

Cognitive deficits and the Paced Auditory Serial Addition Test performance among patients with multiple sclerosis

Eija Rosti-Otajärvi

Cognitive deficits and the Paced Auditory Serial Addition Test performance among patients with multiple sclerosis

Eija Rosti-Otajärvi



Department of Psychology, University of Helsinki, Finland

Department of Neurology, Seinäjoki Central Hospital, Finland

Department of Neurology and Rehabilitation, Tampere University Hospital, Finland

Academic dissertation to be publicly discussed,
by due permission of the Faculty of Behavioural Sciences
at the University of Helsinki in Auditorium I at the Department of Psychology
on the 16th of January, 2009, at 12 o'clock

UNIVERSITY OF HELSINKI
Department of Psychology
Studies 55: 2008

Supervisors: Docent Laura Hokkanen, PhD
Department of Psychology
University of Helsinki
Finland

Docent Päivi Hämäläinen, PhD
Masku Neurological Rehabilitation Centre
Finland

Reviewers: Professor Ralph Benedict, PhD
School of Medicine and Biomedical Sciences
State University of New York at Buffalo
USA

Docent Iiro P. Jääskeläinen, PhD
Department of Biomedical Engineering and
Computational Science
Helsinki University of Technology
Finland

Opponent: Docent Marja Hietanen, PhD
Department of Neurology
Helsinki University Central Hospital
Finland

ISSN 0781-8254
ISBN 978-952-10-5105-0 (pbk.)
ISBN 978-952-10-5106-7 (PDF)
<http://www.ethesis.helsinki.fi>
Helsinki University Printing House
Helsinki 2008

To Venla and Ville

CONTENTS

ABSTRACT	5
TIIVISTELMÄ	6
LIST OF ORIGINAL PUBLICATIONS	7
ABBREVIATIONS	8
1 INTRODUCTION	9
1.1 Multiple Sclerosis	10
1.2 Cognitive aspects in MS	13
1.2.1 Prevalence and characteristics of MS-related cognitive impairment	15
1.2.2 The natural progression of cognitive decline in MS	18
1.2.3 Neuroimaging and disease variables correlates of cognitive dysfunction	19
1.3 Neuropsychological evaluation of MS patients' cognitive performances	21
1.4 The Paced Auditory Serial Addition Test (PASAT)	24
1.4.1 Different versions of the PASAT	24
1.4.2 Factors influencing the PASAT performance	26
1.4.3 The PASAT performance among MS patients	27
1.5 Measures of neurological disability in MS	29
1.5.1 Validity and reliability of the measurement tool	29
1.5.2 Clinical measurement tools in MS	30
2 AIMS OF THE STUDY	32
3 METHODS	33
3.1 Subjects	33
3.2 Clinical and neuropsychological tests	35
3.3 Procedure	36
3.4 Statistical analyses	37
4 RESULTS	40
4.1 The cognitive performance of relapsing-remitting MS patients (Studies I and III)	40
4.1.1 The frequency and characteristics of cognitive impairment (Study I)	40
4.1.2 The evolution of cognitive performances (Study III)	42
4.2 PASAT's sensitivity and specificity (Study I)	46
4.3 MS patients' responding patterns on the PASAT (Study II)	48
4.4 PASAT's different scoring methods (Study II)	50
4.5 PASAT's susceptibility to change (Study III)	51
4.6 Reliability and practice effects of the PASAT (Study IV)	52
5 DISCUSSION	54
5.1 The frequency, characteristics, and evolution of cognitive deficits among relapsing-remitting MS patients	54
5.2 Validity of the PASAT	56
5.2.1 PASAT's sensitivity and specificity in MS-related cognitive dysfunction	56
5.2.2 MS patients' responding patterns on the PASAT	58
5.2.3 The effect of different scoring methods on PASAT's sensitivity and specificity	60
5.2.4 PASAT's susceptibility to change in longitudinal setting	61
5.3 Reliability of the PASAT	62
5.4 Methodological considerations	64
5.5 Clinical implications	66
6 CONCLUSIONS	69
7 ACKNOWLEDGEMENTS	71
8 REFERENCES	73
ORIGINAL PUBLICATIONS	84

ABSTRACT

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system, characterized especially by myelin and axon damage. Cognitive impairment in MS is common but difficult to detect without a neuropsychological examination. Valid and reliable methods are needed in clinical practice and research to detect deficits, follow their natural evolution, and verify treatment effects. The Paced Auditory Serial Addition Test (PASAT) is a measure of sustained and divided attention, working memory, and information processing speed, and it is widely used in MS patients' neuropsychological evaluation. Additionally, the PASAT is the sole cognitive measure in an assessment tool primarily designed for MS clinical trials, the Multiple Sclerosis Functional Composite (MSFC).

The aims of the present study were to determine a) the frequency, characteristics, and evolution of cognitive impairment among relapsing-remitting MS patients, and b) the validity and reliability of the PASAT in measuring cognitive performance in MS patients.

The subjects were 45 relapsing-remitting MS patients from Seinäjoki Central Hospital, Department of Neurology and 48 healthy controls. Both groups underwent comprehensive neuropsychological assessments, including the PASAT, twice in a one-year follow-up, and additionally a sample of 10 patients and controls were evaluated with the PASAT in serial assessments five times in one month.

The frequency of cognitive dysfunction among relapsing-remitting MS patients in the present study was 42%. Impairments were characterized especially by slowed information processing speed and memory deficits. During the one-year follow-up, the cognitive performance was relatively stable among MS patients on a group level. However, the practice effects in cognitive tests were less pronounced among MS patients than healthy controls. At an individual level the spectrum of MS patients' cognitive deficits was wide in regards to their characteristics, severity, and evolution.

The PASAT was moderately accurate in detecting MS-associated cognitive impairment, and 69% of patients were correctly classified as cognitively impaired or unimpaired when comprehensive neuropsychological assessment was used as a "gold standard". Self-reported nervousness and poor arithmetical skills seemed to explain misclassifications. MS-related fatigue was objectively demonstrated as fading performance towards the end of the test. Despite the observed practice effect, the reliability of the PASAT was excellent, and it was sensitive to the cognitive decline taking place during the follow-up in a subgroup of patients.

The PASAT can be recommended for use in the neuropsychological assessment of MS patients. The test is fairly sensitive, but less specific; consequently, the reasons for low scores have to be carefully identified before interpreting them as clinically significant.

TIIVISTELMÄ

Multippeliskleroosi (MS) on keskushermoston krooninen tulehduksellinen sairaus, jolle on ominaista erityisesti myeliinin ja aksoneiden vaurioituminen. Kognitiiviset häiriöt ovat MS-taudissa yleisiä, mutta häiriöitä on vaikea havaita ilman neuropsykologista tutkimusta. Valideja ja reliaabeleja menetelmiä tarvitaan kliinisessä työssä ja tutkimuksessa häiriöiden havaitsemiseen, niiden etenemisen seurantaan sekä hoitojen vaikutusten todentamiseen. Paced Auditory Serial Addition Test (PASAT) on tarkkaavuuden ylläpidon ja jakamisen, työmuistin sekä informaation prosessoinnin nopeuden arviointimenetelmä, ja sitä on yleisesti käytetty MS-potilaiden neuropsykologisessa arvioinnissa. Lisäksi PASAT toimii ainoana kognitiivisena testinä lähinnä lääkeainetutkimuksiin kehitetyssä arviointivälineessä, Multiple Sclerosis Functional Compositessa (MSFC:ssä).

Tämän tutkimuksen tarkoituksena oli selvittää a) relapsoivaa-remittoivaa eli pahenemisvaiheittain etenevää MS-tautia sairastavien potilaiden kognitiivisten häiriöiden yleisyyttä, luonnetta ja etenemistä sekä b) PASAT:n validiteettia ja reliabiliteettia MS-potilaiden kognitiivisen suoriutumisen arvioinnissa.

Tutkimusaineiston muodosti 45 MS-taudin relapsoivaa-remittoivaa muotoa sairastavaa potilasta Seinäjoen keskussairaalan neurologian yksiköstä sekä 48 tervettä kontrollihenkilöä. Molemmat ryhmät arvioitiin kattavalla neuropsykologisella tutkimuksella sisältäen PASAT:n kahdesti vuoden seurannan aikana sekä lisäksi 10 potilaan ja kontrollin ryhmä arvioitiin PASAT:lla sarjoittaisissa arvioinneissa viisi kertaa kuukauden aikana.

Kognitiivisten häiriöiden yleisyys oli tässä tutkimuksessa relapsoivaa-remittoivaa MS-tautia sairastavilla potilailla 42%. Häiriöille oli luonteenomaista erityisesti informaation prosessoinnin hidastuneisuus sekä muistihäiriöt. Ryhmätasolla MS-potilaiden kognitiivinen suoriutuminen säilyi suhteellisen vakiona vuoden seurannan aikana. Harjoitusvaikutukset kognitiivisissa testeissä jäivät kuitenkin vähäisemmiksi MS-potilailla kuin terveillä verrokeilla. Yksilötasolla MS-potilaiden kognitiivisten häiriöiden kirjo oli laaja, niin niiden luonteen, vaikeusasteen kuin etenemisenkin osalta.

PASAT oli kohtuullisen tarkka MS-tautiin liittyvien kognitiivisten häiriöiden tavoittamisessa ja 69% potilaista luokiteltiin oikein kognitiivisesti heikentyneiksi tai säilyneiksi kun laajaa neuropsykologista arviota käytettiin "kultaisena standardina". Itseraportoitu hermostuneisuus ja heikot aritmeettiset taidot näyttivät pitkälti selittävän väärinluokittelua. MS-taudille tavanomainen väsyvyys oli objektiivisesti osoitettavissa suoriutumisen heikentymisenä testin loppua kohden. Havaituista harjoitusvaikutuksista huolimatta PASAT:n reliabiliteetti oli erinomainen ja se oli herkkä tavoittamaan potilaiden alaryhmässä esiintulevan kognitiivisen heikentymisen seurannassa.

