.

Methods
For use with functional MR imaging, a block design of the test was created, in which planning stages were contrasted with counting of coloured balls. For nine healthy participants, multisection echo-planar functional MR imaging was performed to assess brain activation based on changes in blood oxygen level. Activation maps for individual participants and a group average map were created.

Results
In the group average map, activation in the dorsolateral prefrontal cortex, the anterior part of the cingulate cortex, the cuneus and precuneus, the supramarginal and angular gyrus in the parietal lobe and the frontal opercular area of the insula was seen. These findings are in agreement with grouped data of previous positron emission tomography results. Functional MR imaging enabled us to investigate brain activation during planning activities with high spatial (and temporal) resolution in individual subjects, showing that the dorsolateral prefrontal cortex was activated in all individual participants studied.

Conclusion
Presented is a working functional MR imaging version of the planning task. The high sensitivity of functional MR imaging may allow the use of this test in patients with possible (pre)frontal disorders.

INTRODUCTION

Planning is defined as the ability to organise cognitive behaviour in time and space[170]. It is necessary in situations in which a goal must be achieved through a series of intermediate steps, each of which individually does not lead directly towards that goal. A well-known test to evaluate planning in neuropsychological research is the Tower of London test[237]. For this test, the participant is instructed to move three different coloured balls to match a target configuration by using a minimum number of moves. Although this test needs spatial processing abilities, it mainly depends on planning. Patients with frontal lobe pathologic abnormalities (e.g. frontal lobe dementia, multiple sclerosis) perform worse than do healthy control participants.

Neuropsychological studies have shown that lesions in the frontal lobe (mainly the prefrontal cortex, which is located anterior to the motor part), might cause problems with planning[237,238]; for a review see Owen[170]. Recent PET and SPECT imaging studies[9,53,160,171] that used the Tower of London test confirmed that brain activity during planning is located mainly in the prefrontal area, particularly in the dorsolateral prefrontal cortex. These data were based on averages of several participants, because these techniques usually have too low sensitivity to detect activation in individual participants reliably.

Functional MRI (fMRI) is a non-invasive technique with which to measure brain activity based on changes in the blood oxygen level[130,168]. Additional advantages of this technique compared with other functional brain imaging techniques are its high spatial and temporal resolution and the ability to study individual subjects. Paradigms applied in PET studies, however, often can not be used without major changes in fMRI, because there are important differences in the test situation of the two techniques. In this study the results of our, for fMRI adapted, version of the planning task are presented.

METHODS

Task paradigm

For application of the test with fMRI, a block design was created, in which an "active" condition concerning planning and a "control" condition without planning were alternated (36 seconds per block, including an instruction; nine blocks in total). With the active condition, the participants are presented a baseline and a target configuration on a single screen [figure 1] viewed through a mirror in the magnet bore. Both configurations consist of three differently coloured balls (blue, yellow and red) placed on three vertical rods which are one, two and three balls in height, respectively.

The minimum number of necessary moves to reach the target has to be planned in mind. One ball can be moved at a time, and only when there is no other ball on top. Sometimes counterintuitive moves are necessary to reach the target; one of the major aspects of planning. The participant holds two air bulbs, and answers by pressing the one corresponding to the side where the correct answer is shown; one of two possibilities displayed at the bottom of the screen. With the control condition, participants simply have to count the yellow and blue balls together and again choose the correct answer (total number of balls) from two possibilities. The display is almost the same as with the active condition, except that more balls are displayed, with every time another number of yellow and blue balls [figure 1].

Every condition block starts with an instruction of four seconds to plan the moves (active condition) or count the balls (control condition). Easy (two to four moves) and difficult (five to seven moves) configurations are presented in separate blocks to make it possible to compare two different levels of planning activity (difficult, easy) and a control situation without planning. The whole test is self-paced; a new trial (in the same block) is presented only after a response is obtained. No feedback regarding the correctness of the answer is provided during the task. After 36 seconds the next block starts with a new instruction [figure 2], regardless of whether the last trial has been responded to. In total 82 whole brain volumes (9 blocks with 9 volumes each and one volume preceding the start of the test) were scanned (one scan was made every 4 seconds) [figure 2].

To ensure the participants were familiar with the procedure, the test was explained and practised outside the MR room before scanning.

Participants

Nine healthy students (five men, four women; mean age 22 years (range 20 - 27)) were evaluated. The ethical review board of the Academic Hospital of the Vrije Universiteit Amsterdam approved of the study and all participants provided informed consent.

Data acquisition

Imaging was performed on a 1.5 T MR system with a standard circularly polarised head coil. Anatomical imaging was performed with a 3D gradient echo T1-weighted sequence (15 ms (TR), 7 ms (TE), 1 (excitation), flip angle: 8 , matrix size: 256 x 256, field of view: 220 x 220 mm, slice thickness: 2mm, number of slices: 82).

Figure 1

Example of the Tower of London screen

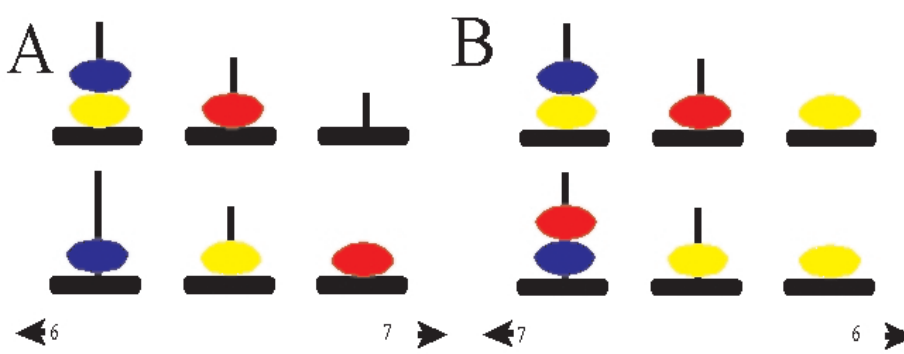
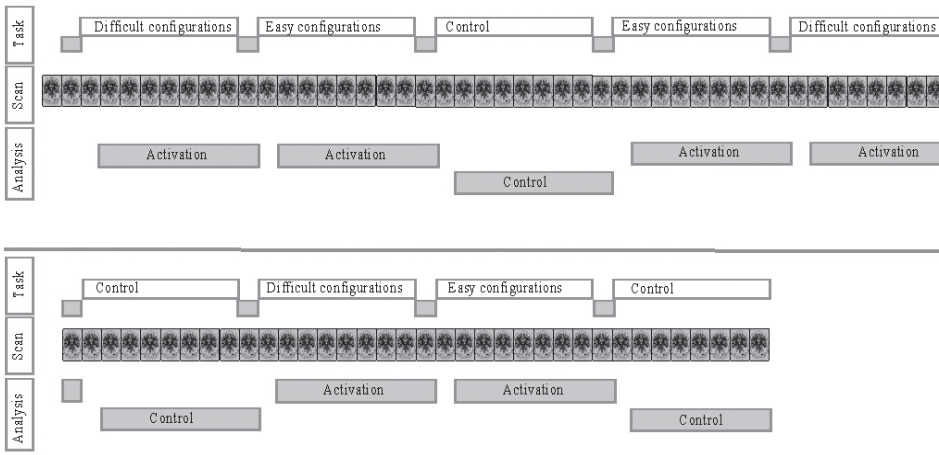


Figure A Sample screen of one of the configurations of a planning problem. Upper part: baseline configuration. Lower part: target configuration.
In this example the participant has to move first the blue ball to the right rod, which is counterintuitive. Thereafter the subject has to place the yellow ball on top of the red ball, the blue ball at its destination, the yellow ball on top of the blue ball, the red ball on the right rod and finally the yellow ball at the target position (sixth move). Two alternatives are presented on each side of the screen, from which the subject had to choose the correct answer. The subject was asked to respond by pressing the air bulb at the corresponding side.
Figure B Sample screen of the control configuration. The subject has to count the yellow and blue balls altogether. In this example, the answer is six, which is indicated on the right side.

Figure 2

Overview of the test, scanning and data analysis



Task paradigm: Easy, difficult planning and counting are performed in blocks. Every block lasts 36 seconds, including a 4 seconds instruction. A total of nine blocks were performed during the test.

Scanning: A total of 82 scans were obtained, including those of a dummy before the test started.

Data analysis: To account for the haemodynamic response delay, a 4 seconds delay in the analysis was used. The images obtained during the instruction (accounting for the haemodynamic response delay) were not used for further calculations. The resulting 71 scans were used for the analysis (24 obtained during the difficult planning problems, 24 obtained during the easy planning problems and 23 obtained during the control stage).

The slices were planned in the coronal plane with a rotation of approximately 30 of the cranial part in the anterior direction, to cover the whole brain in the least possible number of slices. For fMRI scanning, a whole brain echo planar imaging (EPI) sequence (4 seconds (TR), 64 ms (TE), 1 (excitation), flip angle: 90 , matrix size: 64 x 128, interpolated to 128 x 128 mm, field of view: 220 x 220 cm, slice thickness: 6 mm, interslice gap: 1.02 mm, number of slices: 23) was used. The EPI slices were planned parallel to the anatomical slices.

Data analysis

The first step of the post-processing was correction of motion artefacts[287], with the consequence of corrupting the first and last slice of each volume, which were discarded from further analysis. Next, the data were

smoothed in-plane, resulting in a full width at half maximum of 5 mm in plane. The following steps were performed with AFNI software[50]. Activation was detected by correlating each time course of each voxel with a box car function representing the "active" and "control" blocks of the paradigm [figure 2]. Also the two levels of planning difficulty were correlated in the same way, without using the control stage images. Voxels with a signal increase during the active condition had a positive correlation coefficient and were called positive activation. The opposite was true for voxels with a relatively reduced signal. The box car function was delayed 4 seconds (1 scan) in time to partly account for the haemodynamic response delay[122]. The scans that corresponded with the time the instructions were displayed, were not used in the analysis [figure 2].

The scans were transformed into Talairach coordinate space[252] by defining reference line landmarks on the anatomic scans. Individual activation maps were calculated and also used to create a group average. Correction for multiple comparisons was performed, accounting for the spatial extent of activation[51,81]. Only voxels with at least a p-value of 10^{-4} where considered active and 3D-clusters of at least 104 mm^3 (i.e. five connected active voxels) were included, resulting in a mean activation map of all participants with an overall p-value < 0.05.
In all individual and group images the macroscopic position of significant activations was defined based on the visible gyral - sulcal pattern to specify the location in more anatomic detail.

RESULTS

All nine subjects were studied successfully. Because we used a self-paced paradigm, the number of answers varied, with a mean of 13.7 (range 9 - 17) answers during both planning conditions together, of which 78.7% were correct (66.7-100%). For the easy configurations a mean of 8.5 (6 - 11) answers were given, of which 82% (57 - 100%) were correct; for the difficult configurations the results were 5.2 (3 - 8) answers, of which 71% (50 - 100%) were correct. With the control condition (only counting) the number of correct answers was 98% (89% - 100%), and the participants gave 36.4 (29 - 48) answers.

Table I

Areas of fMRI activation during the Tower of London task; planning condition (mean of all subjects).

Active area	Centre of peak activation*			Vol. (mm^3)	Subjects active	
	RL	AP	IS		N	Individuals
Middle frontal gyrus and adjacent part of inferior frontal sulcus, left	28	-11	59	7254	9	1,2,3,4,5,6,7, 8,9
..., right	-28	-16	54	8741	9	1,2,3,4,5,6,7, 8,9
Cingulate gyrus, anterodorsal part, left	9	-38	22	1836	6	2,3,5,6,7,9
Cuneus and precuneus, around parieto-occipital sulcus, left and right	1	70	33	10142	7	2,3,4,6,7,8,9
Supramarginal and angular gyrus (parietal lobe), left	38	62	50	1141	7	2,3,4,6,7,8,9
Insula, anterior part, left	29	-23	7	1027	5	1,2,6,7,8
Cerebellum, left	39	66	-33	1164	7	1,2,4,5,7,8,9
..., right	-39	56	-37	452	4	3,4,6,7
Lateral occipital gyrus, left	31	80	27	672	5	2,4,6,7,8
..., right	-45	67	20	2684	7	1,2,4,6,7,8,9

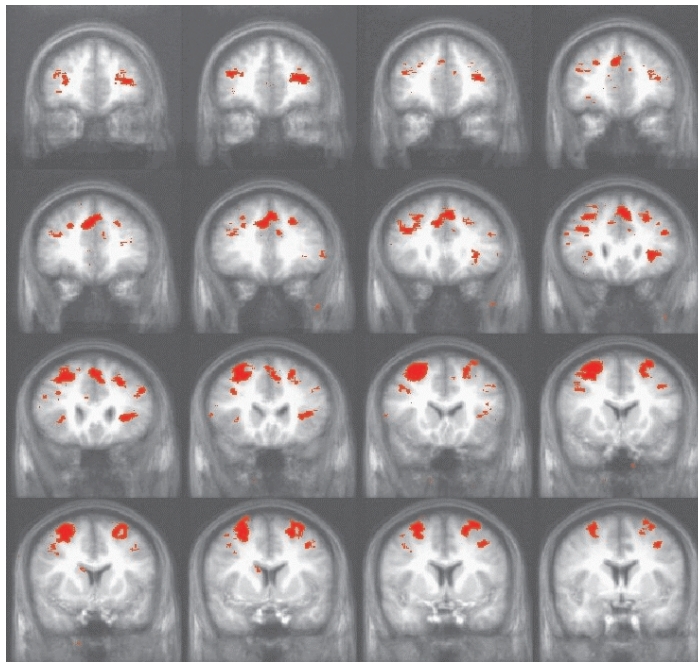
* direction in Talairach space (from negative to positive) RL = right / left; AP = anterior/ posterior; IS = inferior/ superior
N = number of subjects which showed activity in the neighbourhood of the centre of the peak activation

Figure 3

Activated areas during the active condition of the Tower of London task.

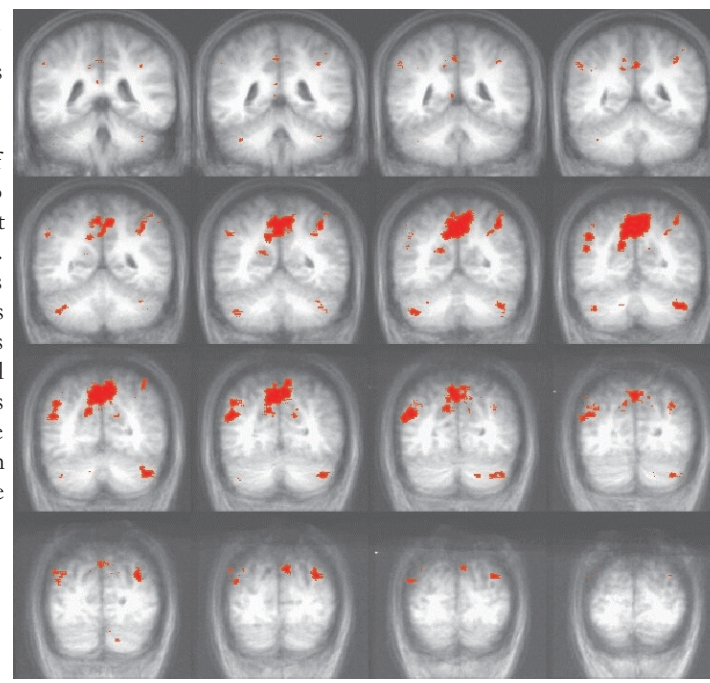
During the active condition (planning stage) of the task, activation (red) on the group average map (shown in Talairach format with coronal orientation) is shown. In the brain area from -3 anterior to +49 posterior no activation was seen.

Fig 3A Frontal regions during planning



Coronal slices of coordinates -44 to -3 (anterior part of the brain). Activity was noted in the dorsolateral prefrontal cortex, the anterior part of the cingulate cortex, a part of the precentral cortex and the frontal opercular area of the insula. The right side shows slightly more activation than the left side.

Fig 3B Parietal / occipital regions during planning



Coronal slices of coordinates +49 to +80 (posterior part of the brain). Activation was noted in the cuneus and precuneus region, the marginal and angular gyrus in the parietal lobe and the cerebellum during the active condition.

Activation in the group average images during the active condition (easy and difficult configurations combined) was seen on both sides in the frontal and parietal lobes, the cerebellum and the insula [figure 3 (a and b); table I]. The frontal area showed activation bilaterally in the middle frontal gyrus and the adjacent part of the inferior frontal sulcus (with some preference for the right hemisphere) and in the anterior part of the cingulate gyrus [Figure 3a]. The parietal and occipital regions involved were the precuneus and cuneus and the left supramarginal and angular gyrus [figure 3b].

Most participants showed activation in the same gyri that were activated on the group average [table I], and activation in the middle frontal gyrus (bilaterally) especially occurred in all participants. We did not find any significant differences in the activation when comparing the two levels of difficulty (easy and difficult planning).

The areas observed with a higher signal in the control condition were the middle part of the cingulate gyrus and the middle part of the insula on both sides, the fusiform gyrus and the pre- and post-central gyrus. The majority of cases (67-100%) showed activation in the same gyri that were activated on the group average. An exception was the activation in the fusiform gyrus, which had a higher signal in the control condition compared with the planning condition, in only 44% of the participants [figure 3; table I].

DISCUSSION

A planning task, such as the Tower of London, has proven to be a task which is sensitive to prefrontal lesions[171,210,238]. A new version of the planning task, adapted for fMRI, is presented. The group analysis showed activation during the planning stages in the dorsolateral prefrontal cortex, the anterior part of the cingulate cortex, the cuneus and precuneus, the supramarginal and angular gyrus in the parietal lobe and the frontal opercular area of the insula. These findings are in full agreement with previous PET results on grouped data[9,53,171]. In addition, fMRI enabled us to investigate brain activation during planning activities with high spatial (and temporal) resolution in individual participants, showing

that the dorsolateral prefrontal cortex was activated in all individual participants studied.