PASAT:n käyttöä voidaan suositella MS-potilaiden neuropsykologisessa arvioinnissa. Testi on kohtuullisen sensitiivinen, mutta vähemmän spesifi, minkä vuoksi matalien pistemäärien syyt täytyy huolellisesti tunnistaa ennen niiden tulkintaa kliinisesti merkittäviksi.

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles, referred to in the text by Roman numerals (I-IV).

- I Rosti E, Hämäläinen P, Koivisto K, and Hokkanen L (2007). PASAT in detecting cognitive impairment in relapsing-remitting MS. *Applied Neuropsychology* 14(2):101-12.
- II Rosti E, Hämäläinen P, Koivisto K, and Hokkanen L (2006). The PASAT performance among patients with multiple sclerosis: analyses of responding patterns using different scoring methods. *Multiple Sclerosis* 12(5):586-93.
- III Rosti E, Hämäläinen P, Koivisto K, and Hokkanen L (2007). One-year follow-up study of relapsing-remitting MS patients' cognitive performances: Paced Auditory Serial Addition Test's susceptibility to change. *Journal of the International Neuropsychological Society*, 13(5):791-8.
- IV Rosti-Otajärvi E, Hämäläinen P, Koivisto K, and Hokkanen L (2008). The reliability of the MSFC and its components. *Acta Neurologica Scandinavica*, 117(6): 421-7.

The articles are reprinted with the kind permission of the copyright holders.

ABBREVIATIONS

ANOVA	Analysis of variance
BDI	Beck Depression Inventory
CHIPASAT	Children's Paced Auditory Serial Addition Task
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
EDSS	Expanded Disability Status Scale
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
ICC	Intraclass correlation coefficient
IQ	Intelligence quotient
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
9HPT	Nine-Hole Peg Test
PASAT	Paced Auditory Serial Addition Test
PET	Positron emission tomography
PPMS	Primary progressive multiple sclerosis
PRMS	Progressive relapsing multiple sclerosis
ROC	Receiver-operating characteristic
RRMS	Relapsing-remitting multiple sclerosis
15D	Self-reported Quality of Life Questionnaire
SD	Standard deviation
SEM	Standard error of the mean
SPET	Single-photon emission tomography
SPMS	Secondary progressive multiple sclerosis
TEA	Test of Everyday Attention
TWT	Timed 25-Foot Walk
VPSAT	Visual Paced Serial Addition Task
WAIS-R	Wechsler Adult Intelligence Scale-revised
WCST	Wisconsin Card Sorting Test
WMS-R	Wechsler Memory Scale-revised

1 INTRODUCTION

Multiple sclerosis (MS) is the most common disabling neurological disease in young and middle-aged adults (McDonald & Ron, 1999). The disease is characterized by a marked variability in the clinical symptoms and their course and the unpredictable nature of the disease trajectory increases the distress it causes to patients. Advances in neuropathology have challenged the historical view of MS merely as a demyelinating disease and made it evident that also widespread axonal damage and grey matter changes are central features of MS (Kidd et al., 1999; Ge et al., 2002). This has emphasized the role of cognitive dysfunction as one of the core symptoms of the disease. MS-related cognitive deficits cannot be predicted from external disease markers like disease duration or physical disability. Nor do the deficits necessarily become apparent in a routine neurological examination or interview because the severe and extensive cognitive impairment or cortical deficits that would be easily recognizable are relative rare (Fischer et al., 1994; Fischer, 1999). Moreover, patients' self-reports can be unreliable because patients may either underestimate their deficits due to reactive denial or a metacognition impairment (Scarrabelotti & Carroll, 1999; Hoogervorst et al., 2001; Sherman et al., 2007) or neuropsychiatric disorders like euphoria (Carone et al., 2005) or others can overestimate them due to depression (Maor et al., 2001; Benedict et al., 2003; Deloire et al., 2006) or fatigue (Deloire et al., 2006). Consequently, MS-related cognitive dysfunction often remains under-diagnosed in clinical practice, and too little is known about the evolution of the deficits. However, deficits should be recognized as early as possibly so that their harmful effects could be reduced. Cognitive impairment is a common (Rao et al., 1991a; Fischer, 2001), functionally disabling disease manifestation among MS patients but difficult to detect without a formal neuropsychological examination. Valid and reliable methods are required in clinical practice, research, as well as in clinical trials.

The Paced Auditory Serial Addition Test (PASAT) (Rao et al., 1991a; Kujala et al., 1995) is widely used among MS patients and acts as a sole cognitive measure in an assessment tool primarily designed for MS clinical trials, the Multiple Sclerosis Functional Composite (MSFC) (Rudick et al., 1997; Cutter et al., 1999). The PASAT

has its unique benefits and limitations, some of which concern MS patients specifically, and therefore PASAT performance should be carefully examined among this particular patient group. Furthermore, there are numerous versions of the PASAT available but not enough evidence to suggest that different versions are equivalent in measuring cognitive functions. Consequently, each version, the Finnish MSFC's version being one, is worthy of independent critical examination.

The purpose of the present study was to evaluate the frequency, characteristics, and evolution of cognitive impairment among relapsing-remitting MS patients, and especially to clarify the validity and reliability of the PASAT in measuring cognitive performances in MS patients.

1.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS), characterized by discrete areas of demyelination and axon injury associated with inflammatory activity. Recent studies have revealed that MS lesions are present in the cortical and deep grey matter of the brain to a greater extent than has been previously recognized (Kidd et al., 1999; Ge et al., 2002). Demyelination and axonal degeneration together lead to cortical brain atrophy (Trapp et al., 1999), but the extent of the cortical pathology suggests that an independent neurodegenerative process is also active (De Stefano et al., 2003). The exact aetiology of MS remains still unknown, but laboratory and epidemiological studies suggest that it is an autoimmune disease, possibly initiated when an infectious agent (e.g. virus) induces a T-cell-mediated immune response in a genetically susceptible individual (Bongioanni et al., 2000; Rohowsky-Kochan et al., 2000). Epidemiological findings of uneven geographical distribution, heightened risk in the areas inhabited by those of North-European descent, familial occurrence, twin studies, and migration studies have all contributed to the prevailing notion that genetic predisposition as well as exposure to environmental agents influence to the appearance of the MS (Casetta & Granieri, 2000; Granieri et al., 2001; O'Connor, 2002). It is assumed that disease acquisition occurs before puberty with a particular event, such as a virus infection, and the disease agent then remains latent in the body, and initiates the

disease process later in life (Poser & Brinar, 2002). Women are approximately twice as likely to develop the disease as men. Onset of the disease rarely occurs before puberty or after the age of 60 years. The incidence peaks at about the age of 30.

MS lesions can develop in numerous locations, including the optic nerves, brain stem, cerebellum, spinal cord, subcortical white matter, and the cortex, and there is hence a wide variation in the symptomatology both between different patients and within individual patients over time. Fatigue is one of the most common and debilitating complaints associated with MS affecting as many as 90% of patients. Other prominent symptoms are muscular weaknesses, deficits in coordination and balance, tingling or numbness in the limbs, double vision, visual deficits, bladder and bowel disturbance, pains, reduced heat tolerance, dysarthria, cognitive dysfunction, and depression (McDonald & Ron, 1999). The unpredictable nature of disease trajectory increases the distress caused by MS; some patients maintain most functions at near normal levels for decades, some deteriorate rapidly in many areas, and some face a fluctuating physical and mental status.

The diagnosis of MS is fundamentally clinical, but many tests such as magnetic resonance imaging (MRI), the examination of the cerebrospinal fluid, and visual evoked potentials are helpful in confirming the clinical suspicion of MS (Polman et al., 2006a). For a diagnosis of MS, evidence of CNS involvement in more than one area (dissemination in “space”) and of CNS involvement at more than one time (dissemination in “time”) are required (Holland et al., 2007). The diagnostic criteria by Poser (Poser et al., 1983) have been widely used in clinical practice as well as in research (see Table 1). More recently, the revised McDonald’s criteria (McDonald et al., 2001) which are more based on radiological findings, were introduced in 2001, and afterwards modified in 2005 (Polman et al., 2005).

Table 1. Diagnostic criteria for multiple sclerosis (Poser et al., 1983)

Category	Attacks ¹⁾	Clinical Evidence	Paraclinical Evidence ²⁾	CSF OB/IgG
Clinically definite	2 2	2 1	and 1	
Laboratory-supported definite	2 1 1	1 2 1	or and	1 1
				+ + +
Clinically probable	2 1 1	1 2 1	and 1	
Laboratory-supported probable	2			+

CSF = Cerebrospinal fluid. OB/IgG = oligoclonal bands or increased production of immunoglobulin G.

¹⁾ The two attacks must involve different parts of CNS, must be separated by a period of at least one month, and must each last a minimum of 24 hours.

²⁾ Paraclinical examinations: evoked response studies, computed tomography (CT), magnetic resonance imaging (MRI). Additionally required that symptoms begin at the age of 10-59 and do not be attributable to another condition.

The disease course in MS is variable, however four main types are generally recognized (Lublin & Reingold, 1996): 1) *relapsing-remitting MS (RRMS)*, which is characterized by clearly defined acute attacks followed by full or partial recovery to the pre-existing level of disability, and by a lack of disease progression in the periods between attacks; 2) *secondary progressive MS (SPMS)*, which occurs after an initial relapsing-remitting phase and is characterized by disease progression with or without occasional relapses, minor remissions, and plateaus; 3) *primary progressive MS (PPMS)*, which is characterized by disease progression from onset, with or without occasional plateaus or temporary minor improvements; and 4) *progressive relapsing MS (PRMS)*, which is characterized by disease progression from onset punctuated by clear acute relapses that are followed by full or partial recovery to the pre-existing level of disability. Additional terms sometimes used to describe particular extreme types of MS include benign and malignant MS. In benign MS, the patient remains fully functional in all neurological systems for extensive periods of time, sometimes even 15 years after disease onset whereas in malignant MS, the disease shows a rapid progressive course, leading to significant disability or death within a few months (Lublin & Reingold, 1996). The course of the illness is initially difficult to predict but in the early stages of the disease the relapsing-remitting form is the most common occurring about 80-85% of patients (Feinstein, 2007). Many of these (almost 60%) enter a phase of progressive

deterioration a variable number of years after symptom onset (Feinstein, 2007) probably when the threshold of progressive axon loss is exceeded (Trapp et al., 1999a, 1999b).

Despite the disabling nature of the disease, life expectancy is not shortened appreciably. Death directly from MS itself is rare, instead patients are often prone to infections, which is a common cause of death. A more favourable disease evolution has been associated with relapsing-remitting disease course, age at onset below 30 years, optic neuritis or other sensory symptoms at presentation (Zaffaroni & Ghezzi, 2000; Sumelahti et al., 2002), and female gender (Zaffaroni & Ghezzi, 2000). A cure for MS does not exist. However, during the past decade major advances have been made in the development of disease-modifying therapies; betainterferon, glatiramer acetate (O'Connor, 2002), and now more recently natalizumab (Polman et al., 2006b) have been shown to have beneficial effects on disease activity by reducing the number of relapses and by slowing down the progression of the disease.

Finland belongs to a high risk region for multiple sclerosis, with prevalences ranging from 100 to 200 per 100 000 in different areas (Sumelahti et al., 2001). There are substantial regional differences in the occurrence of MS in Finland. Sumelahti et al. have reported that during years 1979-1993 the incidence in Uusimaa has been 5.1 / 100 000 person-years, which represents the average of our country, while at the same time the incidence was over double being 11.6 / 100 000 person-years in Seinäjoki, a figure among the highest reported worldwide (Sumelahti et al., 2001; Sumelahti et al., 2003). Overall there are approximately 6000 MS patients currently living in Finland.

1.2 Cognitive aspects in MS

The term cognition refers to individual's high-level information processing functions which comprises of many discrete but together working abilities. These include comprehension and formation of speech, visual perception and construction, calculation ability, attention, information processing, memory and learning, as well as executive functions such as planning, flexibility, fluency, and self-monitoring (Lezak, 1995). Each of these concepts can further be divided into subsystems, but only the most essentials from the perspective of the present study - namely attention, working memory, and

information processing speed – are defined in more detail below. They are all theoretically distinguishable, yet highly complex, modular, and interactive systems. A clear and universally accepted definition of these concepts has not appeared in literature, but commonly attention has been divided into four descriptive aspects (Lezak, 1995): 1) *Focused or selective attention* refers to the capacity to highlight the one or two important stimuli or ideas that are being dealt with while suppressing awareness of competing distractions; 2) *Sustained attention* refers to the capacity to maintain attentional activity over a period of time; 3) *Divided attention* involves the ability to respond to more than one task at a time or to multiple elements or operations within a task, as in a complex mental task; and 4) *Alternating attention* allows for shifts in focus and tasks. The term *working memory* commonly implies a system for the temporary holding and manipulation of information during the performance of a range of cognitive tasks such as comprehension, learning, and reasoning (Baddeley, 1986). And finally, the concept of *information processing speed* is regarded to represent how quickly different types of cognitive processing operations can be carried out (Salthouse, 1996).

Already in the 1870's Jean-Martin Charcot, the French neurologist responsible for describing the various symptoms of MS and for providing the disease with its current name, wrote that most MS patients experience “a marked enfeeblement of the memory, conceptions are formed slowly, the intellectual and emotional faculties are blunted in their totality” (Charcot, 1877). In contrast to Charcot's observations, clinicians for the greater part of the 20th century espoused a widely-held view that intellectual or cognitive deficits in MS were rare, occurring in less than five percent of patients, and if present, generally confined to patients with severe physical disability (Kurtzke, 1970). For over a century, MS neuropathological studies have focused on the breakdown of the myelin sheath and in regards to cognitive functions it was thought that higher cognitive functions remain mostly unaffected. The fact that brain areas influencing the cognitive functioning are noticeably wider and more complex, and that also subcortical networks have a remarkable part in these processes, got far too little attention. The current knowledge about more extensive neuropathology of MS than previously assumed including widespread axonal damage and involvement of grey matter changes has re-emphasized the role of cognitive dysfunction as a symptom of the disease.

The functional consequences of MS-related cognitive impairment can be striking. Cognitive deficits have a multidimensional impact on patients' quality of life affecting physical independence, employment, social and recreational activities (Rao et al., 1991b), driving skills (Kotterba et al., 2003; Lincoln & Radford, 2008), rehabilitation outcome (Langdon & Thompson, 1999), as well as caregiver strain (Chipchase & Lincoln, 2001). However, cognitive dysfunction in patients with MS is under-diagnosed and the meaning of the deficits to patients' entire situation is still not sufficiently recognized.

To develop effective diagnostic, clinical trial, and rehabilitative methods to this functionally disabling disease manifestation, precise information about the characteristics and natural history of cognitive deficits in MS is needed. The literature describing prevalence, characteristics, and natural progression of MS-related cognitive dysfunction, as well as its relationship to other disease variables are briefly reviewed in the subsequent sections.

1.2.1 Prevalence and characteristics of MS-related cognitive impairment

Estimations of the frequency of cognitive impairment among MS patients vary in the literature depending on the research setting, the neuropsychological and statistical methods used as well as the characteristics of the study samples (Amato et al., 2006b). The community-based surveys show prevalence estimates from 43% to 46% and hospital-based studies from 54% to 65% of cases (Amato et al., 2006b). The common consensus based on these studies indicate that about 50% of all MS patients suffer from cognitive impairment.

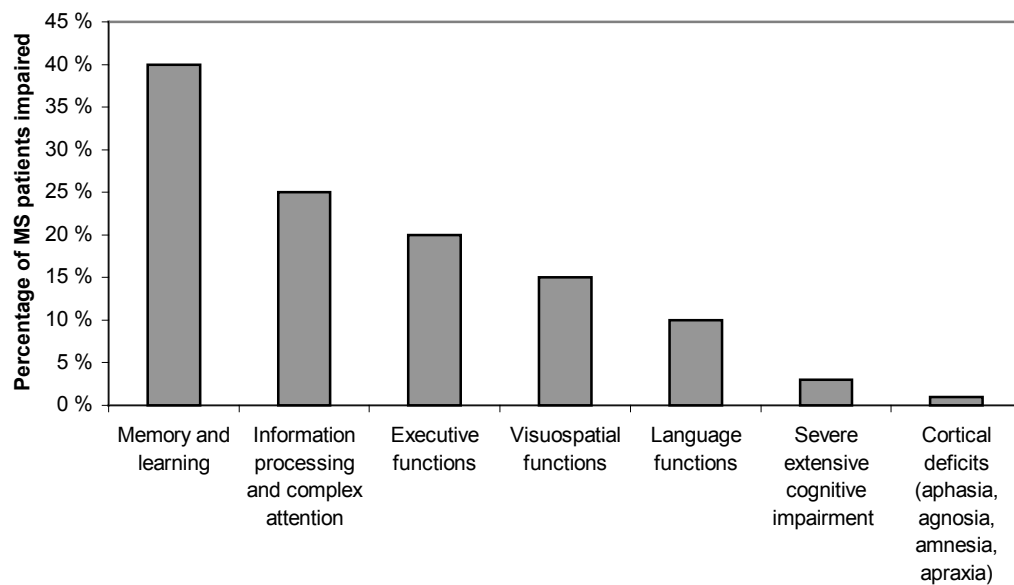


Figure 1. Prevalence of MS patients' cognitive impairment in different domains at a group level (Fischer et al., 1994; Fischer, 1999, 2001; Benedict et al., 2006a modified). However, individual patients vary considerably in their patterns of dysfunction.

MS-related cognitive dysfunction is often heterogeneous in nature and thus varies among patients, but certain patterns do emerge among patient groups. Figure 1 summarizes the estimated prevalence rates of different cognitive deficits in their order of commonness. Memory and learning appear to be the most frequently disrupted cognitive domains (Rao, 2004; Calabrese, 2006; Rogers & Panegyres, 2007). MS-related deficits have been found across several memory subsystems and retrieval conditions, therefore memory deficits can be widespread varying only by degree (Kujala et al., 1996a; Thornton & Raz, 1997). The most common pattern in learning dysfunction involves inefficient learning, which is characterized by deficient first-trial recall, mildly inconsistent recall across further learning trials, and mildly deficient recall after delay (Fischer, 2003). In general, explicit, episodic, free recall, and retrieval have been reported to be often impaired; semantic, recognition, and encoding less frequently impaired; and implicit, autobiographical, procedural, and storage to be relatively intact (Fischer, 2001; Bagert et al., 2002; Calabrese, 2006; Ghaffar & Feinstein, 2007; Rogers & Panegyres, 2007).

Reduced information processing efficiency, in particular, is thought to underlie and be the core feature of cognitive problems observed in MS (e.g. Demaree et al., 1999; DeLuca et al., 2004; Henry & Beatty, 2006). The significance of information processing

deficits is also emphasized by the fact that they may impact other aspects of cognitive functions (Calabrese, 2006; Feinstein, 2007). Impaired information processing has been observed primarily in two areas: working memory and processing speed (Archibald & Fisk, 2000), latter regarded as the primary problem compared with performance accuracy or working memory (DeLuca et al., 2004; Kalmar et al., 2004; Lengenfelder et al., 2006). The simple attention span performance generally remains intact and deficits are more obvious in complex attention performances, like selective, alternating, and divided attention (Litvan et al., 1988a; DeLuca et al., 1993; Fischer, 2001). Similarly, dual-task performance has been found to be more impaired compared with single-task condition (D'Esposito et al., 1996).