Previous studies have indicated that activation associated with this task performance occurs especially in the prefrontal cortex [9,53,160,170,171,237]. Three PET studies that evaluated the Tower of London test in healthy controls [9,53,171] will be discussed in comparison with our results.

The PET studies of Baker et al.[9], Owen et al.[171] and Dagher et al.[53] used a block paradigm in which the participants had to plan the moves and press on a touch screen the number of moves[9] or perform each move separately by pressing on a touch screen the ball that has to be moved and thereafter the place to which it had to be moved[53,171]. With the control condition, the participants did not need planning, but only had to view the subsequent moves[9] or press the touch screen at the highlighted locations corresponding with locations pressed during the planning condition[53,171]. Dagher et al. not only analysed the activation during planning, but the planning stages were analysed also in a parametric way, based on task complexity[53].

The three aforementioned PET studies (group analysis) showed frontal lobe activation, in the dorsolateral prefrontal cortex bilaterally (predominantly right hemisphere), the anterior cingulate gyrus bilaterally and some frontal lobe motor areas. Activation was also noted in other frontal areas, but not with complete consistency across the three studies; Owen et al.[171] activated the left medial frontal cortex, Baker et al.[9] activated the right rostrolateral prefrontal cortex. All three studies also showed activation in the caudate nuclei (the left one in the study of Baker et al., the right one in the other two PET studies). In addition to the frontally located activated areas, activation was also seen in the right anterior insula (frontal opercular area), the medial parietal cortex (precuneus) bilaterally, the left inferior parietal cortex, the right superior parietal cortex bilaterally, the lateral occipital cortex and the left cerebellum and vermis[9,53,171]. Those areas are probably activated not only by the planning process itself, but also by the motor and visual processes needed to perform this planning.

In the study of Dagher et al.[53], the activated areas during planning could be divided, as a result of the parametric analysis, into those that did not correlate with the task complexity, such as the areas belonging to the dorsal stream of visual input (visual and posterior parietal cortical areas) and the execution of arm movements

(frontal lobe motor areas), and those that correlated with the task complexity, such as lateral premotor cortex, rostral anterior cingulate cortex, dorsolateral prefrontal cortex bilaterally and the right dorsal caudate nucleus.

In our fMRI study, we found globally the same activated areas as in the aforementioned PET studies [table I]. Concerning the frontal areas, we observed significant activation in the middle frontal gyrus and the adjacent part of the inferior frontal sulcus, the precentral cortex and the anterior part of the cingulate gyri. As in the PET studies, activation was also seen in the caudate nuclei, but the volume of this activation was below our cluster size limit. We found only one main difference with the PET studies. In our experiment, the occipital lobe and the primary motor areas were more active during the control condition. This could be explained by the fact that in the control condition the total number of configurations processed was higher.

One of the main areas activated during this planning task is the dorsolateral prefrontal cortex. Activation in this area is thought to be associated with active processing of both spatial and nonspatial information. Left - right differences probably exist, but there is no consensus regarding the nature of those differences. Baker et al.[9] refer to literature on PET studies in which the spatial information is predominantly represented in the dorsolateral prefrontal cortex of the right hemisphere, whereas nonspatial working memory should be positioned predominantly at the left side. In our study, we noted bilateral frontal activation with a slightly larger activated area on the right side. This may be taken to indicate that spatial information processing is a prominent feature of the Tower of London paradigm. Such a suggestion seems quite logical in view of the test, moreover activation of the precuneus and inferior parietal lobe has been associated with spatial processes and is correlated with prefrontal activity[9,53].

In contrast with the study of Dagher et al.[53] who found complexity related activation when performing a parametric analysis on five difficulty levels, including one-move-problems (which require almost no planning), no differences in activation were found in our study when comparing the easy and difficult conditions. This could be explained by the decreased amount of data, our design of only two levels and the too small a

difference of the two levels of planning. Another possible explanation is the difference in the response to be given, in our test one number, in the study by Dagher et al. the whole planning sequence, of which the last requires probably more planning activities.

Regarding the interpretation of the test score, for all except one participant, the test score was clearly beyond chance expectations (i.e. more than 50% correct answers). The test score is of assistance only in determining whether the participant has performed the test, or when no activation or activation in unexpected areas is seen, which was not the case in our participants. With the non imaging versions of the test, the reliability of the test scores within individual subjects is sometimes criticised. Our study tried only to localise the underlying brain areas activated, so the test score, and thereby its within subjects reliability, was less important for our goal. The high intersubject concordance for prefrontal activation may relate to the fact that for this test it is not the number of correct answers, but the process of planning (resulting in a correct answer or not) that is the most important determinant.

One of the main ideas regarding the use of fMRI was to study subjects individually [table I]. All nine subjects tested showed significant activation in the dorsolateral prefrontal cortex when analysed individually. The other areas that showed activation in the group analysis were also seen in most participants. Future research with fMRI will enable us to correlate those findings with individual parameters.

CONCLUSION

The Tower of London test was successfully adapted for fMRI and the activated areas found were consistent with previous PET studies, especially in the prefrontal cortex. Also, fMRI allowed us to demonstrate significant activation in individual subjects. The dorsolateral prefrontal cortex was active in all individual participants. The benefits of the fMRI procedure could enable us to use this adapted version of this test to evaluate individual patients with presumed prefrontal dysfunctions.

3.3 THE fMRI ADAPTED PASAT TEST

Adapted from: Journal of Neurological Sciences

A paced visual serial addition test for fMRI.

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J. Neurol. Sci, 2003 (213), 29 - 34

Abstract

OBJECTIVE

The Paced Auditory Serial Attention Task (PASAT) is an attention and information processing task used in patients with diffuse brain disorders, like cerebral trauma and multiple sclerosis. Based on the PASAT we used an adapted version of the test to assess several cognitive functions with fMRI. In this study we investigated the activation pattern on a group and individual level and upon parametric stimulation.

METHODS

Nine young, healthy, right-handed subjects (mean age 24 years) were studied. The test contrasts an adding-and-memory stage with a control stage in a block design, at two different speeds. Group average maps (random effects analysis, $p = 0.05$) were created to identify the brain areas subserving this task. For each area found active in the group map, the percentage of individuals showing activation in that same anatomical area was calculated.

RESULTS

Group activation was localized in the superior and inferior parietal lobe bilaterally, the superior frontal gyrus bilaterally, the left medial frontal gyrus, the left inferior frontal gyrus and adjacent part of the insula, the anterior part of the cingulate gyrus and some cerebellar areas. For the main activated areas, 78-100% of the individual subjects showed activation in that same area.

Contrasting the low speed with the high speed condition yielded activation with a considerable individual variation.

CONCLUSION

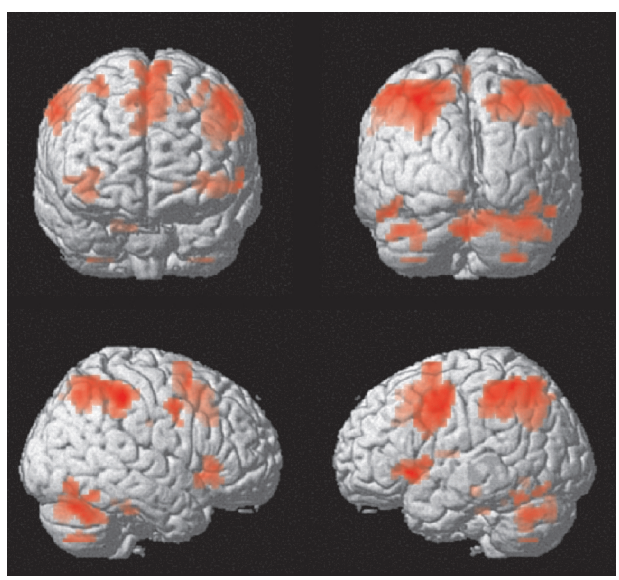
The group mean activated areas were located mainly in the frontal and parietal lobes and those areas were also activated in the majority of the subjects, indicating limited inter-individual variation, rendering this test suitable for clinical applications in a variety of neurological disorders.

INTRODUCTION

fMRI is used to study cognitive processes. In certain diseases, like multiple sclerosis (MS) and traumatic brain injuries, diffuse pathological processes are present. Patients with diffuse cerebral damage show a lower test score on the Paced Auditory Serial Addition Test (PASAT developed by Gronwall[90]) than healthy controls[223], for example after cerebral concussion[90]. The level of performance on the PASAT is also lower in patients with disorders characterized by lesions diffusely distributed over the brain, like in MS[202]. Attention demanding (controlled) information processing underlying more complex cognitive skills is in general more slowed in MS patients[58]. To be able to assess cognitive deterioration by means of fMRI, we used a task based on multiple cognitive abilities, requiring the support of various brain areas throughout the brain. Since the PASAT and the Paced Visual Serial Addition Test (PVSAT)[82], a visual version of the test, fits the above requirements, we developed an fMRI version of this task.

Figure 1

Projections on the brain of the active areas of the adding-and-memory versus control stages (group map, random effects analysis).



Brain surface representation of the activity, calculated from the individual subjects activation maps using a random effects analysis (p = 0.05)

The PASAT test consists of 60 random digits which are sequentially presented from audio tape. The subject is instructed to add the last digit to the preceding one, for every number heard. The resulting sum has to be vocalized before the next digit is presented. Different presentation rates have been used (typically 2 or 3 seconds per digit)[90]. The PASAT imposes high demands on the subject's working memory capacity, requiring controlled information processing (attention), visual memory, good auditory functioning and calculating abilities[239].

The purpose of our study was to administer an attention task in an fMRI setting, and to study the inter-individual variation and the parametric qualities of the brain activity. We hypothesized that the activated areas, when attending to and processing visual stimuli, would be located mainly in the parietal and frontal lobes.

METHODS

Data acquisition

Imaging was performed on a 1.5 T MR system with a standard circularly polarized head coil. Anatomical imaging included a transverse 3D gradient echo T1-weighted sequence (15/7/1 [TR/TE/excitations]; flip angle: 8 ; in plane resolution: 0.86 x 0.86; slice thickness: 2 mm; number of slices: 82). For fMRI, a whole brain echo planar imaging (EPI) sequence (4000/60/1; flip angle, 90 ; in plane resolution: 3.44 x 3.44 mm; slice thickness: 4.0 mm, number of slices: 36) was used, planned parallel to the anatomical slices, which were used to superimpose the fMRI data on.

The stimuli were projected on a screen, viewed by the subject via a mirror placed on top of the head coil in the magnet bore.

Task

Different conditions, from which a functional contrast can be calculated, are needed in an fMRI design. For this reason, our test contrasts a "memory-and-addition" (further called the adding) stage to a control stage. During the adding-stage the subject performs the same task as during the original PASAT. Every digit presented is added to the one preceding it. The auditory cues in the adding stage of the original PASAT test were replaced by sequentially presented visual cues (digits) as in the PVSAT[82] and the subjects were instructed to mentally process

these digits but to refrain from vocalizing the answers, which was done to prevent motion artefacts. We could not acquire answers, because other types of answering will interfere with the functions tested. During the control stage, subjects had to fixate on a cross, in the centre of the screen and were instructed to pay attention to the moment a digit was presented again, which was the moment the adding stage resumed.

In the test, we applied two different conditions, presented in adding (A) and control (C) blocks. Each block had a duration of 140 sec (35 scans). The presentation rate of each block was either 2.5 or 3.5 seconds per item. The presentation order of the blocks was [A 2.5] - [C 3.5] - [A 3.5] - [C 2.5] - [A 2.5] - [C 3.5] - [A 3.5] - [C 2.5].

Subjects

Nine healthy students (6 men, 3 women; same educational level), mean age 24 years (range 19 - 30) were evaluated. All subjects were right-handed and had an optimal visual acuity. The ethical review board of the Vrije Universiteit Medical Center Amsterdam approved the study and all subjects gave written informed consent.

Before scanning, the test was explained and practised outside the MR suite. In the magnet bore the test was practised once more, this time without answer registration (as was the case during the scanning session).

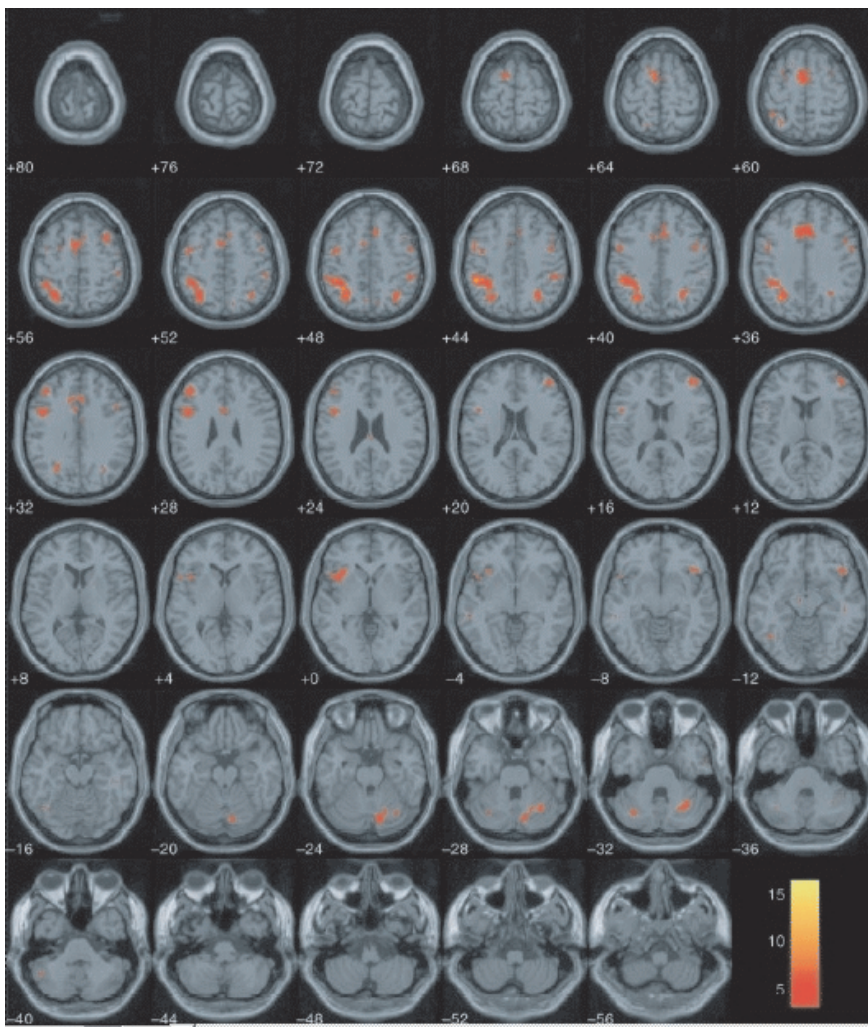
Data analysis

The data analysis was performed with SPM99b [Available via www.fil.ion.ucl.ac.uk/spm/spm99.html]. The EPI data were realigned and normalized (and resliced 3x3x3 mm) into standardized coordinate space approximated on the Talairach and Tournoux space[252]. Next, the data were smoothed using a Gaussian filter set at 6 mm full width at half maximum. The time series of each normalized voxel was correlated with a reference waveform representing the test-model, convolved with a haemodynamic response function. We contrasted in this way the attention/information processing stages with the control stages, and also the high speed versus the lower speed task conditions of the attention/information processing stage were contrasted.

Individual activation maps were calculated applying per voxel a p-value of 0.005, with a 3D-cluster restriction of at least five adjacent active voxels. The group results were calculated using random effects analysis[286]. For this analysis, the activation map of each individual was used in a one sample t-test ($p = 0.05$, corrected for multiple comparisons).

Figure 2

Random effects analysis of the adding-and-memory versus control stages (group map)



Transverse slices of the active areas calculated from the individual subjects activation maps using a random effects analysis ($p = 0.05$). Left side of the images represents left side of the patient (view from above).

Besides the contrast of the adding versus the control stage, the contrast between the high and low speed condition was calculated. To address the consistency of the activated areas found in the group analysis, for each anatomical area found on the group map, the number of individuals with activation in that same anatomical area was determined.

RESULTS

The whole group random effect analysis of the processing information stages (both speeds together) contrasted with the control staged showed bilateral (left size larger than right) activation in superior and inferior parietal lobe (BA 7/40), superior frontal gyrus (BA 6) bilaterally (L > R), left medial frontal gyrus (BA 9), left inferior frontal gyrus (BA 44, 47) and adjacent part of insula, the anterior part of the cingulate gyrus (BA 32), and several areas in the cerebellum. For details of the activated areas see figure 1 and 2 and table I.

The whole group activation pattern was globally the same for all individual subjects [see table I]. For all activated areas 56-100% of the individual subjects showed activation in that same area. This percentage was even higher (78-100% of all subjects) when selecting only areas with more than 35 adjacent active voxels. Some anatomical areas, like the left superior and inferior parietal lobe, the right superior frontal gyrus and the cingulate gyrus, showed activation in all subjects studied.

Group analysis comparing the high versus the low speed of the adding stage [A3.5 vs A2.5] showed some small activated areas [see table II]. The largest area of activation was seen in the right inferior frontal gyrus (BA 44), while smaller activated areas were seen in the medial frontal gyrus (BA 6/10) bilaterally, the right cingulate gyrus (BA 24), the left superior parietal lobe (BA 7), the right cuneus/ precuneus region, the left pulvinar, the right caudate nucleus and the cerebellum bilaterally. For this contrast however, the individual results did not compare well with the group result: of all the areas activated in the group map only 11-67% of the subjects showed activity in that same area. The left superior parietal lobe and the cuneus/ precuneus region on the right was the most consistently activated area (67%).

The reversed contrast (areas more activated during the slower speeds) did not show any activation in the group analysis.