It has been argued that most executive functions may be affected by MS. Abstract reasoning, problem-solving, planning/sequencing, temporal ordering, frequency monitoring, cognitive estimation (Fischer, 2001), shifting and inhibition along with fluency (Foong et al., 1997; Drew et al., 2008) have all often found to be impaired. In executive functions the predominant problem may be in generating concepts as opposed to perseverative responses (Feinstein, 2007). However, studies that examine a broad range of executive functions have been rare. Additionally, executive functions are complex cognitive functions, deficits of which mainly come out in "real-life" situations, and therefore they are also difficult to measure psychometrically. Moreover, the so-called executive tests are highly multifactorial in nature.

Visual processing deficits have been described in patients with MS, although their exact nature and severity often remain unclear (Rao, 2004). Deficits in the perception of faces and of pictures as well as geometric figures have been reported, while pure visual agnosias are quite rare (Fischer, 2001). Deficits in visuospatial functions may be slightly less common than other visual perceptual disorders in MS (Fischer, 2001). In all, impairments of visual perception have received only little systematic study, possible because of the complicated interpretation of visuospatial and visuoconstructive abilities where performance can be compromised by primary motor, sensory, or visual deficits often related to MS.

Repetitive speech, comprehension, grammar, and syntax are generally intact, although mild deficits in naming, fluency, and sentence span occur with some regularity (Fischer et al., 1994; Kujala et al., 1996b; Brassington & Marsh, 1998; Bagert et al.,

2002). According to meta-analytic review the phonemic and semantic verbal fluency tests are equivalent in their sensitivity to the presence of deficits in MS (Henry & Beatty, 2006). Moreover, the mechanisms of speech production are frequently impaired, resulting in dysarthria.

MS is typically related to mild to moderate decline of some cognitive functions, whereas severe and extensive cognitive impairment or cortical deficits (aphasia, agnosia, amnesia, and apraxia) are relatively rare (Fischer et al., 1994; Fischer, 1999). However, also dementia does occur in MS, although with much lower frequency than mild cognitive impairment (Benedict & Bobholz, 2007). Additionally, it has been suggested that also a possibly underdiagnosed cortical variant of MS with extensive cognitive decline and depression as the primary symptom may exist (Zarei et al., 2003; Zarei, 2006). Consequently, at an individual level the spectrum of MS-related cognitive deficits and their severity can be wide.

Cognitive fatigue can be a central part of the MS neuropsychological symptom complex and perhaps even the most disabling symptom of the disease. Consequently, its assessment in tests and by general observation is an essential part of any neuropsychological examination. The term cognitive fatigue usually refers either to a subjective feeling of a mental fatigue or to an objective decrement of cognitive performance during sustained attention tasks (Krupp, 2004). Consequently, most fatigue-assessment strategies can be categorized as either self-rating questionnaires or performance-based measures of cognitive functioning by measuring the decrement in performance over time in a single task or during the entire neuropsychological evaluation (Krupp, 2001). The define relationship between subjective fatigue and objective signs of cognitive fatigue has however been elusive (Krupp, 2004).

1.2.2 The natural progression of cognitive decline in MS

Although the presence of cognitive impairment in multiple sclerosis is well documented in cross-sectional studies, the course and evolution of cognitive decline in MS is less well known. Part of the studies in the previous literature report a stable cognitive status at follow-up (Jennekens-Schinkel et al., 1990; Mariani et al., 1991; Sperling et al., 2001), and part a decline in MS patients' cognition in the long run (Feinstein et al.,

1992; Amato et al., 1995; Kujala et al., 1997; Amato et al., 2001; Zivadinov et al., 2001a). Various methodological factors probably contribute to the controversial results: variation in the follow-up times (1-10 years), in the patient samples (heterogeneity in disease course, physical impairment, cognitive status, and sample size), and neuropsychological tests (brief and restricted vs. comprehensive batteries) have all been considerable. Some of the previous studies (Mariani et al., 1991; Hohol et al., 1997; Sperling et al., 2001) have also suffered from a lack of appropriate control groups and therefore subtle cognitive decline in follow-up might have been obscured because of normal practice effects related to neuropsychological tests. In medium term (one to four years) follow-up, the cognitive decline is commonly characterized by considerable individual variability suggesting that the initial existence of a cognitive impairment may constitute a risk factor regarding further cognitive decline (Kujala et al., 1997; Lensch et al., 2006; Feinstein, 2007). In long term (10 or more years) follow-up, cognitive dysfunction may become more frequent, affecting more cognitive domains and may link more closely to physical disability (Amato et al., 2001; Feinstein, 2007).

1.2.3 Neuroimaging and disease variables correlates of cognitive dysfunction

The relationship between cognitive test performance in MS patients and indices of cerebral pathology has been explored through structural brain imaging (computed tomography [CT], magnetic resonance imaging [MRI]), functional brain imaging (functional magnetic resonance imaging [fMRI], positron emission tomography [PET], single-photon emission tomography [SPET]), as well as electrophysiological measures (event-related potential [ERP]) (Rao, 2004). Cognitive impairment has been found to correlate moderately to strongly with 1) cerebral lesion burden on T2-weighted MRI (Rao et al., 1989; Rovaris et al., 1998); 2) brain atrophy (especially in the corpus callosum and periventricular area) (Rovaris et al., 1998; Zivadinov et al., 2001b; De Stefano et al., 2003); 3) microscopic pathology both in lesions and in normal-appearing brain tissue (Rovaris et al., 1998; Zivadinov et al., 2001b); and 4) cerebral glucose metabolism rates (Blinkenberg et al., 2000). Recent studies have indicated that brain atrophy is even more important cerebral predictor of impaired cognition in MS than

conventional MRI lesion burden (Benedict et al., 2004a, 2006b; Houtchens et al., 2007). Both central, especially enlargement of the third ventricle width (Benedict et al., 2004a, 2006b; Tekok-Kilic et al., 2007) and thalamic atrophy (Houtchens et al., 2007), as well as cortical atrophy (Benedict et al., 2006b; Tekok-Kilic et al., 2007) have been found to predict cognitive dysfunction. Also regional lobar atrophy connections to specific cognitive disorders have been found, such as the connection between temporal lobe atrophy and memory performance (Benedict et al., 2005). It is assumed that demyelination, axonal and neuronal loss as well as cortical lesions within the cerebral hemispheres all contribute to cognitive impairment in MS (Bagert et al., 2002). In addition to structural, also electro-magnetic, metabolic, and functional changes in central nervous system have been shown to be related to cognitive deficits in MS (Rao, 2004). Therefore, it has been argued that cognitive impairment in MS is not merely a result of tissue destruction, but rather a consequence of balance between tissue destruction, tissue repair and adaptive functional reorganization (Hoffmann et al., 2007).

In terms of the disease course, it is probable that cognitive functions are more vulnerable in chronic-progressive disease than in the relapsing-remitting form (Heaton et al., 1985; Beatty et al., 1989; Amato et al., 2006b; Lensch et al., 2006), although this has not been a completely constant finding (Beatty et al., 1990; Rao et al., 1991a). Instead, MS patients' neuropsychological deficits have either not been found to correlate or only weakly correlate with physical disability, disease duration (Beatty et al., 1990; Rao et al., 1991a), amount of relapses, or age at diagnosis (Beatty et al., 1990).

The relationship between depression and cognitive dysfunction in MS is complex in regards e.g. to causality, the overlap between neurovegetative symptoms of depression and symptoms of MS, as well as the so-called threshold effect that links cognitive difficulties to more severe depressive symptomatology only (Siegert & Abernethy, 2005; Feinstein, 2006). Earlier studies failed to find a clear association between the two (e.g. Krupp et al., 1994; DeLuca et al., 1995), whereas in more recent studies a clinically significant depression has been found to correlate with and exacerbate information processing speed, working memory and executive functioning deficits (see reviews Siegert & Abernethy, 2005; Feinstein, 2006).

In sum, cognitive impairment may encompass virtually all the MS disease stages and progression types independently of the degree of physical disability (Amato et al.,

2006b; Fischer et al., 1994). Cognitive and neuropsychiatric deficits can appear without, or long before, clinical neurological or physical findings (Haase et al., 2003; Zarei et al., 2003; Zarei, 2006). Therefore, if the MS patients' cognition is estimated solely based on their physical disability, disease duration, or emotional state, interpretations can be totally misleading.

1.3 Neuropsychological evaluation of MS patients' cognitive performances

The cognitive status of a MS patient is difficult to evaluate without formal neuropsychological assessment because in an interview patients may overestimate their deficits due to depression (Maor et al., 2001; Benedict et al., 2003; Deloire et al., 2006) or fatigue (Deloire et al., 2006), or underestimate them due to reactive denial or metacognition impairment, anosognosia (Scarrabelotti & Carroll, 1999; Hoogervorst et al., 2001; Sherman et al., 2007) or neuropsychiatric disorders like euphoria (Carone et al., 2005). Prone to underestimation are especially those with dramatic cognitive changes (Marrie et al., 2005). Due to the variable anatomical distribution of MS cerebral lesions, the cognitive impairment in MS is heterogeneous in character and therefore the examination requires a variety of neuropsychological tests (Lezak, 1995). The choice of tests may vary, depending e.g. on the referral question, the clinical neuropsychologist's training, the patient's characteristics or tolerance for neuropsychological testing. Because one of the main features of MS-related cognitive decline in addition to memory deficits is a reduced and slowed information processing efficiency and attention tests have been found to be sensitive indicators of these deficits, especially attentional tests have been recommended to be included in the neuropsychological test battery of MS patients (Kujala et al. 1995; Hohol et al., 1997; Demaree et al., 1999). General recommendations of core neuropsychological tests to be used in the evaluation of MS patients' cognitive performance have also been published, such as those of Cognitive Function Study Group of the USA National Multiple Sclerosis Society (Peyser et al., 1990) (see Table 2). This test battery has some problems however; it is time-consuming and contains several tests that are nonstandardized (Benedict et al., 2002), insensitive or

poorly suited to longitudinal studies, or particularly vulnerable to practice effects (Beatty, 1999).

Table 2. Core battery of neuropsychological tests according to Peyser et al. (1990)

Cognitive function	Neuropsychological test
Global dementia screen	Mini-Mental State Examination (Folstein et al., 1975) Information subtest from WAIS-R (Wechsler, 1981)
General fund of information	Symbol Digit Modalities Test (Smith, 1973)
Attention / concentration	Auditory A's; Auditory Trials A (Lezak, 1995) Paced Auditory Serial Addition Test (Gronwall, 1977) Modified Stroop Test (Stroop, 1935)
Memory	Logical Memory from WMS-R (Wechsler, 1987) California Verbal Learning Test (Delis et al., 1987) 7/24 Spatial Recall Test (Barbizet & Cany, 1968)
Language functions	Abbreviated Boston Naming Test (Caine et al., 1986) Controlled Oral Word Association Test (Benton & Hamsher, 1976) Abbreviated Token Test (Benton & Hamsher, 1976)
Visuospatial functions	Abbreviated Hooper Visual Organization Test (Hooper, 1958) Modified Block Design subtest from WAIS-R (Wechsler, 1981)
Abstract / conceptual reasoning	Wisconsin Card Sorting Test (Heaton, 1981) Raven's Standard Progressive Matrices (Raven, 1960) Comprehension subtest from WAIS-R (Wechsler, 1981)

Later, the Minimal Assessment of Cognitive Function in MS (MACFIMS) was introduced as an ideal, minimal record of neuropsychological function in MS (Benedict et al., 2002). This is a 90-minute neuropsychological battery composed of seven tests, covering those cognitive domains that are most commonly affected in MS.

The frequency of cognitive dysfunction in MS and its wide impact on everyday functioning has led to an increasing consensus that a neuropsychological assessment should accompany the neurological examination and become a factor in therapeutic decision-making (Amato & Zipoli, 2003). It is however impractical and impossible to refer all MS patients for a comprehensive neuropsychological evaluation due to limited resources. Several screening batteries comprising of short tests known to measure the cognitive functions most vulnerable in MS have therefore been developed: the Neuropsychological Screening Battery for MS (NPSBMS) (Rao et al., 1991a), the Brief Repeatable Battery (BRB) (Rao & Society, 1990; Bever et al., 1995), the Screening Examination for Cognitive Impairment (SEFCI) (Beatty et al., 1995), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Aupperle et al., 2002), and batteries introduced by Beatty & Goodkin (1990) and Basso et al. (1996), among others. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) has repeatedly been shown to be insensitive in detecting cognitive changes in MS patients

(Beatty & Goodkin, 1990; Kujala et al., 1997). Individual tests, such as the Symbol Digit Modalities Test (Smith, 1973), the Paced Auditory Serial Addition Test (Rao et al., 1991a; Kujala et al., 1995), Clock Drawing Tests (Strauss et al., 2006), and the MS neuropsychological Screening Questionnaire (Benedict et al., 2003, 2004b) have been suggested to be relevant cognitive screening instruments instead (Rogers & Panegyres, 2007). However, as the diversity of cognitive changes among MS patients sets challenges to screening methods, their applicability remain limited and they cannot be regarded as a noteworthy alternative to a comprehensive neuropsychological examination.

Interpretation of the neuropsychological test results of the MS patients can be confounded by several factors, including e.g. variation in premorbid level of functioning, depression, anxiety, fatigue, motivation, dysarthria, visual/sensory/motor impairments, and medications (Benedict et al., 2002). Therefore, the test selection demands special attention. General recommendations for the neuropsychological test battery for MS patients can be summarized as follows: The test battery needs to be 1) comprehensive, assessing thoroughly the cognitive, emotional, and behavioural functioning; 2) sensitive to characteristics of MS-related cognitive problems; 3) able to be administered in a way that does not cause excessive fatigue (Mahler, 1992); 4) yield both quantitative and qualitative data; 5) comprised of tests that have a demonstrated reliability and validity; 6) have alternate forms for use in repeated testing over time (Rao, 2004); as well as 7) allow for the above mentioned confounding factors to be taken into account in the interpretation of the test results (Benedict et al., 2002). An additional tool can be a cognitive questionnaire for both the patient and the informant / caregiver (Benedict et al., 2003; Sartori & Edan, 2006).

Cognitive deficits can remarkably hamper patients' quality of life. Consequently deficits should be recognized as early as possible. Thorough neuropsychological assessments are useful in identifying areas of cognitive strengths and weaknesses and provide a basis for suggesting compensatory strategies. Comprehensive evaluation is often needed to determine the working ability, re-education possibilities, the driving ability or prerequisites for cognitive retraining. Cognitive deficits may incorrectly be attributed to obstinacy, deliberate provoking, depression, attempts to seek attention or sympathy, or lack of motivation. This causes additional stress and hampers coping. It is

important to inform both the patient and their family members about the cognitive strengths and weaknesses as well as their effects on daily life. This in itself can help to find better ways to solve problems caused by the deficits. In addition to psychometric tests, essential parts of the clinical neuropsychological evaluation are the interview of the patient and informant (complemented as needed with questionnaires), the qualitative observation and interpretation, and in all the holistic approach in the evaluation process taking into account the emotional, behavioural, and confounding aspects.

1.4 The Paced Auditory Serial Addition Test (PASAT)

1.4.1 Different versions of the PASAT

The Paced Auditory Serial Addition Test (PASAT) is a demanding, multifactorial task, mainly measuring sustained and divided attention, working memory, and information processing speed (Gronwall, 1977; Gronwall & Wrightson, 1981; Lezak, 1995; Tombaugh, 2006). Several versions of the PASAT exist, and they differ on factors such as the number of trials administered, the number of items within each trial, the length of interstimulus intervals, the modality (auditory or visual), and the medium through which the task is presented (i.e. audiotape or computer).

The roots of the PASAT go as far as to the 1950's when the Visual Paced Serial Addition Task (VPSAT) was developed as an instrument for stimulus-response research (Sampson, 1956). In the 1970's the visual version was converted to an auditory task, the Paced Auditory Serial Addition Task (PASAT), which was originally introduced as a clinical tool to measure the severity of and the recovery from a brain injury, and especially to provide an estimate of the speed of information processing (Gronwall, 1977). In the test the examinee is asked to listen to a recorded series of single digits (from 1 to 9) and to add each number to the one presented previously. The original version includes the same quasi-random series of 61 digits in four trials with an increasing digit presentation rates of 2.4, 2.0, 1.6, and finally 1.2 seconds.

The original Gronwall's task has been suggested to lead improved performance due to practice effects, therefore Levin et al. (1987) introduced a revised version of the PASAT in the 1980's. This version consists of four unique series of 50 numbers

presented at increasing speed with the original interstimulus times. The Children's Paced Auditory Serial Addition Task (CHIPASAT) was developed to assess attention in children after head injury (Johnson et al., 1988) and it consists of five series of 61 numbers presented with interstimulus times of 2.8, 2.4, 2.0, 1.6, and 1.2 seconds. The sequence of digits is designed so that no answer exceeds 10 whereas in the adult version also larger numbers are presented and the summations range up till 18. Additionally, the different PASAT versions available vary in their interstimulus intervals (e.g. two-second as regarded a "difficult" condition and three- or four-second regarded as "easy" conditions), in numbers of trials (e.g. one [PASAT-50] or two [PASAT-100] trials administrations), and in presentation modality (auditory or visual computerized versions of the PASAT). For MS patients, the number of interstimulus intervals and presentation rates of the original PASAT were subsequently modified by Rao and colleagues to include a one trial 3.0 second (PASAT-3) and a 2.0 second (PASAT-2) versions (Rao et al., 1991a). A more recent innovation has been an adaptive format of the PASAT where the interstimulus intervals are adjusted based on examinee's performance level (Adjusting-PSAT; (Tombaugh, 1999)).

The most commonly used scoring method for the PASAT performance is to count the total number of *correct responses*. An alternative method is to count *dyad scores* (Snyder et al., 1993; Fisk & Archibald, 2001), where a dyad is scored when two consecutive correct answers are given. This is presumed to have higher sensitivity to impairment (Strauss et al., 2006). A *percent dyad score*, which consists of the percentage of total correct responses accounted for by dyads, can also be calculated (Snyder et al., 1993; Fisk & Archibald, 2001). Finally, a *chunking score* represents the number of correct responses that followed a skipped response (Strauss et al., 2006). Computer versions typically provide more scoring options (Wingenfeld et al., 1999).

Nowadays, the PASAT is administered to a variety of clinical populations including at least those with traumatic brain injury (O'Jile et al., 2006), MS (e.g. Kujala et al., 1995; Benedict et al., 2004b; Deloire et al., 2005;), Parkinson's disease (Dujardin et al., 2007), obstructive sleep apnea (Felver-Gant et al., 2007), chronic fatigue syndrome (DeLuca et al., 1993; Johnson et al., 1997), depression (Johnson et al., 1997), schizophrenia (Townsend et al., 2001), pain disorder (Sjogren et al., 2000), epilepsy (Prevey et al., 1998), attention deficit hyperactivity disorder (Schweitzer et al., 2006),

systemic lupus erythematosus (Shucard et al., 2004), cancer (Sjogren et al., 2000), and asthma (Weersink et al., 1997).