Table I

Activations for the adding versus control stages (random effects group map)

Area (Brodmann area)	SPM coordinates			nr of voxels	T-statistic	%subj active
Sup. parietal lobe (7), Inf. parietal lobe (40) [L]	-30	-60	48	170	14.76	100%
Inf. parietal lobe (40) [R]	63	-36	45	24	7.11	67%
Inf. parietal lobe (7/40) [R]	27	-60	45	14	6.29	56%
Sup. frontal gyrus (6) [R]	30	6	60	15	9.94	100%
Sup. frontal gyrus (6) [L]	-3	-3	63	39	5.97	78%
Med. frontal gyrus (9) [L]	-45	9	36	115	9.67	89%
Med. frontal gyrus (32/8) [R]	3	27	36	7	6.68	67%
Inf. frontal gyrus (45) /Insula [L]	-33	21	3	13	9.56	78%
Cingulate (32) [L]	-9	24	33	36	15.86	100%
Cerebellum [R]	33	-60	-27	13	10.34	89%
Cerebellum [L]	-36	-66	-36	9	5.9	89%

Random effects analysis results.
The first two columns show the area and the SPM coordinates of the voxel with the peak activity (the left number represents the left-right coordinate, where minus is left; the middle number represents the anterior-posterior coordinate, where minus is posterior; and the last number is the top-bottom coordinate where minus is the bottom). The third column gives the number of active voxels of the cluster containing the "peak" voxel, followed by the t-value. The last column shows the percentage of the individuals with activation in that same area.

Table II

High versus slow speed (random effects group map)

Area (Brodmann area)	SPM coordinates.			nr of voxels	T-statistic	% subj active
Sup. parietal lobe (7) [L]	-15	-51	57	34	12.16	67%
Precuneus / Cuneus [R]	24	-60	18	37	9.23	67%
Med. frontal gyrus (6) [R]	33	3	57	9	12.38	44%
Med. frontal gyrus (6) [L]	-12	15	48	45	8.62	44%
Inf. frontal gyrus (44) [R]	45	9	18	113	11.19	33%
Cingulate gyrus (24) [R]	12	33	-3	56	19.24	44%
Thalamus (Pulvinar) [L]	-24	-15	9	15	8.31	22%
Caudate nucleus [R]	21	-6	18	12	8.31	11%
Cerebellum [L]	-12	-42	-39	24	11.36	22%
Cerebellum [R]	27	-66	-51	24	9.87	22%

Two speeds contrasts, random effects analysis.
The first two columns show the area and the SPM coordinates of the voxel with the peak activity (the left number represents the left-right coordinate, where minus is left; the middle number represents the anterior-posterior coordinate, where minus is posterior; and the last number is the top-bottom coordinate where minus is the bottom). The third column gives the number of active voxels of the cluster containing the "peak" voxel, followed by the t-value. The last column shows the percentage of the individuals with activation in that same area.

DISCUSSION

We adapted a test that assesses attention, information processing, visual memory, working memory and calculating abilities for fMRI. Brain activity, supposedly associated with those functions, was found in the following areas: bilaterally in the superior and inferior parietal lobe, bilaterally in the superior frontal gyrus, in the left medial frontal gyrus, left inferior frontal gyrus and adjacent part of the insula, the cingulate gyrus (anterior part), and several

cerebellar areas. The activated areas were quite consistent, as evidenced from the fact that for all areas larger than 35 adjacent voxels, 78-100% of the individual subjects showed activation in that same area.

The test is a fMRI-adapted version of the PASAT, incorporating an activation and control stage. The original PASAT test requires sustained and divided attention capacity, information processing and demands in terms of calculating functions and working memory. We expected the fMRI version to address similar cognitive processes. The results we found are in line with this hypothesis. A specific aspect of this task, adding the last digit to the preceding one for every number seen, draws heavily on executive control, because each addition has to be suppressed and working memory content has to be continuously updated to produce the correct answers. Brain networks associated with executive control include the anterior cingulate cortex and supplementary motor area, the orbitofrontal cortex, dorsolateral prefrontal cortex, parts of the basal ganglia and the thalamus[23,67,178,193]. Visual information processing has been found to activate the precentral gyrus of the frontal lobe, parietal lobe areas and part of the temporal lobes[46,47,189]. Sustained attention, also needed in this task, is subserved by right frontal-parietal areas (right parietal cortex (BA 7), right dorsolateral and middle frontal lobe and anterior cingulate gyrus) and the locus coeruleus[48,49,102,137,174]. Mathematical functions are supposed to be subserved by the left parietal lobe.

A recently published study of Staffen et al.[246], using the attention task in a similar design and scanning only a portion of the brain, found only right cingulate cortex (BA 32) activation in their healthy subjects group. In contrast with our results other frontal areas did not show significant activation. One of the reasons for this can be that our task takes longer to complete and demands more information processing and working memory. However, in a group MS patients, they also found activation in some frontal cortex areas (BA 6, 8 and 9, right side and BA 39, left side), probably because the relative demand in that group was higher and therefore reached significance. Their conclusion that this meant an adaptative change in the patients group, may however be disputable. All sorts of differences in the studied populations (age, educational level, disease severity) can be a cause of the difference in the results. Besides those mentioned, neuroplasticity, neural changes in reaction on the disease processes, is also an explanatory factor.

To investigate changes in brain activation patterns as a result of increased task demands, i.e. when the information processing system is put under more pressure, we have applied a parametric design in which to different speeds of digit (stimulus) presentation were used. Comparing the two speed stages, activation in the right inferior frontal gyrus, the medial frontal gyrus (BA 6/10) bilaterally, the right cingulate gyrus (BA 24), the left superior parietal lobe (BA 7), the right cuneus/ precuneus region, the left pulvinar, the right caudate nucleus and the cerebellum bilaterally was seen. However, the individual variation of the speed contrast was considerable. This might indicate that processing speed is important, but that optimal processing speed may not be the same for all individuals. Further work is needed to clarify which speed is most optimal and if there are changes between healthy and diseased subjects.

CONCLUSIONS

In conclusion, the fMRI-adapted attention task, activates areas involved in a broad set of cognitive functions (including the attention and working memory functions) including the superior and inferior frontal gyrus bilaterally, the left medial frontal gyrus, the cingulate gyrus, the superior and inferior parietal lobe bilaterally, and some areas in the temporal lobe and cerebellum. The procedural differences between our test and the original PASAT test (no overt responding, different speeds in one test, existence of a control stage) are most likely not essential for the attentional and memory aspects of the test. The consistency of the results in individuals compared to the group random effects analysis indicate that the test is suitable for further research of cognitive functioning in patients with widespread brain damage, such as multiple sclerosis.

Contrary to evaluating one selected cognitive sub process, studying patients with widespread brain damage is better done with tests which need the 'whole brain'. The changes in time of the activated areas and their volume can be used as an indicator of the disease process or recovery. For further implementation and understanding these changes, more research is needed into inter-individual reproducibility and factors that are involved in explaining the variation.

CHAPTER 4

fMRI TESTS IN MS PATIENTS

4.1 TOWER OF LONDON TEST IN MS PATIENTS

Adapted from: Multiple sclerosis

An fMRI study of planning-related brain activity in patients with moderately advanced MS.

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Multiple sclerosis, 2004 (10), 549 - 555

Abstract

OBJECTIVE

Cognitive impairment occurs in a substantial number of multiple sclerosis (MS) patients and often includes frontal lobe dysfunction. We used functional magnetic resonance imaging (fMRI) to study planning, an executive function, in moderately impaired MS patients.

METHODS

An fMRI version of the Tower of London test was used to study patterns of brain activation in 23 MS patients and 18 healthy controls. The median score on the expanded disability status scale for the MS patients was 4. fMRI data were analysed using whole brain random effects analysis as well as region of interest (ROI) based methods to assess group effects. Within the MS group, associations with behavioural data and measures of disease severity (lesion load from structural MRI) were examined.

RESULTS

Test performance in MS patients was significantly worse than in controls. Group analysis for the MS patients and the controls showed for both groups globally the same areas of activation, located in the frontal and parietal lobes bilaterally and the cerebellum. Although visual inspection suggested a larger extent of activation in the MS group, no statistically significant differences between groups were found. In the ROI analysis, statistically significant larger extent of activation was only found in the cerebellum. No association between disease severity and brain activity could be determined in the MS group.

CONCLUSION

In MS patients with moderate disability and structural damage, the pattern and extent of brain activation during planning were maintained despite poorer performance. In contrast to other studies showing increased activity, the failure to do so in our group may reflect exhaustion of adaptative mechanisms.

INTRODUCTION

Cognitive dysfunction is common in multiple sclerosis (MS) patients, occurring in 30 - 60% of all patients[18,202,260]. Cognitive functions primarily dependent on the frontal lobes, like planning, are more often affected than, for example, language. Previous studies have shown a relation between total lesion load on magnetic resonance imaging (MRI) scans and cognitive impairment, with significant albeit not very high correlations[83,203,244,250]. Some studies also found a relation between regional lesion loads and certain test scores[133,244,250]. The functional basis of cognitive impairment, and the role of the lesions, however, is largely unknown.

Functional imaging studies of MS patients so far have mainly concentrated on motor function[24,25,40,70,136,205]. Only a few studies focussed on cognitive functions, for example memory[178,282,283], attention[179,246] and language functions[194]. Functional imaging studies on planning, an executive function known to be impaired in MS patients[80], have not been reported.

Recently we adapted the Tower of London (ToL), a well-known planning task, for use with fMRI[135]. In the present study we applied the ToL task using fMRI in MS patients. The goal of our current study was to evaluate whether cognitive fMRI research applying this task is feasible in MS patients, and if so a) which brain areas are used by MS patients during this planning task, b) whether this is different from controls and c) whether there is a relationship between lesion load, test results, and brain activation patterns.

METHODS

Subjects

We studied 23 MS patients and 18 healthy controls, comparable for age, sex, education (years of schooling) and handedness [table I]. The subjects were selected for adequate hand function and vision as well as sufficient understanding of the instructions given prior to the test. The patients were selected from a larger group of MS patients (n = 33) who had undergone more detailed cognitive testing previously; 10 MS patients could not be included in the present study because they had inadequate

hand function or vision or did not understand the test; by contrast, only one subject considered for the control group had to be excluded. The level of disability as measured by the expanded disability status scale (EDSS) score indicated mild to moderate disability. The ethical review board of the Vrije Universiteit Medical Centre Amsterdam approved of the study and all subjects gave written informed consent.

Table I

Descriptive data of the study groups.

	Patients	Controls
sex	12 men / 11 women	12 men / 6 women
age	44.9 years (SD 9.7)	36.6 years (SD 10.6)
education	9.8 years (SD 2.3)	10.9 years (SD 3.1)
handedness	20 right / 3 left	14 right / 4 left
disease duration	2 - 15 years	n.a.
EDSS	median 4.0 (1.0 - 6.5)	n.a.

The EDSS is the expanded disability status scale score for MS patients in which 0-3 represents mild disability and 3-6 moderate to significant disability.
SD is the standard deviation. n.a. is not applicable.

Task paradigm

In the fMRI version of the Tower of London task[135], the subjects are presented a baseline and a target configuration on a single screen [figure 1a]. Both configurations consist of three differently coloured balls (blue, yellow and red) placed on three vertical rods which are one, two and three balls in height respectively. The minimum number of necessary moves to reach the target has to be planned in mind. One ball can be moved at a time, and only when there is no other ball on top. Sometimes counterintuitive moves are necessary to reach the target; one of the major aspects of planning.

Two possible answers were displayed at the left and right lower corners of the screen. Subjects were instructed to respond by pushing a button corresponding with the side the answer was

displayed. Six different levels of planning depth were randomly presented in two groups: 2-4 moves ('easy') and 6-8 moves ('difficult'), presented in separate blocks. This planning condition was alternated with a control condition, during which the subjects simply had to count the total of the yellow and blue balls and again choose the correct answer from two possibilities. The display is almost the same as in the active condition, except that more balls are displayed [figure 1b], with every time a different total number of yellow and blue balls.

The test is divided in blocks, each starting with an instruction, displayed on the screen. The test is self-paced, with a maximum block length of 40 seconds. More specific details of the tests have been described elsewhere[135]. In total 122 whole brain volumes (12 blocks of 10 volumes each and two volumes preceding the start of the test) were scanned (one volume was scanned every 4 seconds). Before scanning, the test was explained, and in addition all subjects practised with easy examples until they fully understood the procedure, and answered correctly.

Data acquisition

Imaging was performed on a 1.5 T MR system with a standard circularly polarized head coil. A whole brain gradient-echo echo planar imaging (EPI) sequence (TR 4 seconds, TE = 64 ms, 1 excitation, flip angle 90 , matrix size: 64 x 128, interpolated to 128 x 128, field of view: 220 x 220 cm, slice thickness: 4 mm, interslice gap: 1.02 mm, number of slices: 23) was used. The stimuli were projected on a screen, viewed by the subject via a mirror placed on top of the head coil in the magnet bore.

For identification of lesions, structural MR imaging was performed including a T2 weighted (TR 2500/ TE 45-90/ 1 excitation) spin-echo sequence. The slice thickness was 3 mm with a 1 mm in-plane resolution, with 42 contiguous slices being scanned to cover the whole brain.

Data analysis

The test scores were calculated for the easy stages, the difficult stages, both planning stages together and the control stages. The score was the number of correct answers minus the number of incorrect answers divided by the total answers given and multiplied by 100%. With an ANOVA test the MS and control group scores were compared with each other.

Lesion load measurements were derived from the structural MR scans. Lesions were identified by visual inspection and marked. Lesion load measurements were

performed on a workstation (Sun, Mountainview, California, USA) using in-house-developed semi-automated seed-growing software based on local thresholding differences (Show-Images), as described earlier[267]. The total volume of hyperintense lesions seen on the T2 images was calculated, as were regional lesion loads in the four main brain areas (frontal, parietal, temporal and occipital).

fMRI data were analysed with SPM99b [www.fil.ion.ucl.ac.uk/spm/spm99.html]. The EPI data were realigned and normalized (and resliced to 3x3x3 mm) to the standard SPM EPI template coordinate space approximating the Talairach and Tournoux space[252]. Next, the data were smoothed using a Gaussian filter set at 8 mm full width at half-maximum (FWHM). The data of each subject were modelled using a box-car function, representing the easy and difficult planning and the control stages, convolved with the standard SPM haemodynamic response function[85]. For each subject the following contrasts were calculated: a) planning versus control stages, b) easy planning versus control stages (EP > C), c) difficult planning versus control stages (DP > C) and d) difficult planning versus easy planning stages (DP > EP) and e) easy planning versus difficult planning stages (EP > DP). Each subject's "contrast images", representing the difference maps between conditions, were then used for further statistical group analysis.

For each contrast (a,b,c,d and e) the group average brain activation was calculated with a one sample t-test in MS patients and controls using the individual contrast images, known as random effect analysis. For each contrast, comparison of groups (MS versus controls) was performed with a two-sided two sample t-test. A p-value of 0.005 (at voxel level, uncorrected for multiple comparisons) was considered significant for all tests.

The individual contrast images were also used in correlation analyses with lesion load and test score as regressor, to test for either positive or negative correlations between regressor and signal difference in a specific contrast.

In a second analysis, the same contrasts as calculated for the group were also calculated for each subject separately, after a smoothing with FWHM of 6 in stead of 8 mm. The individual activation maps were calculated applying a p-value of 0.005 per voxel, with a 3D-cluster restriction of at least five adjacent active voxels. For the five areas with the highest volume of activation in the group analysis, the percentage of

subjects showing activity in that particular area was determined.
In a third analysis, we used a region of interest (ROI) approach to analyse the data. We defined ROIs corresponding with the active areas of the group activation map of the healthy controls. For all voxels contained in a given ROI, the number of active voxels of the contrast image was determined in each individual, with AFNI98[50]. The number of voxels in MS patients and controls, which were normally distributed, were compared with Student's t-test (with $p < 0.05$). Those measurements were also correlated with the test score and the lesion load measurements and entered into a multiple regression analysis with test score, age, disability score and lesion load as regressors.

RESULTS

All patients and controls performed the test without technical problems. The behavioural test scores of the Tower of London test were significantly worse for the MS patients than for controls [table II]. This was most evident for the scores of the easy planning stage ($p = 0.006$). The scores of the difficult planning stage were relatively low in both groups, indicating a ceiling effect[261].

Table II
Test results.

	MS patients			Controls			ANOVA
	Mean nr answ.	Mean test score	SD	Mean nr answ.	Mean tests score	SD	p-value
Total planning	16.1	70.46 %	18.14 %	22.0	79.48 %	7.51 %	.039
Easy	9.0	62.43 %	26.43 %	11.8	81.05 %	12.84 %	*.006*
Diffic	7.1	34.28 %	24.43 %	10.2	35.73 %	22.89 %	.846
Control	38.0	75.92 %	24.11 %	55.4	85.25 %	6.49 %	.088

The mean total lesion load of the MS group was 9.4 cm^3 (range 0.6 - 36.4). The correlation of the total lesion load with the sum of the frontal and parietal lesion load was very high ($R = 0.95$, $p < 0.001$). We did not find a correlation between test score of easy and difficult planning and total lesion load, frontal lesion load or parietal lesion load.

General effect of planning: main effects for whole brain analysis.

The planning versus control stages contrast (planning; (EP+DP) > C) of the healthy control group showed activity in the frontal and parietal lobes as well as the cerebellum. In the frontal lobe the activation was located in the middle frontal gyrus bilaterally and the left superior frontal gyrus. Activated areas in the parietal lobes included the precuneus bilaterally and the supramarginal gyrus/ inferior parietal lobe bilaterally. In the cerebellum and the right inferior temporal gyrus, some smaller activated areas were found additionally [table III, figure 2a].