1.4.2 Factors influencing the PASAT performance

The PASAT has acquired a reputation of being an aversive and frustrating task regardless of examinee's cognitive status (Roman et al., 1991; Lezak, 1995; McCaffrey et al., 1995; Holdwick & Wingenfeld, 1999; Fos et al., 2000; Aupperle et al., 2002; Diehr et al., 2003; Strauss et al., 2006). The presentation tempo during the PASAT is pressurized, making the task stressful, therefore also noncognitive factors such as frustration (Lezak, 1995; Strauss et al., 2006) or depression (Thornton & Raz, 1997; Arnett et al., 1999) may interfere with performance. Consequently, the task has been used experimentally to induce stress (Lejuez et al., 2003; Feldner et al., 2006) and to increase fatigue (Johnson et al., 1997). Therefore, modifications of the traditional PASAT such as short forms or Adjusting-PSAT may be helpful in reducing discomfort and effects of possible fatigue by shortening the task.

Results on the effects of demographic variables on the PASAT performance have been partly contradictory. In some studies (Diehr et al., 1998; Diehr et al., 2003; Amato et al., 2006a) education has been found to be a significant predictor of PASAT performance, while in other studies (Brittain et al., 1991; Wiens et al., 1997) the effects of education have remained marginal. On the other hand, the intelligence quotient (IQ) has consistently been found to be a critical factor to the PASAT performance (Egan, 1988; Brittain et al., 1991; Deary et al., 1991; Roman et al., 1991; Sherman et al., 1997; Wiens et al., 1997; Crawford et al., 1998). Age is related to the PASAT performance in most samples; the majority of investigations have documented performance levels declining with age (Brittain et al., 1991; Roman et al., 1991; Wiens et al., 1997; Diehr et al., 1998; Diehr et al., 2003), especially after age 50 (Roman et al., 1991). The exceptions to this trend are studies involving young adults, those however may suffer from too limited an age range (Ward, 1997; Wingenfeld et al., 1999). As for the effect of sex a consistent finding has been that there are no clear and clinically meaningful differences between genders in the PASAT performance (Brittain et al., 1991; Wiens et al., 1997; Wingenfeld et al., 1999; Diehr et al., 2003).

Special concerns about significant practice effects of the PASAT have widely been noticed both in normal and in neurologically impaired subjects (Gronwall, 1977; Dyche & Johnson, 1991; McCaffrey et al., 1995; Schächinger et al., 2003; Beglinger et al., 2005; O'Jile et al., 2006), including patients with MS (Bever et al., 1995; Johnson et al., 1997; Cohen et al., 2000; Fischer et al., 2000; Patzold et al., 2002; Beatty et al., 2003; Barker-Collo, 2005; Benedict, 2005; Nagels et al., 2008). Additionally, plenty of evidence exists to suggest that performance on the PASAT is affected by mathematical ability (Gronwall & Wrightson, 1981; Sherman et al., 1997; Chronicle & MacGregor, 1998; Tombaugh et al., 2004; Wills & Leathem, 2004).

1.4.3 The PASAT performance among MS patients

Because the PASAT is assumed to measure especially information processing efficiency and attention (Lezak, 1995; Strauss et al., 2006), the key characteristics of MS-related cognitive decline, it has been used widely with MS patients, and it is viewed as one of the most important measures of cognitive dysfunction in multiple sclerosis (Benedict et al., 2002). Repeatedly the PASAT has been recommended to be used as a component of neuropsychological test battery in MS patients; it was in its entire form included in the above mentioned core battery of neuropsychological tests (Peyser et al., 1990), as well as in its 2.0 s and/or 3.0 s interstimulus form in the briefer cognitive tests batteries, such as in NPSBMS (Rao et al., 1991a), BRB (Rao & Society, 1990; Bever et al., 1995), MACFIMS (Benedict et al., 2002), and in battery introduced by Beatty (1999). The PASAT-3 has also been recommended as a core measure in clinical trials involving MS patients (Rudick et al., 1997; Cutter et al., 1999). Commonly, the PASAT has been used as a part of neuropsychological examination among other neuropsychological tests (Rao et al., 1991a; DeLuca et al., 1993; Kujala et al., 1995; D'Esposito et al., 1996; Kujala et al., 1997; Rovaris et al., 1998; Fischer et al., 2000).

The fMRI and the PET studies conducted on healthy subjects have revealed an increased activation during the PASAT performance in great number of neural systems; especially the anterior cingulate, frontal, superior temporal, and parietal cortices, cerebellum, and white matter tracts connecting them (Lockwood et al., 2004; Mainiero et al., 2004; Audoin et al., 2005; Forn et al., 2008). MS subjects have found to have a

different pattern of cerebral activation during their PASAT performance, recruiting more brain regions (mainly from frontal brain areas) than healthy controls (Staffen et al., 2002; Audoin et al., 2003; Mainero et al., 2004; Forn et al., 2006). This has been interpreted as an evidence of neuronal plasticity to compensate for the presence of demyelinating pathology (Staffen et al., 2002; Audoin et al., 2003; Mainero et al., 2004; Forn et al., 2006) and regarded as one explanation for cognitive fatigue causing temporary decline in cognitive performance (DeLuca, 2005).

In crosssectional studies, MS patients have consistently had impaired performance on the PASAT relative to healthy controls (Litvan et al., 1988b; DeLuca et al., 1993; Kujala et al., 1995; Diamond et al., 1997; Fisk & Archibald, 2001; Benedict et al., 2004b; Deloire et al., 2005; Lengenfelder et al., 2006; Solari et al., 2007). Only few studies without this finding have been published (Fisk & Archibald, 2001; Staffen et al., 2002; Audoin et al., 2003). It also been suggested, that even if MS patients do not perform more poorly than healthy controls on the PASAT, the fact that they require additional cerebral activation to achieve the same result implies altered processing capacity (Staffen et al., 2002; Audoin et al., 2003; Feinstein, 2007). In longitudinal studies, stability (Hohol et al., 1997; Kujala et al., 1997; Sperling et al., 2001; Camp et al., 2005) as well as decrease (Kujala et al., 1997; Zivadinov et al., 2001a; Ozakbas et al., 2005) in MS patients' PASAT performance over time has been noticed.

MS patients' reported dropout rates in this stressful and emotionally demanding PASAT test have been substantial; 17% of patients refusing to attempt the test and 6% of patients quitting in mid-administration (Aupperle et al., 2002). Moreover, cognitive fatigue may reflect to MS patients' PASAT performance (Schwid et al., 2002; Schwid et al., 2003; Nagels et al., 2008). The findings about the effects of depressive symptoms to MS patients' PASAT performances have partly been contradictory; general depression ratings have not been found to relate to performance (Johnson et al., 1997), but still it has been concluded that clinically significant depression increases the severity of information processing slowness and working memory deficits as measured by the PASAT (Thornton & Raz, 1997; Arnett et al., 1999; Demaree, Gaudino, & DeLuca, 2003).

In addition to generally lower total score, the MS patients tend to give significantly fewer series of two (Snyder et al., 1993; Kujala et al., 1995; Fisk & Archibald, 2001;

Snyder et al., 2001; Solari et al., 2007) or more (Kujala et al., 1995) correct consecutive responses on the PASAT than healthy control subjects. They seem to "chunk" the presented information into more manageable portions by skipping items intermittently. This strategy decreases the item difficulty by circumventing the need to perform several cognitive tasks simultaneously (Snyder et al., 1993; Fisk & Archibald, 2001). Because cognitively impaired MS patients may have different patterns of responding on the PASAT than healthy controls and their manner of responding may decrease the difficulty of the task itself thereby possibly masking the real changes in performance, the concern about using only the standard scoring system has been raised (Fisk & Archibald, 2001).

1.5 Measures of neurological disability in MS

1.5.1 Validity and reliability of the measurement tool

In quantitative research, validity and reliability are the most important qualities of a measurement tool. Validity can be defined at the most basic level as the degree to which a test actually measures what it is intended to measure (Strauss et al., 2006). The major types of the validity are: 1) *content validity*, which refers to the extent to which the concepts used in the measure are in accordance with the theory, are operationalized, and cover the phenomenon in question; 2) *construct validity* is concerned with the degree to which a particular measure relates to other measures used in measuring the same concept; 3) *criterion-related validity*, in which the value indicated by the measure is compared with the value which serves as a criterion for the validity (Leong & Austin, 1996). Other validity subtypes, including convergent, divergent, predictive, treatment, clinical, and face validity, are subsumed within these three domains (Strauss et al., 2006). In fact, the validity can be seen as an unitary concept: the validity types mentioned above are very often interrelated (Leong & Austin, 1996).

Reliability refers to the extent to which a test is measuring an attribute in a consistent and repeatable way (Leong & Austin, 1996). Different types of reliability can be determined: consistency or homogeneity of the test within itself (*internal consistency*), consistency or stability over time (*test-retest or intrarater reliability*),

consistency across alternate forms (*alternate form reliability*), and consistency across raters (*interrater reliability*) (Strauss et al., 2006).

1.5.2 Clinical measurement tools in MS

The severity of MS is usually assessed by the use of functional scales that measure the degree of impairment or disability. Because the interest to test potential medical therapies in MS has increased also the trial design has become more important. However, clinical outcome assessment in multiple sclerosis is challenging due to the diversity and fluctuating nature of MS symptoms. Precise and universally accepted assessment tools for use in clinical trials have been difficult to develop. A number of rating scales exist to assess the degree of disability in patients with MS. The most important of these and widely used is the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The EDSS measures MS-related impairment of eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel / bladder, visual, mental functions, and other. However, a number of limitations have been identified in the use of EDSS and the major problems relate to standardization, sensitivity, reliability, and interrater variability. Furthermore, it focuses on locomotor function, while other key clinical dimensions of MS, such as cognitive functions, remain inadequately assessed (Whitaker et al., 1995).