In the MS subjects essentially the same areas in the frontal and parietal lobe were active. The cerebellum showed quite extensive activation. Smaller activated areas were seen in the left parahippocampal gyrus, the right thalamus and the middle temporal gyrus on the right side [table III, figure 2b]. The apparently greater activation in the MS group suggested by visual inspection (compare figure 2b with 2a) did not reach statistical significance in a direct comparison with controls by means of a two sample t-test in SPM. In a further analysis we compared the quartile of MS patients with the worst test score against those with the best score. Again, this comparison did not reveal significant differences between groups. Similarly, when comparing the quartile of patients with the lowest and those with the highest lesion load, no significant difference in activation was found.

Easy versus difficult planning.

We also investigated the influence of the difficulty of the presented planning problems. For the easy planning versus control [EP > C] as well as the difficult planning versus control [DP > C] contrast the same areas were active as was the case for both planning stages together [(EP+DP) > C]. This was true for the healthy control group as well as the MS patients. This may reflect the ceiling effect observed in the behavioural data, and others have suggested studying those levels of complexity in a parametric design[261]. No differences between the MS and healthy controls groups were found for these contrasts with a two sample t-test.

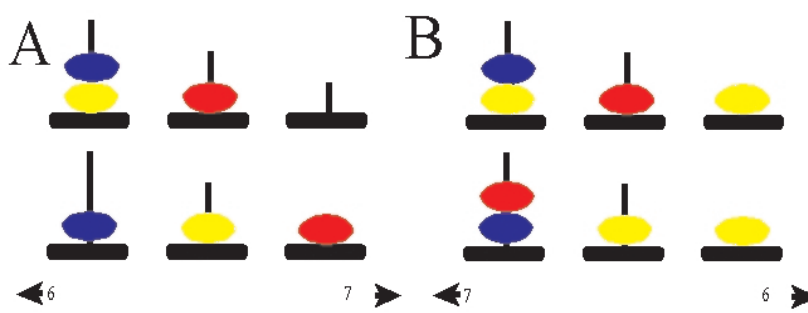
Table III

Activated areas in MS and controls: Planning (easy and difficult combined) vs control stage. (transformed to Talairach coordinates)

Controls							
cluster			voxels				Area
voxels	max T	p-value	coordinates				
287	6.17	.015	53	-57	33	R	Parietal lobe, Supramarginal Gyrus
339	6.09	.007	6	-62	34	R	Precuneus
283	5.52	.016	-42	-71	39	L	Precuneus, Inferior Parietal Lobule
107	5.42	.315	-18	29	54	L	Superior and Middle Frontal Gyrus
178	4.88	.090	33	34	45	R	Middle Frontal Gyrus
59	4.12	.689	-39	-69	-35	L	Cerebellum, Inferior Semi-Lunar Lobule
87	3.98	.445	36	-63	-38	R	Cerebellum, Inferior Semi-Lunar & posterior lobe
22	3.30	.972	48	-16	-27	R	Inferior Temporal Gyrus
MS patients							
cluster			voxels				Area
voxels	max T	p-value	coordinates				
317	6.16	.010	45	-62	39	R	Inferior Parietal Lobule
560	6.04	.001	-36	17	43	L	Superior and Middle Frontal Gyrus
274	5.24	.019	39	-54	-39	R	Cerebellum, Posterior Lobe, Tonsil & Pyramis
1182	5.07	.001	3	-53	-19	R	Cerebellum, Anterior Lobe, Culmen
250	4.76	.027	-45	-53	47	L	Inferior Parietal Lobule
434	4.44	.002	30	37	45	R	Middle Frontal Gyrus
344	4.38	.007	9	-56	44	R	Precuneus
122	4.02	.237	-24	-35	5	L	Parahippocampal Gyrus
24	3.78	.958	0	-15	1	R	Thalamus
11	3.35	.995	59	-4	-14	R	Middle Temporal Gyrus

The difficult versus easy planning [DP > EP] contrast revealed activation in the right superior and middle frontal gyrus, the left insula and the left and right superior temporal gyrus for the control group and only in the left superior frontal gyrus for the MS group. The reversed contrast (areas more active during the easy than the difficult stages [EP > DP]) showed activated areas in right inferior frontal gyrus, the right precuneus, the left fusiform gyrus, the left and right middle occipital gyrus and the cerebellum bilaterally for the control group and in the right precentral gyrus, the middle temporal gyrus bilaterally and the left side of the pons for the MS group. A two sample t-test comparing the results of the two groups did not reveal any significant differences for any of the contrasts. This was also the case, when comparing only the 19 patients and the 17 healthy controls which gave answers during all stages of the test, leaving out, based on the test score, those persons that might not have performed parts of the test as expected.

Figure 1
Tower of London example screen



Example of the screens shown during the fMRI Tower of London test. A) shows a planning stage example; B) shows a control stage example. The figures at the bottom of the screen represent the answers the subjects have to choose from by responding with the hand indicated by the arrows.

ROI based analysis.
To determine the inter-individual variability, for each activated area in the group mean, the number of individuals with activation in that same area was evaluated. Considerable inter-individual variation is present in extent of the activated areas, and the main areas seen in the random effect analysis are active in about half of the MS subjects (50 %) and controls (> 55 %). When the p-value was set less strict, more than 80% of the subjects showed activation in all the areas active in the group. The extent of activation in individual subjects in areas identified by the group maps was also quite variable. Subjects in both groups showed this type of variation, but it was by visual inspection more pronounced for the MS subjects.

The results of the ROI analysis (with AFNI) are shown in table IV. There was a significant difference between the MS and the control group in a direct comparison for the cerebellar region ($p = 0.01$). While a higher mean number of active voxels for MS patients was also observed for other regions, these trends were not statistically significant. As for the whole brain analysis, no significant correlation was found between the number of voxels defined ROIs, and the lesion load, test score, disability score or age.

Table IV

Signal by region	MS patients	Controls	
	Mean	Mean	p-value
Frontal Left	400	388	0.056
Frontal Right	388	444	0.070
Parietal Left	376	256	0.011
Parietal Right	420	360	0.019
Precuneus region	540	496	0.022
Cerebellum	216	92	0.001

Mean percentages of voxels within ROIs as determined on the group maps, significantly activated in the individual subjects.

DISCUSSION

In this study we used fMRI to study brain activation during performance on the ToL in MS patients and controls. For both controls and MS patients we found activation comparable with previous fMRI[135] and PET studies[9,160,170]. Our sample of MS patients, with mild to moderate disability, performed worse than a healthy control group on the Tower of London task (ToL), but the accompanying brain activity measured with fMRI was certainly maintained in the MS group. Differences between control and MS groups did not reach statistical significance.

Both the MS group and the controls showed the main centres of activation in the frontal lobes (left middle and superior frontal gyrus and right middle frontal gyrus), the parietal lobes (the inferior parietal lobe bilaterally and the right precuneus region) and the cerebellum bilaterally. Although visual inspection of cerebral activity in MS patients and controls suggested differences, showing for the MS group more activation in the cerebellum and right frontal lobe area, the groups did not differ significantly when a direct statistical comparison was performed. In a second, ROI based analysis, brain activation was found to be significantly increased for the MS patients only in the cerebellum. In many cognitive and motor studies cerebellar activity is being reported. Some explain this as being related to repeated activities, but a confounding effect of motor activity could also be an explanation.

The areas activated during performing this test are comparable with those described in the literature. In a previous study using the same test[135], healthy young controls also showed activity in the middle frontal gyrus and adjacent part of the inferior frontal sulcus bilaterally, the precuneus-cuneus region bilaterally, the left supramarginal and angular gyrus and the cerebellum bilaterally. In that study activity was also seen in the lateral occipital gyrus bilaterally, the anterodorsal part of the left cingulate gyrus and the anterior part of the left insula, regions not encountered in the group's mean of the current study. A major difference between this and the previous study is the age and educational level of the healthy controls, which indicates that younger and higher educated

subjects may use additional brain areas for additional strategies.

It should be noted that the MS patients scored significantly worse than controls on the computerized version of the ToL we used in our study. Foong et al.[80] describe a comparison of 42 MS patients with 40, age and education matched, controls in their performance on several 'frontal lobe tasks', including the regular ToL. As in our study, they found impairment in the frontal lobe functions, which could not be explained by an intelligence decline. Some of the test results, especially those of the more difficult tests, correlated with frontal lobe lesion load.

The ToL performance score of our subjects did not correlate with frontal lobe lesion load (or total lesion load). Some studies found a correlation between frontal lobe lesion load and impaired frontal lobe functions[44,80,227,250]. However, impaired frontal lobe functions have also been seen in patients with relatively low frontal lobe lesion loads[44]. An explanation might be that the frontal lobe functions (the executive functions) rely on a wide neural network[30]. Another possible explanation may relate to changes in the normal appearing white matter[71,72].
One of the most intriguing findings in our study is that MS patients, although performing significantly worse than controls, maintain a similar pattern of cortical activation during a planning task. This indicates that reduced performance is not necessarily associated with reduced activation, even though quite a few of our patients had significant structural brain abnormalities and marked disability. This paradox might be explained by subcortical fibre disruption in the frontal circuits subserving planning, even though cortical activity is maintained (and certainly not diminished). Apparently, this adequate amount of cortical activity in the MS patients is not translated into adequate executive function in these mildly to moderately disabled patients. However, the great inter-individual variation in both groups, could have limited the statistical power to detect possible existing differences between the two groups.

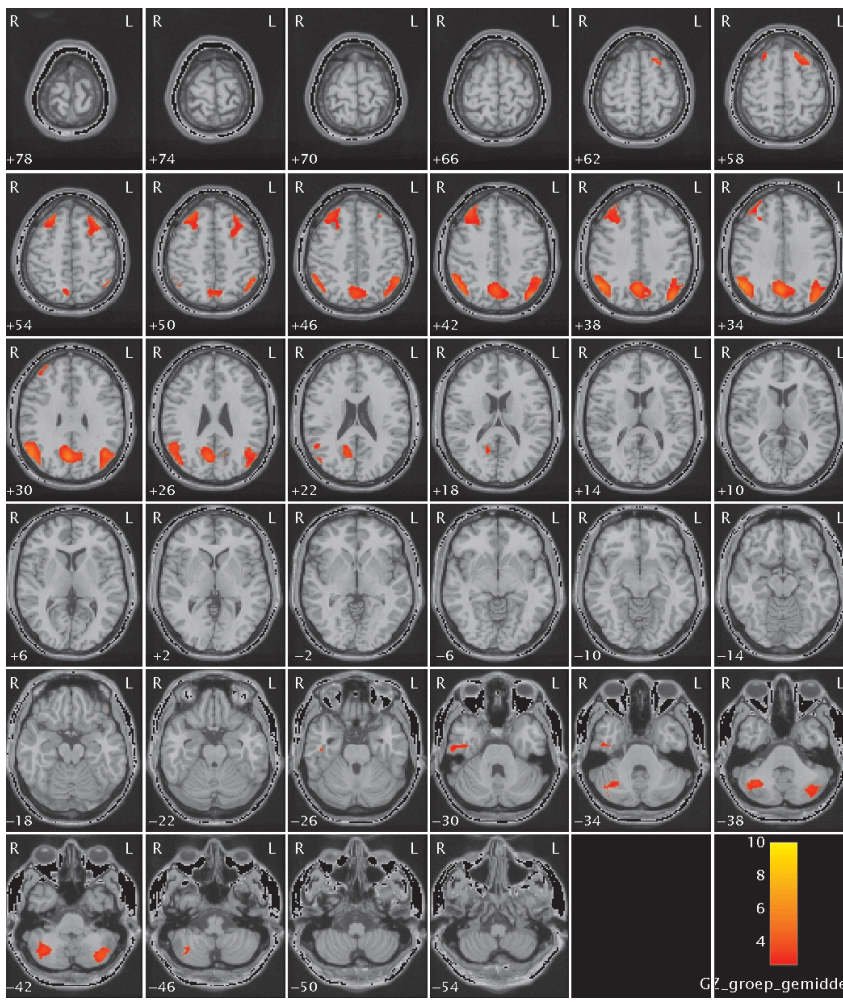
In earlier stages of MS it has previously been found that patients with minimal disability have enhanced cortical activation under certain conditions, and are thus able to functionally compensate for (subcortical) brain damage[24,25,206,218]. Some of these studies even indicate that the amount of brain activation is significantly associated with T2 lesion load, an observation we can not confirm on the basis of our

data. We can only speculate that in our patients with more advanced disease and consequently higher lesion loads these compensatory mechanisms have been exhausted or are counteracted by the fact that tissue damage, once reaching a certain level, limits the possibility for more extended activation.

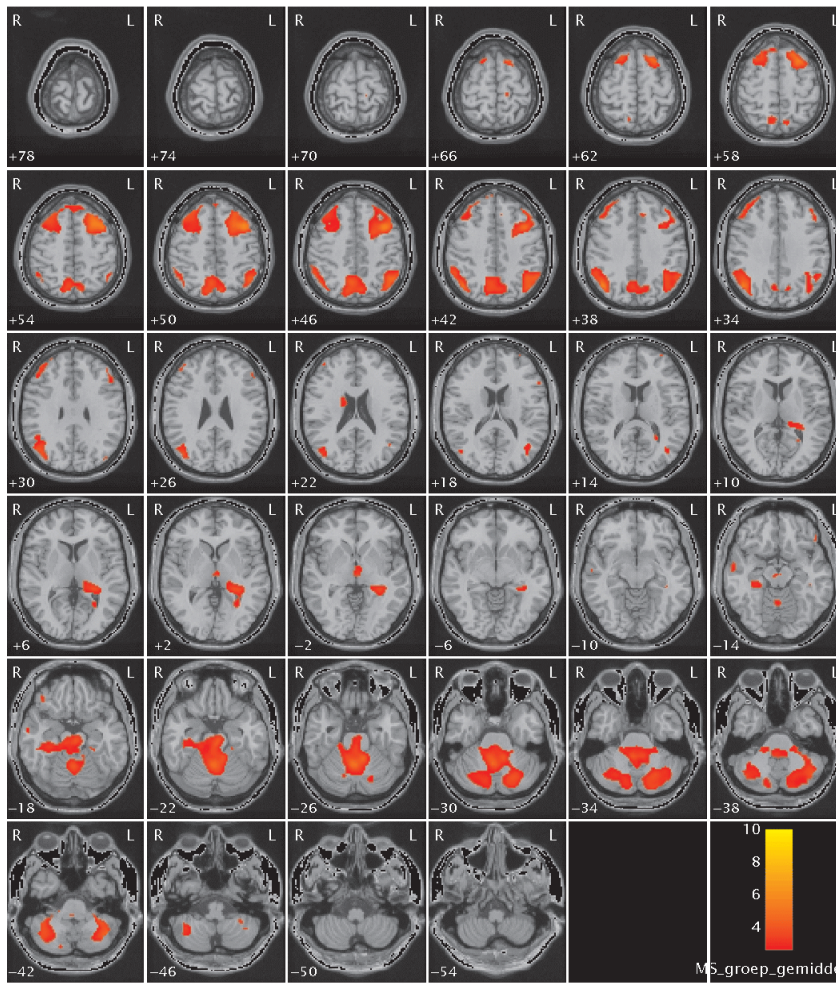
Figure 2

Random effects analysis of the planning versus control stage group map

a) healthy controls



b) MS patients



Transverse slices of the group activation maps using a random effects analysis (p = 0.05). Left side of the images represents left side of the subject (view from above). Note that the areas that are activated, are roughly similar for both groups, but appear slightly more extensive in the MS group. In a direct comparison none of those differences reached significance.

4.2 VISUAL ACTIVATION PATTERNS IN OPTIC NEURITIS PATIENTS

Adapted from: Neurology

Visual activation patterns in patients with optic neuritis: An fMRI pilot study.

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Neurology, 1998 (50), 1896-1899

Abstract

OBJECTIVE
We studied the use of functional MRI (fMRI) with visual stimulation.

METHODS
Studied in nine patients with unilateral optic neuritis. Eight healthy subjects served as controls.

RESULTS
Patients showed reduced activation upon stimulation of the affected eye, on average 33% (range 0 to 156%) of the average monocular activation in the control group. Decreased activation was also seen for the unaffected eye (61% of control values, range 3 to 133%).

CONCLUSION
We conclude that fMRI with visual stimulation is feasible in patients with optic neuritis and deserves future study.

INTRODUCTION

Optic neuritis (ON) is characterized by monocular visual failure with a relatively rapid onset (hours to days). Typically, recovery of the clinical symptoms occurs within days or weeks. However, some abnormalities, like diminished colour vision and reduced contrast perception, can persist for a longer period. In unilateral ON, not only the clinically involved eye but also the other eye usually shows MRI abnormalities[55].

Functional MRI (fMRI) measures changes in MRI signal that occur upon brain activation caused by the changes in the concentration of deoxygenated haemoglobin[169]. We investigated the feasibility of fMRI of visual activation patterns in patients with unilateral ON.

METHODS

Subjects

We examined nine patients with the clinical diagnosis of clinically strictly unilateral ON, without a history of previous visual failure (mean age 33 years, range 23 to 43; 5 men). On the day of scanning, best-corrected visual acuity (distance vision) was determined with the Snellen chart and ranged from 0.17 to 1.0 for the affected eye (1.0 is perfect acuity; average 0.75). The unaffected eye had visual acuity equal to 1.0 in all patients. Onset of visual failure occurred 7 days to 12 years before scanning. Eight patients were diagnosed with relapsing-remitting MS (mean time of diagnosis 3.25 years before scanning, range 9 years before to 6 months after). One patient was examined in two separate sessions, first in the acute phase (acuity = 0.60) and 10 days later after recovery (acuity = 1.0). Eight healthy volunteers, each with visual acuity of 1.0, without ocular refraction anomalies, history of vision loss, or colour blindness, served as controls (mean age 31 years, range 21 to 39; 6 men).

Data acquisition

Imaging was performed with a 1.5-T MR unit. For functional imaging, a gradient echo, echo planar imaging (EPI) sequence (repetition time: 4 seconds; echo time: 64 msec; flip angle: 90 , resolution: 1.56 × 3.13 mm,

interpolated to 1.56 × 1.56 mm) was used. Twelve 5 mm thick slices (interslice gap 1 mm), positioned parallel to the calcarine fissure, were acquired. Structural imaging was performed with either a 3-D gradient echo or a multislice spin echo T1-weighted sequence.

Visual stimulation paradigm

For visual stimulation, the subjects were wearing light-emitting diode goggles that emitted a red homogeneous light flashing at 8 Hz. First, both eyes were stimulated simultaneously (BES) with an on/off paradigm: 12 EPI scans were acquired at rest (darkness, 4 seconds per scan, 48 seconds total), 10 during visual stimulation (40 seconds total), 10 at rest, 10 during stimulation, 10 at rest. Second, each eye was stimulated separately in a random order among subjects: 102 EPI scans with the same on/off periods were acquired. The first two EPI scans were discarded for the analysis.

Table I

Data of activation in the control group (n = 8)

Control no.	ACT% left	ACT% right	ACT% both	ASYM%
1	0.85	0.70	0.92	0.10
2	0.61	1.08	0.51	0.28
3	1.08	1.23	1.38	0.07
4	1.40	1.21	1.01	0.07
5	0.97	1.25	1.15	0.12
6	0.86	1.35	0.85	0.22
7	1.18	0.80	0.95	0.19
8	0.24	1.18	1.22	0.66
average				0.21

Relative activation (ACT%) is calculated by dividing the size of each control's activated volume by the total average in the control group. The last column shows the relative asymmetry between left- and right-eye stimulation (ASYM%).

Data analysis

A 3-D matching procedure was performed to correct for small motion artifact[287] and the first and last image of each scan was discarded. Activation was detected by cross-correlating pixel time curves with a box car function[10] shifted in time over 4 seconds (1 scan) at onset and 8 seconds (2 scans) at offset of stimulus to account for the haemodynamic response delay. Per voxel, $p = 2 \times 10^{-5}$ (assuming Gaussian variance of noise about the box car function[10], and only clusters of at least 4 side-connected voxels were included in the activation maps, thereby increasing statistical significance[81]. Relative activated volumes (ACT%) were determined: with BES, the size of the activated volume in each patient was divided by the average volume activated during BES in the control group. With stimulation of the unaffected eye separately (UES) and the affected eye separately (AES), the size of the activated volume was divided by the total average activation in the control group upon stimulation of the left and right eye separately. Furthermore, in each subject the relative difference between left- and right-eye stimulation (ASYM%) was calculated by (|left - right|)/(left + right).

RESULTS

Analysis of amplitude and timing of signal response of activated voxels did not show differences between patients and controls or between UES and AES.

Stimulation of both eyes together.

The average activated volume in the control group was 15.4 cm^3, ranging from 7.9 to 21.3 cm^3 (table I shows breakdown of relative contribution). The data of one patient (no. 1) were lost because of a computer error. In the total patient group (patients 2 to 9 [first observation], patient 1 omitted), the average ACT% was 68% (range 3 to 150%, table II). Only one patient (no. 6) had ACT% greater than 1.0. Patient 9, who returned for a second examination after 10 days, showed an increase of ACT% from 3% (first examination, acuity = 0.60) to 11% (second examination, acuity = 1).

Recovered patients (patients with acuity 0.80 who also reported recovery subjectively, nos. 1, 2, 5, 6, 7, 9 [second observation])

Table II
Patient data

	Activated volumes								
	Affected		Unaffected		Both				
Patiënt no	Absolute (cm^3)	ACT%	Absolute (cm^3)	ACT%	Absolute (cm^3)	ACT%	ASYM%	Acuity affected eye	Onset time ON
1	0.00	0.00	1.13	0.10	*	*	1.00	1.00	1 mo
2	2.02	0.17	13.21	1.12	13.27	0.86	0.73	0.80	20 mo
3	0.13	0.01	7.21	0.60	3.69	0.24	0.96	0.60	29 mo
4	5.96	0.51	8.01	0.68	11.35	0.74	0.15	0.17	7 mo
5	1.17	0.10	5.58	0.47	7.69	0.50	0.65	1.00	10 y
6	18.37	1.56	15.66	1.33	23.16	1.50	0.08	1.00	11 mo
7	3.21	0.27	5.82	0.49	11.79	0.76	0.29	0.80	12 y
8	~	~	~	~	11.95	0.78	~	0.50	12 mo
9 (1)	0.00	0.00	0.87	0.03	0.45	0.03	1.00	0.60	7 d
9 (2)	0.67	0.06	0.82	0.07	1.66	0.11	0.10	1.00	17 d
Recovered average	4.24	0.36	7.04	0.60	11.51	0.75	0.48	0.93	
Not recovered average	2.03	0.17	5.20	0.44	5.17	0.34	0.70	0.46	
Total average	3.86	0.33	7.12	0.60	10.42	0.68	0.61	0.72	

Absolute and relative sizes of activated volumes are shown for monocular stimulation ([un]affected) and for stimulation of stimulation of both eyes together (both). Relative activated volumes (ACT%) are calculated dividing the size of activation in each patient by the average of the control group (table I). Relative differences between the left and right (ASYM%) are greater than the average in the control group (table I). Recovered patients show more activation for the affected and unaffected eye compared with patients who were not recovered. The last two columns show the visual acuity at the moment of scanning of the affected eye and the time of onset before scanning of optic neurits.

* Data lost because of computer error ~ motion artefact ON = optic neuritis

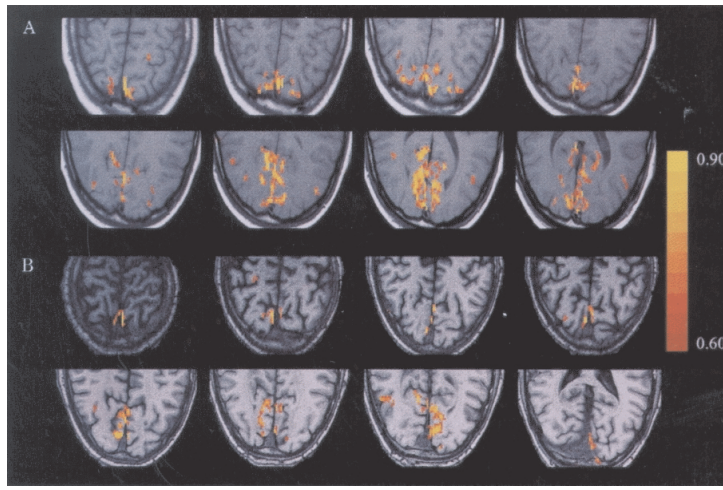
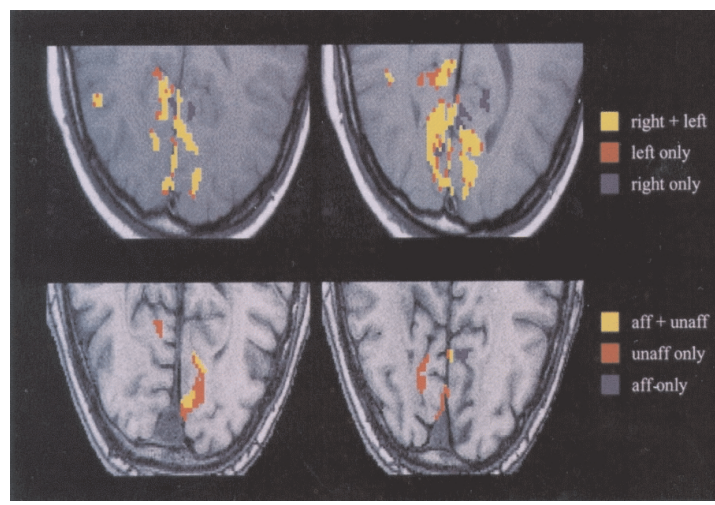


Figure 1

Example of an activation pattern in the occipital regions of 8 of the 12 scanned slices for control subject 5 of table I (two upper rows, A) and patient 5 from table II with an acuity of 1.0 (two bottom rows, B) during stimulation of both eyes together. Activation maps are superimposed on structural images (A: spin echo; B: gradient echo), and the colour bar on the right shows the colour-coded correlation coefficients. The patients shows much smaller activated volumes.

Figure 2



Activated volumes of the control subject (top) and the patient (bottom) in figure 1 in two slices near the calcarine sulcus. Yellow areas are activated with both stimulation of the left and the right eye. Blue areas are only activated with stimulation of the right (control) or affected (patient) eye, whereas the red voxels show significant signal increases only with stimulation of the other eye. The healthy control shows more activation and a smaller difference between left and right than does the patient.

showed more activation on average (ACT% = 75%) than did non-recovered patients (ACT%= 34%), although activation remained reduced compared with controls (100% by definition) (figure 1).

Monocular stimulation.

The average activated volume in the control group was 11.8 cm^3, ranging from 2.9 to 16.4 cm^3 (see table I for breakdown of relative contribution). One patient (no. 8) showed motion artifacts, and the data were not used in the analysis. All controls showed a relative difference in activation between left- and right-eye stimulation (average ASYM% 21%, range 7 to 66%).

With AES in the patient group, the average ACT% was 33% (see table II). Also with UES, a smaller activated volume was seen; ACT% was 60% on average. ASYM% was 61% (range 8 to 100%). Average activation was highest in the recovered group for AES (recovered: ACT% = 36%; not recovered: ACT% = 17%) and also for UES (recovered: ACT% = 60%; not recovered: ACT% = 44%) (see table II). The recovered patient with ACT% > 1.0 in all three paradigms (patient 6) was the only patient showing more activation with AES than with UES. Note that patient 9 showed an increase of activation after recovery, both for AES (ACT% increased from 0 to 6%) and UES (ACT% increased from 3 to 7%). In figure 2 activation patterns of left- and right-eye stimulation are shown for a healthy subject and the patient in figure 1.

DISCUSSION

In unilateral ON patients, stimulation of the affected eye results in a smaller activated volume in comparison with the unaffected eye, even when patients have recovered visual acuity. Furthermore, stimulation of the unaffected eye shows a decreased volume of activation compared with controls. The results show a trend for recovered patients to display more activation than non-recovered patients, both for the affected and the unaffected eye. One recovered patient showed discrepant data, giving more activation than controls and more activation for the affected eye than the unaffected eye.

Although differences in activation between the two eyes are also seen in healthy subjects (probably caused by eye dominance[225], patients showed much larger differences. Disturbed conduction at the level of the optic nerve of the affected eye will result in decreased activation in the visual cortex. The observed reduced activation during UES is in agreement with visual evoked potential findings[84,191]. Apparently, not only the clinically affected eye but also the other eye shows visual disturbances. Possibly this optic nerve is less "unaffected" than presumed. Another explanation might be that neurons responding to input from both eyes show decreased activity when stimulated only by the unaffected eye in case of a history of unilateral ON.

Difficulties remain in drawing conclusions from these results; eight of the nine patients suffered from MS and probably had different lesions. Time constraints precluded extensive conventional imaging, and we therefore could not correct for this confounder. Furthermore, visual acuity was measured in suboptimal circumstances with a Snellen chart; nearby vision, visual field defects, and other determinants were not taken into account. By definition, visual acuity before the ON was unknown, as was ocular dominance[225].

However, the purpose of the pilot was to determine the feasibility of fMRI with visual stimulation in patients with ON. The fact that marked differences were found between affected and unaffected eyes as well as between controls and patients suggests that fMRI studies may be useful to further study ON. We suggest that future studies focus on patients with acute ON, without a diagnosis of MS, and include longitudinal follow-up. Also, more extensive neurophysiological testing (nearby vision, visual field, as well as contrast and colour vision defects), and fat-suppression MRI techniques for visualizing the lesion in the optic nerve, may be useful to better understand fMRI changes in ON.

4.3 CANNABIS fMRI STUDY IN MS

Adapted from: Neuroscience Imaging

Cannabis effects on brain activation in MS patients. A pilot study using fMRI.

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Abstract

OBJECTIVE

Cannabis is widely used by multiple sclerosis (MS) patients to relieve pain and spasticity, although the exact effects of Cannabis on brain functioning are not well known. We performed a pilot study using functional magnetic resonance imaging (fMRI) to study the effects of Cannabis on cognitive and motor functions in MS patients.

METHODS

Seven subjects with progressive MS were scanned in a randomized fashion, after intake of an extract of Cannabis sativa or placebo. The subjects performed an attention and information processing task, a motor task and as a negative control, a visual task. Group analyses included the effects of drug and order of administration. In individual subjects the spatial extent of activation was studied, and a change of 20% considered as being significant.

RESULTS

In most subjects the same regions were activated during both administrations, especially for the visual light flash paradigm. The group analysis showed no significant effect of Cannabis or order of scanning in any of the tasks. On an individual level, especially during the cognitive and motor task, differences in the spatial extent of activation were found: in some subjects the extent of activation increased after Cannabis intake, while in others it decreased.

CONCLUSION

No systematic effects of Cannabis could be established at a group level. In agreement with previous PET studies, our fMRI data suggest that this may be caused by interindividual differences in brain activity changes, indicative of a heterogeneity in pharmacological and clinical effects.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. The clinical manifestations can include almost any neurological symptom, including motor problems and cognitive dysfunction. Surveys suggest that there is widespread use of Cannabis among patients with MS for relief of disturbing symptoms, especially pain and spasticity. Despite the fact that Cannabis is known to alter brain functioning, and is used by many patients, the exact effects of Cannabis on the human brain are not well known. Beneficial effects, mostly on spasticity or tremor, have been described in some small groups or case studies[7,45,153,234]. Those studies have suggested a range of applications for cannabinoids in MS, including the alleviation of muscle spasms, tremor, ataxia and bladder dysfunction. Side effects have also been recognized, especially in intoxicated persons, and those include problems with short-term memory and attention, motor skills and reaction time, and skilled activities (including frontally localized functions).
In a randomized, double-blind, placebo-controlled, two-fold cross-over study of 16 patients[120], it was unable to demonstrate any significant improvement of signs and symptoms by treatment with orally administered cannabinoids. However, several recent and much larger studies, using the same products, show a trend in favour of active treatment on subjective outcome measures of pain and spasticity[268,289].

Several recent PET studies demonstrated significant Cannabis effects on brain functioning in healthy subject[26,147,148,149,166,272]. However, for obvious reasons this invasive and time demanding technique can not be repeated frequently. This is however a necessity to acquire more knowledge about the in vivo effects of Cannabis on cognitive and motor functions. Therefore we performed a feasibility study using functional MRI (fMRI), which is a non-invasive brain imaging technique based on differences of magnetic properties of oxygenated and non-oxygenated haemoglobin. fMRI measurements can be repeated many times without side effects.

In this study we investigated in MS patients brain activity after intake of Cannabis. During fMRI scanning subjects performed three tests: a cognitive task, a motor task

and a visual task. We hypothesized, based on the cannabis effects described above, to find globally different patterns of activation when using cannabinoids in comparison with a placebo, especially in the cognitive task and the motor task. The visual task was merely used as a control condition.

METHODS

Subjects

We studied 7 MS patients (6 M / 1 F), with a mean age of 49.1 years (range 42-56 years). All subjects had a diagnosis of clinically definite MS[192], all more than 10 years ago. All had progressive disease (5 PP, 2 SP); the median EDSS was 6.5 (4.0 - 7.5). All had previously used Cannabis for short periods of time, but all stated not to have used it in the last six months. The only regular used medication by four of the subjects was anti spasm medication.

The subjects underwent two identical fMRI examinations, with a one week interval. One hour before scanning they took, orally, placebo or Cannabis sativa plant-extract (which contained a standardized delta-9-tetra-hydrocannabinol (THC) content (10 mg), 20 to 30% cannabidiol and less than 5% other cannabinoids (Society for Oncological and Immunological Research, Germany))[120,268,289]. The order of intake of study medication was blinded and based on randomization. However, they all could tell afterwards at which time they received the Cannabis capsule. The subjects were selected for adequate hand function and vision in order to allow compliance with study procedures. All subjects were right-handed.

The ethical review board of the Vrije Universiteit Medical Center Amsterdam approved of the study and all subjects gave informed consent.

Data acquisition

Imaging was performed on a 1.5 T MR system with a standard circularly polarized head coil. A whole brain echo planar imaging (EPI) sequence (4 seconds (TR), 64 ms (TE), 1 excitation, flip angle: 90 , matrix size: 64 x 128, interpolated to 128 x 128 mm, field of view: 220 x 220 cm, slice thickness: 4 mm, interslice gap: 1.02 mm, number of slices 23) was used. The stimuli were projected on a screen, viewed by the subject via a mirror placed on top of the head coil in the magnet bore.

fMRI paradigm

During each fMRI session three tests were performed. The first test was an attention and information processing task, an adaptation for fMRI of the Paced Auditory Serial Addition Test (PASAT)[134]. This fMRI test contrasts a 'memory-and-adding' stage to a control stage. During the 'memory-and-adding' stage the subject performs a task in which every digit presented must be added to the preceding one. The auditory cues in the adding stage of the original PASAT test were replaced by sequentially presented visual digits in the center of the screen, and the subjects were instructed to mentally process these digits but to refrain from vocalizing the answers. During the control stage, subjects had to fixate on a cross located in the center of the screen and were instructed to pay attention to the moment a digit was presented again, which was the moment the adding stage resumed. The adding stages were administered at four different speeds, the control stage at one speed. Each stage lasted 84 seconds (21 scans). The order of administration was: Add (3.8 sec per digit) - Add (3.2 sec per digit) - Cont (2.6 sec per cross presentation) - Add (2.6) - Add (1.9) - Cont (2.6) and this whole sequence was repeated one time.

The motor task was second in line. Via an instruction on the screen, subjects were asked to either perform sequential finger opposition with both hands simultaneously, or to lie quietly in the scanner. The active part was self-paced to ensure that subjects were able to maintain the movements during a block of 40 seconds (10 scans). The movement stage was performed 5 times, with 4 stages of rest in between (also lasting 40 seconds).