In 1994 as a response to perceived difficulties with the EDSS the USA National Multiple Sclerosis Society sponsored an international workshop to review and evaluate the variety of outcome tools then available for use in MS (Whitaker et al., 1995). After comprehensive research the Task Force developed a new scale, the Multiple Sclerosis Functional Composite (MSFC) based on analyses of pooled data from natural progression studies and from placebo groups in clinical trials (Rudick et al., 1997; Cutter et al., 1999). The MSFC was not designed to comprehensively assess all possible treatment effects in cognitive or physical functions (Fischer, 2003). The cognitive test to be included in the MSFC would, at best, be one that could identify large beneficial or adverse effects of a treatment, but not necessarily effects that are subtle or effects in domains not covered by the instrument (Fischer, 2003). The PASAT had several features that made it recommendable for this purpose: it is brief, multidimensional, it

taps the key characteristics of MS-related cognitive dysfunction which also are vulnerable to deterioration over time (Fischer, 2003), and its sensitivity to treatment effects had already been demonstrated in several MS trials (Smits et al., 1994; Fischer et al., 2000; Cohen et al., 2002). Consequently, the one trial PASAT-3 was included as a cognitive measure into the MSFC. In addition to PASAT, the MSFC comprises of a quantitative test of leg function and ambulation, the Timed 25-Foot Walk (TWT), and a test of arm function, the Nine-Hole Peg Test (9HPT) (Rudick et al., 1997; Cutter et al., 1999).

The Task Force recommended the MSFC be included in future MS trials, and suggested further validation studies be carried out (Rudick et al., 1996, 1997; Cutter et al., 1999). Previously, the MSFC's validity has been studied by examining correlations with the EDSS (Cutter et al., 1999; Cohen et al., 2000; Kalkers et al., 2000; Cohen et al., 2001), with disease type and course (Kalkers et al., 2000), with MRI parameters (Kalkers et al., 2001a, 2001b; Rudick et al., 2001), and with patients' self-reported symptoms and quality of life (Miller et al., 2000). No investigations have previously been carried out to evaluate how the abbreviated version of the PASAT used as a part of the MSFC relates to a comprehensive neuropsychological assessment.

2 AIMS OF THE STUDY

The basic aims of the present study were to determine a) the frequency, characteristics, and evolution of cognitive impairment among relapsing-remitting MS patients, and b) the validity and reliability of the PASAT in measuring cognitive performances in MS patients.

Specifically, aims were to determine:

1. The frequency, characteristics, and change in one-year follow-up of cognitive impairment among relapsing-remitting MS patients (Studies I and III)
2. PASAT's sensitivity and specificity in detecting MS-related cognitive dysfunction (Study I)
3. MS patients' responding patterns on the PASAT (Study II)
4. The effect of different scoring methods on PASAT's sensitivity and specificity in detecting MS-related cognitive dysfunction (Study II)
5. PASAT's susceptibility to change in one-year follow-up (Study III)
6. PASAT's intrarater and interrater reliability and practice effects in weekly assessments (Study IV)

3 METHODS

3.1 Subjects

Originally a letter of invitation describing the study was mailed to 62 relapsing-remitting MS patients who were diagnosed and treated at the Department of Neurology, Seinäjoki Central Hospital. Forty-five of them (73%) expressed interest in participating in the study. All patients met the criteria of clinically definite MS according to Poser et al. (1983) and patients with a history of drug or alcohol abuse, a psychiatric disorder, acute relapses, or nervous system disorder other than MS were excluded. All 45 patients who agreed to participate and were assessed at baseline were also assessed a year later, there were no drop-outs. Forty-four of the patients received betainterferon treatment at the baseline and 42 at the follow-up study. Subjects in the control group were staff of Seinäjoki Central Hospital, or friends, acquaintances, or nonblood relatives of the MS patients who volunteered for the study. Exclusion criteria for the controls were the abuse of drug or alcohol, psychiatric history, or any neurological disease. To verify the information obtained from both patients and controls regarding their past medical history, all available hospital records were examined. The subjects of the present study (studies I, II, and III) were hence 45 relapsing-remitting multiple sclerosis patients and 48 healthy controls. The detailed demographic and clinical characteristics of all subjects are presented in Table 3.

In study IV, the subjects were 10 clinically definite relapsing-remitting MS patients who met the criteria by Poser et al. (1983) and 10 healthy controls. Exclusion criteria for the patients and for the controls were the same as above. The patient group was statistically comparable with controls with respect to age ($p = 0.912$), gender ($p = 1.0$), and education ($p = 0.853$).

The study protocol was approved by the Ethics Committee of Seinäjoki Central Hospital. All subjects took part in the studies voluntarily and provided a written informed consent before participating.

Table 3. Demographic and clinical characteristics of the MS and control groups at baseline

Descriptive variables	MS (<i>n</i> = 45)	Controls (<i>n</i> = 48)	<i>P</i> -value for significance between groups #	Cognitively impaired MS (<i>n</i> = 19)	Cognitively intact MS (<i>n</i> = 26)	<i>P</i> -value for significance between groups *
Age in years, mean (range, SD)	42.7 (22-56, 8.3)	42.3 (25-54, 7.4)	0.786	43.5 (27-56, 7.8)	42.2 (22-55, 8.7)	0.815
Sex (Female / Male)	33 / 12	33 / 15	0.627	15 / 4	18 / 8	0.691
Education in years, mean (range, SD)	13.1 (8-25, 3.5)	13.2 (8-18, 2.5)	0.852	12.5 (9-19, 3.2)	13.5 (8-25, 3.7)	0.545
BDI, mean (range, SD)	8.8 (0-30, 7.7)	2.7 (0-19, 4.3)	< 0.001	11.7 (0-30, 9.3)	6.6 (0-20, 5.5)	0.001 ^a
Nervousness Questionnaire, mean (range, SD)	11.2 (1-36, 9.8)	6.0 (0.9–24.8, 5.7)	0.004	10.4 (1-36, 10.8)	11.7 (1-35.8, 9.1)	0.007 ^c
15D, mean (range, SD)	0.82 (0.51-0.96, 0.11)	0.96 (0.82-1.0, 0.04)	< 0.001	0.76 (0.51-0.94, 0.1)	0.86 (0.68-0.96, 0.1)	< 0.001 ^{a,b}
Current employment status						
Employed	15	45	-	3	12	-
Half-time employed	8	-	-	1	7	-
Student	1	1	-	-	1	-
Unemployed	1	1	-	1	-	-
Retired	20	1	-	14	6	-
EDSS, mean (range, SD)	2.9 (0-7, 1.6)	-	-	3.7 (1-7, 1.9)	2.3 (0-4, 1.0)	0.01 ^b
Years since the onset of first symptoms, mean (range, SD)	12.9 (1-34, 7.6)	-	-	14.2 (4-34, 7.8)	11.9 (1-28, 7.5)	0.319
Disease duration (years), mean (range, SD)	9.0 (1-27, 6.0)	-	-	10.7 (2-27, 6.9)	7.9 (1-22, 5.1)	0.185
Age at onset MS (years), mean (range, SD)	34.6 (17-50, 9.1)	-	-	34.1 (18-50, 9.8)	34.9 (17-48, 8.7)	0.755
The number of relapses during the last year, mean (range, SD)	0.7 (0-4, 1.1)	-	-	0.6 (0-3, 1.0)	0.8 (0-4, 1.2)	0.725
Time (months) since the last relapse, mean (range, SD)	27 (1-192, 33.5)	-	-	32.8 (3-192, 45.4)	22.6 (1-66, 20.4)	0.803

SD = Standard deviation; BDI = Beck Depression Inventory; 15D = Self-reported Quality of Life Questionnaire; EDSS = Expanded Disability Status Scale.

#Statistical comparisons are conducted between MS patients and controls.

*Statistical comparisons are conducted between controls, cognitively impaired, and intact MS patients. In disease variables between cognitively impaired and intact MS patients.

^aControls ≠ impaired and intact. ^bImpaired ≠ intact. ^cControls ≠ intact.

3.2 Clinical and neuropsychological tests

Clinical and neuropsychological methods used in the study are introduced in Table 4. An extensive neuropsychological examination was conducted for each subject in a session lasting 120 to 180 minutes. The test battery was designed to assess a wide range of cognitive abilities previously found to be impaired in MS patients. These tests were grouped into six categories according to the functions they are traditionally taken to measure (Lezak, 1995), the analysed variables and subgrouping can be seen in Table 5. The reliability of the model (internal consistency) was confirmed by computing Cronbach's alpha for all six cognitive domains: information processing and attention ($\alpha = 0.84$, 95% confidence interval (CI) = 0.79-0.89), memory and learning ($\alpha = 0.90$, 95% CI = 0.87-0.93), visuospatial abilities ($\alpha = 0.74$, 95% CI = 0.64-0.82), executive functions ($\alpha = 0.68$, 95% CI = 0.57-0.77), language functions ($\alpha = 0.66$, 95% CI = 0.53-0.76), and arithmetic functions ($\alpha = 0.86$, 95% CI = 0.78-0.90).