The third and final task was a simple visual stimulation test in which the subjects had their eyes open, wearing light emitting diode (LED) goggles (Grass Instruments, Quincy, Mariland). The goggles produced light flashes at a frequency of 8 Hz stimulating the full field of view of both eyes. Blocks of visual stimulation lasting 40 seconds (10 scans), were alternated with equally long periods of total darkness (4 times each), beginning with visual stimulation.

Data analysis

The fMRI data were analysed with SPM99b [Available via www.fil.ion.ucl.ac.uk/spm/spm99.html]. The MRI EPI data were realigned and normalized (and resliced to 3x3x3 mm) to the standard SPM EPI template coordinate space approximating the Talairach and Tournoux space [252]. Next, the data were smoothed using a Gaussian filter set at 6 mm

full width at half-maximum (FWHM). The data of each subject were modelled using a box-car function, representing the different test stages, and convolved with the standard SPM haemodynamic response function[85].
Brain activation during Cannabis was compared to placebo for each test a) using a fixed effects analysis ($p < 0.05$, corrected for multiple comparisons) and b) using individual contrast images within the framework of a random effects analysis with a paired t-test ($p < 0.05$, corrected for multiple comparisons).
Secondly, activation maps were calculated applying a p-value of 0.005 per voxel , with a 3D-cluster restriction of at least five adjacent active voxels. The number of activated voxels during the Cannabis and placebo session were compared, for each task, using a paired sample t-test ($p < 0.05$).
Thirdly, individuals were analysed: activation change between Cannabis and placebo on an individual level was defined significant when there was more than 20% difference in the number of activated voxels between sessions.

RESULTS

A summary of activation volumes for all three tests is provided in table I.
The *information processing task* was successfully administered and scanned twice in six subjects; the seventh subject was unable to perform the test. In those six subjects, the first and second session showed activation in the frontal and parietal lobe, as well as the cerebellum.
No significant differences were found between Cannabis and placebo in any of the statistical tests described in the method section. Individual analysis learned that there were less activated voxels in three subjects and more activated voxels in one subject during Cannabis as compared to the placebo session. As shown in table I and figure 1, in some subjects individual changes are very marked, sometimes exceeding 100% of baseline activation.

The *motor task* was scanned without problems in six subjects for both sessions. In one subject the data could not be used because of movement of the head during the motor stages. This task showed reasonably consistent sensomotor cortex and cerebellar activation in four subjects during both sessions,

Table I

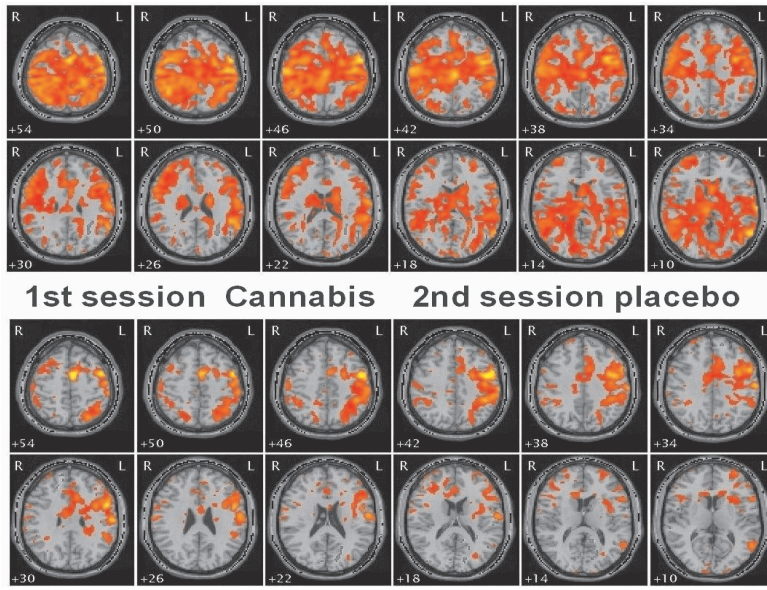
Activated volumes (number of voxels) during cognitive, motor and visual stimuli.

	Characteristics			
nr	type	EDSS	age	sex
1	PP	6.5	50	F
2	SP	7	42	M
3	PP	6	53	M
4	PP	7.5	52	M
5	PP	4	46	M
6	PP	4	45	M
7	SP	7	56	M

The patients characteristics describe the MS type, the EDSS (expanded disability status scale as measure of disease severity), the age and the gender of the subjects. The columns cognitive, motor and visual describe the activated volumes during those tests. In the column comp the session with the highest volume of activity is indicated. Whereas Plac or Cann implicate that the placebo or the Cannabis session showed more than 20% increase in activated volume compared to the other session, eq indicates the absence of a 20% difference (n.a. is not available). The * indicates that changes in activation on the visual task were due to changes in the areas outside the occipital cortex.

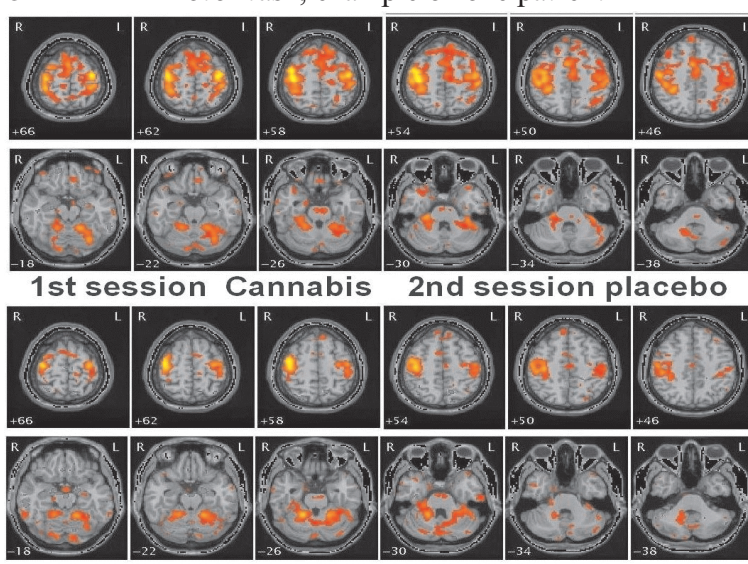
	Cognitive			Motor			Visual		
nr	Cann.	placebo	comp	Cann.	placebo	comp	Cann.	placebo	comp
1	5352	6281	eq	7061	4457	Cann	1626	2345	eq *
2	4244	4094	eq	n.a.	n.a.	n.a.	15408	3888	eq *
3	3916	12202	Plac	779	1992	Plac	1947	1774	eq
4	3085	4661	Plac	10104	4651	Cann	6830	6950	eq
5	28130	7156	Cann	9842	9304	eq	5714	9907	eq *
6	10423	15578	Plac	5935	10724	Plac	5892	6003	eq
7	n.a.	n.a.	n.a.	22058	11297	Cann	4404	4977	eq

Figure 1 Information processing task; example of one patient



Results of the information processing task of one subject (nr 5): Cannabis (upper) and placebo (lower) session. Red and orange are the voxels significantly activated.

Figure 2 Motor task; example of one patient



Results of the motor task of one subject (nr 1): Cannabis (upper) and placebo (lower) session. Red and orange are the voxels significantly activated.

while one subject had only small areas of significant activation in both sessions. The extent of the activation was variable across sessions and subjects (example shown in figure 2). None of the group comparisons revealed detectable difference between Cannabis and placebo. Individual analysis showed more activated voxels during the Cannabis session in three subjects, while in two subjects the placebo session showed more activated voxels.

The *visual task* showed consistent activation of the visual cortex in six subjects during both sessions. The seventh subject showed activity during only one session. No significant group differences were found. There were no subjects with more than 20% difference in the occipital regions between sessions. Besides activation in the visual cortex, some subjects showed also activation in the other lobes, especially during the Cannabis session.

Most subjects could not report major behavioural or cognitive changes during both the test sessions. Only one subject had experienced some hallucinations after intake of the test medication (appeared to be Cannabis).

DISCUSSION

There presently is considerable interest in the therapeutic use of cannabinoids in MS. Recently, several studies have been performed that address the clinical effects and mechanisms of action of cannabinoids in MS [8,45,119,120,153,234]. Although the complex biology of the cannabinoid system is becoming clearer, the understanding of how these compounds exert their action in MS is still in its infancy. Building on previous PET studies in healthy subjects, we here present the first study investigating Cannabis effects on brain functions in MS subjects with the use of fMRI, a non-invasive neuroimaging technique with the possibility of repetition as great advantage.

The three fMRI tests used, evaluating cognitive, motor and visual function respectively, showed activated areas at expected locations in most subjects. In individual subjects differences when comparing activation after intake of Cannabis and placebo were striking, sometimes exceeding 100%. However, not one of the three tests, showed significant group differences when comparing Cannabis with placebo intake.

Mainly because the Cannabis effects were not uniform across all the subjects. The observation that individuals show different responses on Cannabis is in line with other observations in clinical studies[7,45,120,121,153,234] and PET studies[26,147,148,149,166,272]. We assume that this individual variability is the main explanation for the absence of a global Cannabis effect when compared to placebo. This is also a possible explanations for the differences between the results of clinical studies and the benefits most subjects experience.

Relevant factors underlying this individual variability are the uptake of Cannabis and its metabolites, especially after oral intake, the availability of THC, the way in which Cannabis and its metabolites work and the density of the different types of receptors. The availability of THC, one of the major effective compounds of Cannabis, has a great inter-individual variability[289]. The absorption of THC in the gut is reasonably good, but the process is unpredictable in time. The delivery, therefore, is widely variable[103]. Pharmacological studies report a biphasic dose-dependent effect of THC. Low dosages mainly inhibit the CB1 receptors, while high dosages have stimulating effects[7,120]. Besides THC, the Cannabis extract used, contains other cannabinoids which roles also are not completely understood.

Cannabis can induce changes in blood flow through a variety of mechanisms. Besides an altered brain functional activity (diffuse or more local in origin with secondary involvement of other brain areas), this could include relaxation of vascular smooth muscle and alterations of the sympathic/ parasympathic equilibrium. In combination with differences in spread of Cannabis receptors, this could explain the difference in reaction on Cannabis intake. The effects of the MS disease process on receptor density are unknown.

As mentioned, PET studies focussing on glucose metabolism and cerebral blood flow, also showed that Cannabis effects are not uniform across healthy subjects. Mathew et al.[148], using ^{15}O-water PET as a tracer to measure CBF, demonstrated an increase in activity of the brain, especially in the frontal cortex bilaterally, the right insula, and cingulate gyrus, the basal ganglia and thalamus, after intravenous THC. For the group receiving a high dose of THC (0.25 mg/min iv) this was the case after 30 minutes, and for the low dose group (0.15 mg/min iv) after 60 minutes. In neither group the occipital cortex showed an increase of activation (not at 30 minutes, nor at 60 minutes). These authors

also found considerable variation in the activation across subjects. The high dose group showed differences in activated areas after 30 minutes compared to 60 minutes. Another study by Mathew et al.[149] globally described the same results, again with considerable individual variation.

Using ^{18}F-FDG to measure glucose metabolism, Volkow and colleagues [271] showed an increase of metabolic activity in the cerebellum after intravenous THC injection, while total brain global changes in cerebral glucose metabolism were variable: three subjects showed an increase, three a decrease, and two showed no changes following THC administration. In a comparable experiment of PET glucose metabolism, these authors[272] showed a variable Cannabis effect comparing sessions before and 24 hours after intravenous THC administration. In 7 subjects an increase of more than 10% was found, in 5 subjects a decrease of more than 10% and in 6 subjects a smaller change (less than 10% difference) was found. The results described above were all performed with the subjects in a resting state, without them completing a task.

O'Leary et al.[166] performed a PET CBF study with a dichotic listening task, with focussed attention instructions, before and after smoking a Cannabis cigarette. In three subjects the test showed an increase of the mean whole brain blood flow, while in two subjects a decrease was noticed. As a group, the five subjects showed an increase in activation in the superior temporal gyri bilaterally, as well as in ventral en mesial parts of the frontal lobe, the insula, temporal lobe and the cerebellum, and a decrease in the motor cortex, the left precuneus, the right occipital lobe and the vermis of the cerebellum. Unfortunately, the manuscript does not provide information on how consistent these findings were between individual subjects.

In our data we noted that the Cannabis effects depend upon the sort of test performed. In a questionnaire by Consroe et al.[45] it was also noted that subjects report a high degree of variation over the total range of symptoms asked for when using Cannabis. Our "control test", a simple visual stimulation task showed far less changes in activated voxels, showing that not all functions changed in the same degree during Cannabis use.

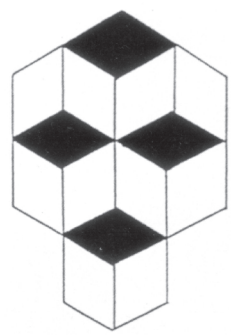
Our study was limited by the small sample size and suggests that further studies should considerably increase the number of subjects studied. Another limitation is the use of a fixed threshold to determine the change on an

individual level and we suggest to include at least one more session to determine interindividual variability on an empirical basis, which can be easier performed with fMRI than with PET. Finally, other Cannabis preparations, dosing regimes or pharmacological assessments may be advantageous to control for interindividual variability. A further missing factor in our study is the THC level in blood. This is an important factor when searching for the exact effects of cannabinoids. However, in this feasibility study the main goal was to show difference in activation after Cannabis use.

In conclusion, our fMRI pilot study showed individual differences after Cannabis or placebo intake. The direction and magnitude of the difference depends on both the subject and the type of stimulus. This is in agreement with other data, also describing an inhomogeneous effect of Cannabis on brain functioning. Therefore significant systematic effects could less likely be found when comparing Cannabis and placebo at a group level.

CHAPTER 5

DISCUSSION



5.1 DISCUSSION

For a good treatment of patients, understanding the cause of the disease is needed. To help patients with their symptoms many aspects of the disease have to be known. Multiple sclerosis (MS), being a diffuse central nervous system (white matter) disease, has, besides motor and autonomic dysfunctions, cognitive impairment as one of the most important problems. Cognitive functions were, although recognized a very long time ago, underestimated for a considerable period of time. The last two decades, this major problem for MS patients, received more attention. More knowledge about the kind of cognitive impairment in MS has been collected since, and MRI has been used extensively to study cognitive impairment in MS.

At the time the studies described in this thesis started, functional MRI, as a relatively easy to use functional imaging technique to investigate brain functions in humans, presented itself. This technique was used in studies on (cognitive) functioning in MS patients. However, to use this technique in the setting of a new patient group, some preliminary work had to be done. First it had to be shown that the technique was also feasible in a MS patient group and specific tests for MS patients had to be designed. This thesis contains some of this preliminary work and the subsequent studies of functional deficits in MS patients.

It has been shown that fMRI can be used in MS studies, but that much more appreciation is necessary for the tests and circumstances, before larger groups can be successfully investigated. In the future this technique can be used as an objective measurement for cognitive functioning, for example in medication studies. Probably it can give more insight in pathophysiological processes of cognitive impairment.

The main research goal underlying this thesis was to describe impairment, especially cognitive impairment, in MS patients, in quantitative terms, with structural and functional techniques.

COGNITIVE IMPAIRMENT IN OUR MS SAMPLES

The prevalence of cognitive impairment in our study samples of MS patients was considerable. However, since data collection did not have the goal of an epidemiologic study, they are not representative of the prevalence in a general MS population.

As is known from literature, different cognitive domains were found to be impaired in our patients. The ANT data showed that attentional domains are impaired. Deficits in various attentional domains, i.e. divided, focussed and sustained attention were found in the MS patients as was a slower response speed compared to controls, even for simple tasks. When higher cognitive demands were imposed in the more complex tasks, differences in speed between controls and MS patients increased dramatically. MS patients were slower in processing visually presented information. Deficits in the peripheral processing stages (visuo-spatial task and response organization task) were less obvious. In addition, MS patients were more susceptible to distraction than controls: speed of performance deteriorated disproportionally in the presence of distracters (memory search task) and irrelevant targets (focussed attention task); both results reflecting a focussed attention deficit. In the attentional flexibility task (divided attention) impairment was found also. High fluctuations in the performance level (differences in tempo during the sustained attention task) were found in MS patients. However, the MS patients were in general not less accurate than controls. As was shown earlier, this study also found that when time is permitted, MS patients can perform (almost) equally well as healthy subjects on most cognitive tasks[62,110].

Also differences in task performance across MS subtypes were found. The differences in task performance were more pronounced in SP and PP patients than in RR patients groups. Attentional flexibility, response organization, and visuo-motor coordination seem to be unaffected in the RR patients investigated in this study.

COGNITIVE IMPAIRMENT AND MR PARAMETERS

Studies investigating the relation between cognitive impairment and MR parameters have shown a reasonable good correlation, in general better than the correlation between clinical parameters and the MR parameters. Cognitive impairment is, in terms of the tests used, a much more diffuse cerebral process than the clinical parameters accounted for in the EDSS, which are for a great deal driven by spinal cord involvement. As a consequence better correlations were found, especially those representing atrophy of the brain and to a lesser degree also for lesion load parameters.

The cognitive test used, the type of MS and the sort of MR parameter for scoring lesions are the major factors contributing to correlation. In three studies described in this thesis a further refinement in correlations was searched for. In the Magnims A.1.2 study (paragraph 2.2, "Neuro-psychological impairment in multiple sclerosis patients: the role of (juxta)cortical lesion on FLAIR") the goal was to evaluate whether cognitive impairment was predicted by (juxta)cortical lesions as depicted by the FLAIR MR sequence. One of the goals in the PsyLiq study (paragraph 2.3, "Brain atrophy and lesion load as explaining parameters for cognitive impairment in multiple sclerosis") was to the see whether MR parameters per region better predicted cognitive impairment. The ANT task was used in two studies (paragraph 2.4, "Information processing characteristics in subtypes of multiple sclerosis" and paragraph 2.5 "Cognitive slowing in MS is strongly associated with brain volume reduction") to describe more specific aspects of cognitive impairment, mainly attention deficits, in MS patients and to correlate those results with MR parameters concerning lesion load and relative brain volume.

The overall number of (juxta)cortical lesions (as shown using a FLAIR sequence) showed a good correlation with a cognitive impairment index. Also, it was shown that this was a better predictor of cognitive impairment than total number of lesions seen on T2 sequences (for which no significant correlation was found). Other studies also found a better correlation between cognitive impairment and cortical or U-fibre involvement[156].

The regional lesions load analysis used in our PsyLiq study showed a correlation with the performance score (of the test using that cognitive function) for certain

regions (supposed to subserve a selected cognitive function selected on basis of neuropsychological literature). However, the study did not find very strong associations, probably because the size of the selected region (too big), the character of MS as a diffuse pathology disease and the character of the (in MS for screening purposes widely used) cognitive tasks used. Relative brain volume, as a measure of brain atrophy, showed better correlations, underlining the diffuse nature of histopathology in MS. However, that the results are not only dependent from diffuse pathological processes, was shown by the absence of significant correlations with the occipital region (as hypothesized).

The ANT task results, also showed correlations with the MR parameters, again better for relative brain volume than for T2 lesion load. This may come as no surprise, since the cognitive domains tested by the ANT are likely widely distributed, rather than localized ones. The cognitive slowing is a general process.

INTERPRETATION OF COGNITIVE IMPAIRMENT MR STUDIES

Although the studies from more recent years showed better correlations between MR parameters and cognitive functioning parameters, both by new MRI techniques and more specific cognitive tasks, the correlations remain relatively low. Many aspects of the role of different lesion types have to be unravelled yet.

Cognitive functions are more diffuse processes, rather using networks across the brain than one single region. In further research more specific tests should be used to evaluate correlations between number of (juxta)cortical lesions in a certain area and cognitive dysfunction in MS patients. Functional MRI can play a role in this research field, because it can locate brain areas active during given task. The lesion load and other MR parameters in those areas can be used for correlations with test results of the specific cognitive task.

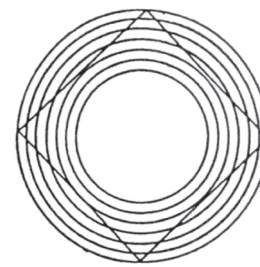
The cognitive tasks used in the current MS research are testing wide spread cognitive functions. This is caused by the fact that most cognitive tasks are selected for MS cognitive impairment screening. The Brief Repeatable Battery is a good instrument in discriminating MS patients from healthy subjects. The tests in this battery are selected for that purpose, not to investigate all cognitive domains equally well or focus on a specific cognitive domain. That more or less the whole brain is involved in those tests is partly represented by the presence of strong correlations with measures of atrophy.

Selecting the right cognitive function to study is important. Unpaced, unlimited speed tasks are far less sensitive in picking up cognitive functional decline in MS. In daily living, paced strategies are important and under too much time pressure, the MS patient's performance declines. Cognitive deficits in MS are not solely based on slowing, as this would not explain (e.g.) the frequent failures on measures of free recall from long-term memory in this group[255,290]. The purpose of the study must therefore determine the sort of task chosen.

Also difficult in investigating the influence of lesions in cognitive impairment in MS patients is the type of lesions that can be made visible with MRI. Besides T2 visible lesions and brain atrophy, there exists MS pathology involves the normal appearing white matter (NAWM), but also the gray matter,

and is characterised by resolving lesions (due to local healing processes) and functional resolution of lesions (by brain adaptative processes). Other MR techniques have to be used to evaluate those sorts of changes. Some pathological processes may be difficult to visualize with MR, play also a role. For example with the FLAIR technique, an improved detection of cortical lesions was possible, leading to better correlations with cognitive performance scores.

Finally the type of MS is important, firstly because progressive patients have in general a longer disease duration, but secondly because the MS types have distinctive characteristics in terms of cognitive impairment; for example PP type patients have a distinct cognitive impairment profile (for example [17,58,101,290]).



fMRI TEST DEVELOPMENT

fMRI as a tool in studying brain function has been introduced more than ten years ago. Different neurologic functions, like motor functioning, visual functions and different sorts of cognitive functions, have been evaluated using fMRI. Initially no (suitable) tests were available to test cognitive functions, let alone tests that specifically focus on those areas mostly impaired in MS patients. To study MS patients cognitive tasks for use with fMRI had to be developed first.

Therefore we adapted a well known cognitive task that especially needs those cognitive areas impaired in many MS patients, the Tower of London task[238]. A planning task, such as the Tower of London, has proven to be sensitive to prefrontal lesions[171,210,238]. Our adaptation of this task for fMRI purposes showed activation during the planning stages in the dorsolateral prefrontal cortex, the anterior part of the cingulate cortex, the cuneus and precuneus, the supramarginal and angular gyrus in the parietal lobe and the frontal opercular area

of the insula. Areas also found to be active during the task by previous PET studies[9,171]. The activated areas in those studies and our study are quite comparable, although small differences in areas activated were seen across studies; a pointer to the influence of variables like subjects variables and small test differences on cognitive functioning. For example some studies showed, more than others, activity in areas probably not activated by the planning process itself, but by the motor and visual processes needed to perform a cognitive task like this. Differences in this respect have to be mainly sought in the "rest" (control) condition of the test.

Before the use of fMRI, a performance score was the only outcome measure that was available. With the advent of fMRI the size and location of activated areas are the major outcome parameters. However, a performance score is always welcome to interpret the results. A disadvantage of outcome scores can be the influence on the task results in terms of activated cognitive areas, because the production of the performance score can be also a cognitive process. Those advantages and disadvantages have to be weighted against each other.
In our Tower of London task, we found it of major importance, also because of the different levels of difficulty that can be applied. The test score is thereby of assistance in determining whether the subject has performed the test well.

The second task we developed, was an adaptation of the PASAT. This task has often been used in MS patients and is part of one of the major scoring systems in MS. We adapted this test, that assesses attention, information processing, visual memory, working memory and primary calculating abilities for fMRI. In this adaptation we choose not to use a performance score, because this interferes to much with the test in an fMRI setting in which certain output channels, like speech, are much less easier to use than outside the MR (because of movement artefacts). Another problem in the fMRI block paradigm setting, is the need for a "resting" (control) stage; especially problematic in an attention task. To overcome this problem as much as possible we used longer block durations. In the light of the plausibility of the activated areas found, we succeeded in a suitable adaptation. The brain activity found was located bilaterally in the superior and inferior parietal lobe, bilaterally in the superior frontal gyrus, in the left medial frontal gyrus, left inferior frontal gyrus and adjacent

part of the insula, the cingulate gyrus (anterior part), and several cerebellar areas. Areas that are supposed to be active during such a task, and comparable with other studies.

A specific aspect of this attention task, adding the last digit to the preceding one for every number seen, draws heavily on executive control, because each addition has to be suppressed and working memory content has to be continuously updated to produce the correct answers. Brain networks associated with executive control include the anterior cingulate cortex and supplementary motor area, the orbitofrontal cortex, dorsolateral prefrontal cortex, parts of the basal ganglia and the thalamus[23,67,178,193]. Visual information processing has been found to activate the precentral gyrus of the frontal lobe, parietal lobe areas and part of the temporal lobes[46,47,189]. Sustained attention, also needed in this task, is subserved by right frontal-parietal areas (right parietal cortex (BA7), right dorsolateral and middle frontal lobe and anterior cingulate gyrus) and the locus coeruleus[48,49,102,137,174]. Mathematical functions are supposed to be subserved by the left parietal lobe.

To investigate changes in brain activation patterns as a result of increased task demands, i.e. when the information processing system is put under more pressure, we have applied a parametric design in which two different speeds of digit (stimulus) presentation were used. Comparing the two speed stages, activation in the right inferior frontal gyrus, the medial frontal gyrus (BA6, BA10) bilaterally, the right cingulate gyrus (BA24), the left superior parietal lobe (BA7), the right cuneus/ precuneus region, the left pulvinar, the right caudate nucleus and the cerebellum bilaterally was seen. However, the individual variation of the speed contrast was considerable. This might indicate that the processing speed is important, and that the optimal processing speed is not the same for all individuals. This again is an indication that fMRI studies have to take many parameters into account.

fMRI TEST APPLICATIONS IN PATIENTS

The main problem evaluating disease pathology with clinical fMRI studies, is the possibility that different levels of energy needed for task performance is the main explaining factor for differences in activated areas. The first clinical MS fMRI studies are mainly descriptive in nature. The number of studied patients is in almost all studies (so far) small. The presented studies showed globally the same areas as in healthy controls are activated in MS patients, but that the volume of active tissue is different and sometimes additional areas are (more) active. Most of the times in patients the extent of the activation is larger, probably because that brain area has to work harder, i.e. recruit more neurons, to compensate for the pathologic condition. This is also seen in motor function paradigms[218]. This idea is supported by the fact that in more impaired patients (i.e. higher lesion loads), who subsequently need more stamina or 'energy' to perform the task, larger activated areas are seen. Some studies have shown also that brain areas not activated in healthy subjects become active (above a certain threshold), another kind of adaptive process. This also is seen especially in more impaired patients, until this compensating mechanism also fails because of the proceeding pathological process.

Most studies using fMRI in MS patients have evaluated motor functioning. Mainly because those fMRI studies can be performed with a relatively simple paradigm, like the movement of one or more fingers. In more complex tasks the activity is also situated in some associated motor areas, which are less active during simple movement tasks. A simple task in healthy controls can be a complex task for patients, or the patient can actually not perform the task. In healthy controls, performing a simple motor task, fMRI showed activation in the contralateral and to a lesser extent ipsilateral primary sensorimotor and premotor cortices in the frontal lobe, the supplementary motor cortex area (SMA), the insula and cerebellum bilateral[70,71,73,123,136,172,197,206,208]. Those activation patterns are reasonably reproducible in subjects over time.

In motor studies on MS patients, performing different paradigms with more or less selected MS patient groups, roughly the same brain areas as in healthy subjects become activated, when a patient performs the movement well[40,70,71,73,136,145,172,173,206,207,208,214,215,

[216,218,221,222]. Mainly depending on the functional state of the limb investigated (and difficulty of the task), the extensiveness of the activated areas differs considerably. When hand motor impairment was complete (paralysis), fMRI showed no activity in the normal brain areas[40]. But a greater activated area was also observed in MS patients that had no paresis, nor have had functional impairment, globally for all MS types. It was seen in patients who are in the progressive stages of the disease, both in secondary progressive MS patients[136,206,217] as well as in primary progressive MS patients[71,218], and also in relapsing remitting MS patients [70,136,206,207,215,221] and even in patients with a clinically isolated syndrome suggestive for MS[74,213,214,219,220].

The lateralisation index, the ratio of activated volume on one side compared to the total activated area, shows less lateralisation in MS patients than in healthy subjects, mainly because of excessive ipsilateral activated motor cortex[136,206].

When a partial motor impairment existed, fMRI showed (in comparison to healthy controls) a greater activated volume. The activation was situated in the primary motor cortex bilaterally, the supplementary motor area bilaterally and some areas of the associate cortex (cingulate motor cortex) and along the fissura Sylvii, corresponding to the secondary somatosensory motor cortex (SII)[40,69,136,172,173,206,207,208].

Besides motor paradigms for fMRI experiments in studies with MS patients, visual paradigms have been used also, especially in optic neuritis patients. Light flashes are a relatively easily to perform paradigm, with only light intensity, flash rate and the visual field stimulated as factors in the task design. In studies on healthy controls, the normal pattern of activation is located in the occipital lobes[154,226,229,257,277]. When the light illuminates just one visual field, the contralateral primary and secondary visual cortical fields, the so called visual (or striate) cortex is activated. When one or both eyes are stimulated, both occipital lobes are activated. Small differences are seen comparing the dominant eye, with the non-dominant eye[225].

In unilateral optic neuritis patients, stimulation of the affected eye resulted in a smaller activated volume in comparison with the unaffected eye, even when patients had recovered visual acuity. Furthermore, stimulation of the unaffected eye shows a decreased volume of activation compared with controls. The results showed a trend for recovered patients to display more activation than non-recovered patients, both for the affected and the unaffected eye.

One recovered patient showed discrepant data, giving more activation than controls and more activation for the affected eye than the unaffected eye. The reason for this is unknown, but can be the result of adaptational mechanisms. Although differences in activation between the two eyes are also seen in healthy subjects (probably caused by eye dominance), patients showed much larger differences. Longitudinal studies and more extensive neurophysiologic testing (nearby vision, visual field, as well as contrast and colour vision defects) have been performed by others[87,154,155,226,229,257,277]. In general the patients showed reduced activation upon stimulation of the affected eye. In a study of our research group, an average of 33% of the activated area of the control group was seen[226]. Decreased activation, although less pronounced, was also seen at stimulation of the clinically unaffected eye (in that particular study 61% of the activated area of the control group[226]). Recovered patients, i.e. visual acuity > 0.8, showed on average a greater activation area at baseline compared to non recovered patients, but still smaller than in the healthy controls. One patient, first scanned in the acute phase, and again scanned after 10 days, showed an increase in activation from 3% to 11% of the activated area of the control group (with an increase in visual acuity from 0.6 to 1.0 at the same time). Although those results can be interpreted as a correlation between visual acuity and size of the active brain area, the 11% score at time of a visual acuity of 1.0 shows this is an oversimplification.

Cognitive functions are more difficult to study than simple motor tasks or visual paradigms, mainly because a cognitive function is more complex in nature (it requires for example input and output processes). Importantly not only the active stage of the task is of great influence for the fMRI results, but also the "rest" (control condition) activity. Those facts cause that far less is known about the situation in healthy subjects, and thereby it is harder to interpret the differences in patients, when not exactly the same task is used. In this stage of brain research, a study paradigm is only by approximation described in terms of cognitive processes needed, and normal active brain areas are not as steady over all studies as for the more simple motor and visual paradigms.

As planned, the for fMRI adapted Tower of London task was used in a group of MS patients. Our sample of MS patients had mild to moderate cognitive impairment.

They performed worse (lower outcome score) than a healthy control group, but the accompanying brain activity measured with fMRI was maintained. As expected, the main centres of activation were located in the frontal lobes (left middle and superior frontal gyrus and right middle frontal gyrus), the parietal lobes (the inferior parietal lobe bilaterally and the right precuneus region) and the cerebellum bilaterally. No statistical significant differences in activation between control and MS groups were observed. Age and educational level of the healthy subjects were confounding factors between groups. The small differences seen between the activation areas in both groups indicate that younger and higher educated subjects may use additional brain areas for additional strategies.
Studies with a simple motor paradigm have shown that subjects with brain pathology probably use additional brain areas to compensate for their impairment, so that functional impairment is not becoming evident. This occurs as long as the healthy brain capacity is sufficient for this adaptation. In cognitive studies this seems to be more difficult to observe[34]. In our patients with more advanced disease these compensatory mechanisms might have been exhausted or are counteracted by the fact that tissue damage, once reaching a certain level, limits the possibility for more extended activation.
The brain areas used do not guarantee a good task performance, because although the MS patients showed the same areas active, the performance score was significantly worse than controls. The scores of the task did not correlate with lesion loads in the frontal region, nor with the total lesion load. This is in concordance with the results seen in the structural imaging studies, in which most of the times none or only low correlations between regional lesion load and task performance of many tasks were seen. Small differences in essential network pathways will be critical in the performance of the task.

We performed a small feasability study of Cannabis intake effects in MS patients. As a spin-off from a Cannabis trial in MS patients, a few patients underwent certain fMRI tasks. The three fMRI tasks we used, evaluating cognitive, motor and visual function respectively, showed activated areas at expected locations in most subjects. In individual subjects, differences when comparing activation after intake of Cannabis and placebo were striking, sometimes exceeding 100%. However, not one of the three tests, showed significant

group differences when comparing Cannabis with placebo intake, probably due to the small sample size and because the Cannabis effects were not uniform across all the subjects. The inter-individual variation is also a possible explanations for the discrepancy between the results of clinical studies and the benefits most subjects experience. The visual stimulation task showed, as expected, less variation in size of the activated area after use of Cannabis compared to placebo, than the cognitive task.

The main conclusion after this study is that, especially with an complex pharmacological biology agent like Cannabis, larger study groups, more uniform MS patients and more physiological identical subjects are necessary, besides registering more parameters. After that, the advantage of fMRI, the numerous times it can be repeated without danger, can be more fully utilized.

AMBIGUOUS INTERPRETATION OF THE FMRI STUDIES

The exact nature of the "active" brain tissue seen in fMRI experiments is not fully understood. Differences are believed to be caused by more oxygen consumption (with regard to the paradox that the venous system behind active brain tissue has a higher oxygen percentage because of overcompensation of the blood flow; questions remain if this is the case for all brain areas and how localised the process is) and therefore represents more neuronal activity. But this neuronal activity can be excitatory or inhibitory. If it is excitatory the question can be raised if it is useful activity. The assumption that more activity means better performing of an area might be an over-simplification. Also, it can be questioned if in MS patients, with lesions around the venes[254], the normal brain regulatory processes are active.

fMRI brain activity differences between MS patients and healthy subjects always have the problem of differences in task performance and task complexity for the subjects as explanation. This aspect has to be accounted for by multiple difficulties and better understanding of the effects of complexity on the brain areas active.

The reason for the activity in a greater brain volume and the activity in other brain areas compared to healthy subjects performing the same test is

therefore speculative. It has been suggested that this might be caused by the presence of subcortical structural damage, so that simple tasks become more complicated. The regions that become active are the areas activated in healthy subjects especially during the performance of more complex tasks. Also the plasticity (adaptational possibilities) of the brain is an explanation; other areas take over functions when the original area can only perform inadequately. This is also known from other diseases, like stroke. The significant correlation between the time since clinical onset and activation in motor areas found suggests that cortical reorganization develops gradually in concomitance with the subclinical accumulation of tissue damage. Extension of cortical activation into areas not (primarily) dedicated to a given function is described for motor and visual function. Further evidence for the plasticity of the brain in MS patients is the results of studies of motor functioning during relapses and recovery, in which is shown that recovery of functions is associated with volume of activated cortex. Adaptation of the brain to overcome cognitive impairment, is at least in the first stages of the disease, a possible explanation for the discrepancy between lesion load and cognitive function scores.

5.2 FUTURE DIRECTIONS

For future research it is necessary to get a better understanding of the parameters, especially physiological ones, that determine brain activity. In MS patients, especially the relationship with disease activity (lesion loads, atrophy, normal appearing white matter, cortical lesions, etc.) has to be further investigated to develop therapeutic strategies and control their effectiveness.
To acquire such knowledge various research steps have to be undertaken.
First, further understanding is needed about the brain areas involved in specific cognitive function. It is even better to speak about the brain areas involved during performance of a specific cognitive test than during a cognitive function. The step from cognitive task to specific test is most of the times involving various (unproven) assumptions.

Most important is the further investigation of the inter-individual and intra-individual differences. Probably much more factors than accounted for in studies so far, are needed to describe better the signal differences. Factors that must be taken into account are gender (and hormonal status), handedness, dominant eye, education, IQ, neuropsychological test experience, food and drinking before the task (especially coffee, tea, other caffeine containing drinks), medication, activities before the task, fatigue, sleepiness, emotions (especially depression) and time of performance during the day.

Therefore much more parameters in and around the subject have to be registered. Also studies of basic brain functioning have to be in concordance with the fMRI study results. Only when, in healthy controls, it is proven that the same brain areas consistently are active, the next steps can be taken. A larger number of subjects studied is a first step compensating for those differences. Brain lesion studies can be used also, as they were used in neuropsychological tests studies in earlier days. Individual patients, with a disease affecting only a circumscribed brain area (vascular incident, chirurgical removed brain tissue), and with specific cognitive problems (tested with a specific cognitive test) can be selected and compared with the normal pattern of brain activity. In those individual patients the validity of the test can be investigated.

The fMRI task designs are adapted versions of existing cognitive tasks. However, the basis for those tests are the performance score. The tasks were developed with the hypothesis of certain cognitive function to be active during such a task. For fMRI purposes in general, tasks have to be developed that activate as few as possible areas in the brain, independent of the cognitive function(s) needed. It is uncertain whether this is possible, because brain function is a network activation rather than a single area at work. For fMRI experiments, especially in MS patients, another regime can probably be followed as well. Tasks that demand many cognitive functions, and thereby large areas of the brain are active, can be used. The size of the active area is than a measure for how much effort the patient makes. But this is probably only true in the beginning in phases of the disease.

Studies on cognitive functions have a great inherent problem, from the perspective of the brain research. The functions investigated always need more than one brain area to be active and the connecting pathways are equally important in fulfilling the task adequately as are the areas processing the function. If the information does not reach the area or is corrupted, the receiving brain area can not process any useful information and therefore no useful output can be generated.

In MS especially the connecting pathways are affected. Functional brain imaging at this point in time can only detect cellular areas that use energy, not the pathways in between. The lesion load in a "cognitively involved" area can be low, while the brain area is not performing the test, and the cognitive score is below normal, because no information reach the area. If a patient can not perform a test at all, few conclusions can be made about the relation with specific lesions. In that respect, some form of performance score is necessary, but makes the task also more complicated and thereby possibly making more areas active.

The MS patient group studied should be as homogenous as possible (type of MS, disease duration, functional impairment) and must be as compatible as possible with the healthy control groups or the influence of (neuro)physiological parameters have to be fully known. A disadvantage of such a very selected MS groups is, that the results can not be extrapolated to the whole MS population at large.

The group size is also important. Small numbers have the main problem that coincidence plays a role, especially because fMRI is always a statistical exercise.

Another main problem for the researcher, although very helpful for patients, is the great adaptive capacities of the brain. When a brain area is damaged, its functions may be overtaken by other brain areas, that can be located almost anywhere in the brain. Performance results are than the same, while completely different brain areas are active.
Especially in MS patients the tasks have to be repeated a number of times during the evolution of the disease, including the exacerbations periods (pre-, during and post-). The subjects can be used as their own controls. In group analysis, the clinical and/or cognitive impairment during such exacerbations has to be preferentially the same across the group, to see if all subjects of that group show the same evolution. This approach might not only lead to better understanding of MS as a disease, but also to the role of certain areas in cognitive impairment. Lesion oriented studies are only a rough technique for determining the place of functional activity in the brain. Adaptative mechanisms can be shown by longitudinal design.

To investigate networks, new techniques like connectivity studies can be applied. The areas active at the same time or after a same time delay are thereby recognized. This will show networks, which probably are in MS less well organized and represents a measure of the severity of the disease.

The end in MS research has not yet been reached. New MR techniques, especially one like fMRI, can not only help with a better understanding of MS and problems MS patients experience, but also gives more basic neurological knowledge. In that respect the studies not only help MS patients, but many other patients with neurological diseases as well.

CHAPTER 6

SUMMARY

Summary

MS is a chronic inflammatory demyelinating disease of the central nervous system. Besides the well known and characteristic somatic disability, MS patients may experience cognitive problems. The impact of these cognitive problems during daily life activities is variable. Severe cognitive disturbances occur in about 10% of the patients. The cognitive impairment itself is heterogeneous, with attention, information processing speed and visuo-spatial working as examples of more often affected domains, while language and praxis are rarely. One could state that the cognitive dysfunction in MS has been "rediscovered", since in fact Charcot already described the problem when describing the disease in 1868.

The purpose of the studies in this thesis was to better understand cognitive impairment in MS, by studying the relation with structural and functional MR parameters.

After a general introduction in chapter 1, in chapter 2 the studies describing a relation between some structural MR parameters and cognitive impairment are presented. It has been known for quite a time that lesions on standard PD, T2 and T1 weighted images (both number and volume) are not strongly correlated with clinical findings. In the studies described in chapter 2 a somewhat stronger relation between cognitive impairment and these parameters becomes clear by using a special MR technique that identifies (juxta)cortical lesions better. Also is described that atrophy and regional lesion load help to improve the clinicoradiological association, although it still remains not very strong. To a certain extent, this reflects the non-specific nature of the neuropsychological tests used. At the end of chapter 2 studies focussing especially on attention and information processing speed and the characteristics in MS patients are described. The impaired attention and information processing speed in MS patients was found to be associated quite strongly with the MRI findings (especially for cerebral atrophy).

Chapter 3 describes an introduction on the technique and implementation of fMRI in our research centre and the development and application of two for fMRI adapted tests, the Tower of London test and the PASAT. Both original tests are especially suitable for MS research, because they probe more than one cognitive domain. The fMRI version of the Tower of London test produces (in young and healthy subjects) activity located in the dorsolateral prefrontal cortex, the cingulate cortex and the cuneus

and precuneus regions, comparable with results from PET studies. The brain activity during the PASAT, also in healthy young individuals, is mainly located in areas in the frontal lobe and the superior and inferior parietal , bilaterally. Although, the adaptations made in both tests to make them suitable for fMRI research, may have changed the main principles of the tests in some way, the activated brain areas are in line with the theoretical expectations derived from the clinical studies with these tests.
In chapter 4 the same tests are used in studies in MS patients and also a study using a light flash paradigm on optic neuritis patients is presented. Using the Tower of London test, MS patients were noted to have activated areas not significantly different from those found in healthy controls with comparable age and education. Also the results do not differ very much from the aforementioned study in young healthy educated subjects. However, the individual results in the MS patients group are much more variable than those in the other groups. Interestingly this occurred in the context of non-reduced behavioural performance, indicating possible compensatory brain activity to maintain function.
The optic neuritis study showed a definite decrease in activity in the occipital cortex in the earlier stages of optic neuritis. At the end of the chapter a very small fMRI feasability study observing Cannabis effects is presented. The results of this study showed quite variable effects of Cannabis between subjects, with no significant effect on group level. The brain activity during more "elementary" brain functions, shows less variation than the activity during the paradigms that make use of more cognitive domains.

The, in this thesis, presented studies have shown that with other than the standard MRI techniques, intriguing results can be achieved in MS research, opening new avenues to the understanding of cognitive processes in MS. To use fMRI in future MS research it is of great importance to know more about the processes that cause brain activity (changes) on fMRI, to more strictly select patient groups and to account for more psycho-physiological parameters (such as time of day, tiredness, use and time of food and drinking, emotional status, and so forth).

Samenvatting

MS is een chronisch inflammatoire demyeliniserende aandoening van het centraal zenuwstelsel. Deze aandoening gaat, naast uiteenlopende andere mogelijke problemen van lichamelijke aard, bij een groot deel van de patiënten gepaard met cognitieve stoornissen. De ernst daarvan, en daarmee de invloed op het dagelijks functioneren, is zeer variabel, maar is in zo'n 10% van de gevallen ernstig te noemen. De cognitieve stoornissen vertonen een heterogeen patroon, waarbij sommige cognitieve domeinen, zoals attentie, informatie verwerkingssnelheid en visuo-spatiële functies, vaker gestoord zijn dan andere, zoals taal en praxis. De laatste jaren zijn deze functiestoornissen bij MS "herontdekt", nadat ze al in 1868 door Charcot, bij de beschrijving van dit ziektebeeld, beschreven waren.

Doel van de in dit proefschrift beschreven onderzoeken bestond uit het verkrijgen van meer inzicht in de cognitieve functiestoornissen, door bestudering van structurele en functional MR-afwijkingen.

Na een introductie in hoofdstuk 1, worden in hoofdstuk 2 de studies besproken die de relatie tussen enkele parameters verkregen uit structurele MR scans en cognitieve functies onderzoeken. Zoals al langere tijd bekend, zijn de laesies (zowel qua aantal als volume) op "standaard" PD, T2 en T1 gewogen opnamen niet sterk gecorreleerd met klinische neurologische parameters. Uit de beschreven studies wordt duidelijk dat cognitieve functiestoornissen een iets sterkere correlatie vertonen met deze MR parameters, dan de gebruikelijke klinische, motorische parameters, door het gebruik van speciale MR technieken die (juxta)corticale laesies beter zichtbaar maakt. Verder in het hoofdstuk wordt getoond dat met andere MR parameters, zoals atrofie en regionale lesion load, de klinisch-radiologische associatie beter is, alhoewel nog steeds niet erg sterk aanwezig. Tot slot worden in hoofdstuk 2 nog twee studies besproken die keken naar met name attentie en informatie verwerkingssnelheid en de karakteristieken daarvan bij MS patiënten. De vaak gestoorde attentie en informatie verwerkingssnelheid bij MS patiënten bleek sterk geassociëerd met enkele MR parameters (vooral cerebrale atrofie).

In hoofdstuk 3 wordt een introductie van de techniek van functional MRI (fMRI) en de implementatie daarvan beschreven. De ontwikkeling van twee voor fMRI gebruik aangepaste testen wordt beschreven, de Tower of

London test en de PASAT. Beide oorspronkelijke testen zijn met name geschikt gebleken voor onderzoek bij MS patiënten, doordat deze testen een beroep doen op meerdere cognitieve domeinen. De voor fMRI gebruik aangepaste versie van de Tower of London test toont in jonge gezonde individuen met name activiteit in de dorsolaterale prefrontale cortex, de cingulaire schors en de cuneus en precuneus regio's, overeenkomend met eerdere PET studies. De hersenactiviteit tijdens de PASAT, eveneens in jonge gezonde personen, is met name gelokaliseerd in meerdere gebieden in de frontale lob en de superior en inferior parietale lob beiderzijds. Opgemerkt dient te worden dat de aanpassing voor fMRI de grondbeginselen van de test wel in enige mate kan hebben veranderd. De actieve gebieden zijn echter overeenkomend met de theoretische verwachtingen.
In hoofdstuk 4 worden deze testen vervolgens gebruikt bij onderzoeken bij MS patiënten en tevens wordt een studie met een lichtflits paradigma bij neuritis optica patiënten beschreven. Gebruik van de Tower of London test toont aan dat bij MS patiënten de geactiveerde gebieden niet significant verschillen met die zoals gevonden bij een qua leeftijd en opleiding vergelijkbare controle-groep. Ook verschillen de resultaten niet wezenlijk met de eerder onderzochte jonge gezonde individuen. Wel blijken de individuele resultaten van de MS groep veel meer van elkaar te verschillen dan de individuele resultaten in de andere groepen. De MS patiënten scoren daarbij niet slechter dan gezonden, hetgeen doet vermoeden dat compensatoire adaptieve mechanismen een rol spelen.

In de discussie volgt een korte bespiegeling van de mogelijke oorzaken van het ontbreken van duidelijke verschillen tussen de groepen, zoals een te heterogene groep MS patiënten, een onvoldoende begrip van de invloed van allerlei fysiologische parameters en het niet bestaan van een een-op-een relatie fMRI activiteit en goed functionerend hersengebied. De studie van de neuritis optica patiënten toont een duidelijk verminderd functioneren van de occipitale cortex in het begin stadium van neuritis optica. Tot slot van het hoofdstuk wordt er een Cannabis studie met gebruik van fMRI bij een zeer kleine groep beschreven. De resultaten daarvan zijn niet eenduidig. Wel tonen ze dat fMRI een hulpmiddel kan zijn bij het bestuderen van hersenactiviteit veranderingen onder invloed van medicatie. Vanuit de fMRI resultaten valt op dat de reactie op Cannabis variabel is. Het blijkt dat de hersenactiviteit tijdens meer "eenvoudige" hersenfuncties minder variatie

vertoont dan tijdens paradigma's die gebruik maken van meerdere cognitieve domeinen.

De in dit proefschrift gepresenteerde studies tonen aan dat met andere dan de standaard MRI technieken, vooruitgang in het MS onderzoek is te boeken, met nieuwe wegen voor een beter begrip van cognitief functioneren van MS patiënten. Voor het slagen van verder onderzoek van MS met behulp van fMRI zal het van groot belang zijn, dat de processen die leiden tot (veranderingen van) de hersenactiviteit op fMRI beter worden begrepen, dat geselecteerd wordt op meer homogene ziekte-groepen en dat meerdere psycho-fysiologische parameters (b.v. tijdstip op de dag, vermoeidheid, gebruik en tijdstip van eten en drinken, emotionele toestand, etc.) mee worden genomen.

CHAPTER 7

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LIST OF ABBREVIATIONS

ACT%	activated percentage
AES	affected eye stimulated
AFNI	software package
ANT	Amsterdam Neuropsychological tasks
ASYM%	asymmetry percentage
BA	Brodmann area
BDI	Beck depression inventory
BES	both eyes stimulated simultaneously
BOLD	blood oxygenation level dependent
BRB	brief repeatable battery (MS cognitive screening test battery)
CBF	cerebral blood flow
CII	cognitive impairment index
CNS	central nervous system
CSF	cerebrospinal fluid
CSE	conventional spin echo MR sequence
CT	computer tomogram
CTRL	controls
EDSS	expanded disability status scale
EPI	echo planar imaging MR sequence
fMRI	functional magnetic resonance imaging
FLAIR	fluid attenuated inversion recovery MR sequence
FSE	fast spin echo MR sequence
FSS	fatigue severity scale
FWHM	full width half maximum
GPI	global performance index of VLGT
IQ	intelligence quotient
MRI	magnetic resonance imaging
MS	multiple sclerosis
MS-FS	multiple sclerosis fatigue severity scale
MT	magnetization transfer MR sequence
NAWM	normal appearing white matter
ON	optic neuritis
PASAT	paced auditory serial addition task
PD	proton density
PET	positron emission tomography
PP	primary progressive type MS patients
PVSAT	paced visual serial addition task
PRI	post response interval
RBV	relative brain volume
ROI	region of interest
RR	relapsing remitting type MS patients
RT	reaction time

SII	secondary somatosensory motor cortex
SDMT	symbol digit modalities test of brief repeatable battery
SD	standard deviation
SMA	supplementary motor cortex area
SP	secondary progressive type MS patients
SPECT	single photon emission computer tomography
SPM	software package
SPR	10/36 spatial recall test of brief repeatable battery
SR	stimulus response
SRT	selective reminding task of brief repeatable battery
T	Tesla
T1	T1 weighted MR images
T2	T2 weighted MR images
TE	echo time (of MR sequence)
THC	delta-9-tetra-hydrocannabinol
ToL	Tower of London task
TR	repetition time (of MR sequence)
UES	unaffected eye stimulated
VAS	visual analogue scale (of pain)
VF	verbal fluency
VLGT	verbal learning and memory test (Dutch)
WLG	word list generation task of brief repeatable battery

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Richard

CURRICULUM VITAE

De auteur van dit proefschrift is geboren op 17 februari 1966 te Amsterdam. In 1984 werd het diploma OVWO behaald aan het Hervormd Lyceum West te Amsterdam. Na uitloting voor de studie geneeskunde werd gedurende één jaar de studie biologie gevolgd ('84/'85). Vervolgens werd in 1990 het doctoraal examen geneeskunde en in september 1994 het arts examen met goed gevolg afgelegd. Dit werd gevolgd door arts-assistentschappen neurologie in het Spaarne ziekenhuis Haarlem ('94/'95) en het Academisch ziekenhuis der Vrije Universiteit ('95/'96). Vervolgens volgde in oktober 1996 een onderzoek baan. Het eerste jaar betrof dit participatie in allerlei onderzoeken, na het eerste jaar werd het promotie onderzoek gestart. In oktober 2001 volgde het begin van de opleiding tot neuroloog (opleider prof. dr . J.J. Heimans) in het VU Medisch centrum te Amsterdam.

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