Table 4. Clinical and neuropsychological methods used in the study

1) Cognitive tests

WMS-R (Wechsler, 1987) / Logical Memory and Visual Reproduction
List Learning of 15 Words (Äikiä et al., 1995)
Rey Osterrieth Complex Figure Test (Osterrieth, 1944)
Immediate and Delayed Recall, and Naming Time of 20 Objects (Kujala et al., 1994; Portin et al., 1995)
Trail-Making A and B (Army, 1944)
Stroop (Stroop, 1935)
WAIS-R (Wechsler, 1981) / Digit Span, Arithmetic, Similarities, Picture Completion, Block Design, Digit Symbol
Test of Everyday Attention (TEA) (Robertson et al., 1994) / Elevator Counting and Elevator Counting with Distraction
Dual Task Performance (Vilki et al., 1996)
Rey Osterrieth Complex Figure Test (Osterrieth, 1944)
Wisconsin Card Sorting Test (WCST) / Nelson's Modified Version (Nelson, 1976)
Semantic (animals) and Phonologic (s-words) Verbal Fluency (Lezak, 1995)
Visual Fluency (Korkman et al., 1998)
Basic Calculations (Ministry of Labour, 1969)

2) Questionnaires

Beck Depression Inventory (BDI) (Beck et al., 1961)
Self-reported Quality of Life Questionnaire (15D) (Sintonen, 2001)
Nervousness Questionnaire

3) Clinical measurements

Expanded Disability Status Scale (EDSS) (Kurtzke, 1983)
Multiple Sclerosis Functional Composite (MSFC) (Rudick et al., 1997; Cutter et al., 1999)
- Timed 25-Foot Walk (TWT)
- Nine-Hole Peg Test (9HPT)
- Paced Auditory Serial Addition Test (PASAT)

WMS-R = Wechsler Memory Scale-revised; WAIS-R = Wechsler Adult Intelligence Scale-revised.

Neurovegetative symptoms of depression have previously been suggested to overlap with MS symptoms, resulting in a false identification of patients as depressed when in fact they only show a high degree of MS symptomatology (Arnett et al., 1999). Therefore a depression score of the BDI without the overlapping symptoms (sleep disturbance, fatigue, lack of appetite, and sexual dysfunction) was calculated.

The questionnaire on self-reported nervousness was designed for the purposes of this study. This questionnaire consisted of five questions (each scored by a 10-cm VAS scale from "not at all" to "considerably") about general tendencies to suffer from stress in social situations, thought-blocking nervousness, and test anxiety. The specific items were: 1) I have a tendency towards mental "blocks" (the thought process blocks) in stressful situations, e.g. in past school exams; 2) I often get fidgety in social situations; 3) I easily get nervous in different situations (e.g. sweating, heart pounding, ear ringing); 4) I was anxious during this assessment; and 5) I feel that my nervousness impaired my performance in tests during this assessment. The total score was formed by summing the five ratings (maximum score 50). Cronbach's alpha for the nervousness questionnaire in the sample was 0.90 (95% CI = 0.87-0.93).

3.3 Procedure

The subjects were examined during early spring 2002 (baseline) and early spring 2003 (follow-up). The methods used in the study (studies I, II, and III) were the same at baseline and at one-year follow-up and are described in Table 4. The author evaluated each subject individually and same experienced neurologist (Keijo Koivisto) assessed all patients with the EDSS and with the motor components of the MSFC (TWT and 9HPT). All subjects participated in the follow-up study.

In study IV, all subjects were examined with the MSFC five times in early spring 2003. During four-week period the subjects underwent five testing sessions spaced one per week, last two on the same day. The time interval between the last two testing sessions was about 15 minutes. The subjects were tested on the same day each week, about the same time of the day and in the same or comparable physical environment. To obtain interrater reliability data, the MSFC was administered by another examiner

during the fifth session. Both examiners were licensed psychologists. A neurologist determined the EDSS scores for the patients on their first visit.

3.4 Statistical analyses

When the performance of two groups was compared, Pearson's χ^2 -test, Mann-Whitney *U*-tests, and Student's *t*-tests were used. When performance of three groups was compared the analysis of variances (ANOVA) and the Kruskal-Wallis tests were used. The Tukey honest significance difference test was used for post hoc pairwise comparisons following ANOVAs and Mann-Whitney comparisons following Kruskal-Wallis tests. The distributional properties of the variables were evaluated using graphical histograms and Kolmogorov-Smirnov test of normality.

The analysed variable of the PASAT was the number of correct (maximum score 60) responses. In study II also missing, and erroneous responses, dyad scores (maximum score 59), and percent dyad scores were determined. The percent dyad score is the proportion of the total correct responses accounted for by the dyads (two consecutive correct answers) and it was calculated using the following formula: $(1 - (\text{total correct score} - \text{dyad score}) / \text{total correct score}) \times 100$.

To identify the cognitively impaired patients, the raw cognitive test scores of the comprehensive neuropsychological examination were first converted to standardized residual scores. The technique was adapted from Rao (Rao et al., 1984, 1991a) to correct for individual differences in premorbid cognitive ability. The demographic variables for both patients and controls (age, sex, and education) were entered in a linear regression model with the 34 cognitive test variables (all except the PASAT). A product of these analyses, the standardized residual score, represents the difference between subjects' predicted and actual test scores. The fifth percentile of residual scores of controls was used as a cut-off point for defining the subjects who "failed" each test. The summary index for each subject was the total number of the failed tests. The fifth percentile of the controls' summary indices (seven or more failed tests) served as a cut-off for defining a subject as "cognitively impaired".

To evaluate PASAT's sensitivity and specificity, a receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cut-off point for the correct PASAT score (Barr, 1997; Zou et al., 1997). This was defined as the score with the greatest combined sensitivity and specificity by 1:1 weighting. Using this cut-off point, subjects were classified as either passed or failed on the PASAT performance. Cognitive impairment was determined by using the summary index of the comprehensive neuropsychological examination.

In study I, a composite score for each of the six different cognitive domains was determined by calculating the average of the standardized residual scores under each domain. Scores were first transformed so that a larger value always indicated better performance.

In study III, the longitudinal change in cognitive performance of the three groups (cognitively impaired MS patients, intact MS patients, and controls) was analysed by comparing the difference in test results between the initial (baseline) and follow-up examinations. The difference was calculated for every subject, and the means of the three groups were compared using the ANOVAs and the Kruskal-Wallis tests. The difference between neuropsychological testing sessions within groups was compared using paired samples *t*-tests and Wilcoxon matched pairs signed tests. Linear regression analysis was used to identify independent factors associated with the change in the PASAT scores. Furthermore, some correlation analyses were carried out.

In study IV, because of variable practice effects during the first testing sessions, intrarater reliability was evaluated by using the intraclass correlation coefficient (ICC) for session 3 vs. session 4. Interrater reliability was evaluated by using the ICC for session 4 vs. session 5. Repeated measures multifactorial analysis of variance, group (MS patients/controls) as a between-subject and the PASAT at repeated testing sessions as a within-subject factor, was used to examine the potential change in the performance over time. Comparisons between the patients' fifth test result with each of the preceding ones were examined using repeated measures analysis of variance with simple contrast. The variability of the PASAT was examined by first subtracting the smallest value from the largest across all sessions for each subject, and then calculating the percentage of this difference with reference to a maximum score of 60.

The statistical analyses were conducted by using the StatsDirect Statistical Software (StatsDirect, 1990-2002) for the ROC Curve analyses and the SPSS Statistical Software (SPSS, 1989-2003) for all other analyses.

4 RESULTS

4.1 The cognitive performance of relapsing-remitting MS patients (Studies I and III)

4.1.1 The frequency and characteristics of cognitive impairment (Study I)

The purpose of study I was to evaluate the frequency and characteristics of cognitive impairment among RRMS patients using a comprehensive neuropsychological examination. Results of cognitive tests for patients with MS and controls are shown in Table 5. In 12 of the 34 cognitive tests, performance of the control group was significantly better than that of the MS group and in 9 of these tests the effect sizes were large ($d \geq 0.80$). The greatest differences in the means between the groups were found in the following tests: Trail-Making A and B, Digit Symbol, WMS-R Visual Reproduction (immediate recall), Rey Osterrieth Complex Figure Test Rey (delayed recall), WCST (perseverative responses), Phonologic Fluency, and Naming Time of 20 Objects. Also on the PASAT, the patients differed significantly from the controls (mean 39.6 ± 12.2 vs. 47.9 ± 10.2 , respectively, $p < 0.001$, Cohen $d = 0.74$).

A significant difference between composite standardized residual score means among MS patients and controls was observed in all six cognitive domains (information processing and attention, $p < 0.001$; memory and learning, $p < 0.001$; visuospatial functions, $p < 0.001$; executive functions, $p < 0.001$; language functions, $p < 0.001$; arithmetic functions, $p = 0.004$). Figure 2 depicts MS patients' test profile in different cognitive domains relative to controls using the subtraction of groups' standardized residual scores.

MS patients failed a significantly greater number of the 34 cognitive tests than controls (mean 7.1 ± 5.9 vs. 1.4 ± 1.9 , respectively, $p < 0.001$). Applying the fifth percentile of controls' summary indices as a cut-off point (seven or more failed tests), 19 MS patients and three controls were classified as cognitively impaired. Therefore, in this patient sample, the frequency rate of cognitive dysfunction was 42%.

Table 5. Results of cognitive testing for multiple sclerosis (MS) patients and controls: raw score means, standard deviations, and the number of patients failing each test. The number of controls failing each test was set at the fifth percentile ($n = 2$)

Cognitive function and test	MS ($n = 45$)	Number of patients failing	Controls ($n = 48$)	<i>P</i> -value for difference between groups *	Cohen <i>d</i>
Information processing and attention					
Trail-Making A (time) (Army, 1944)	38.7 $\pm$ 16.7	18	26.5 $\pm$ 7.5	< 0.001*	1.02
Trail-Making B (time) (Army, 1944)	95.4 $\pm$ 44.1	21	66.9 $\pm$ 15.6	< 0.001*	0.97
Stroop (Stroop, 1935) (colour/word interference-time)	60.8 $\pm$ 18.2	15	50.1 $\pm$ 10.3	0.002	0.76
WAIS-R (Wechsler, 1981)					
Digit Span	13.6 $\pm$ 2.7	3	15.0 $\pm$ 3.2	0.05	0.47
Digit Symbol	46.3 $\pm$ 13.1	21	59.2 $\pm$ 11.6	< 0.001*	1.05
TEA (Robertson et al., 1994)					
Elevator Counting	6.7 $\pm$ 0.7	9	7.0 $\pm$ 0.2	0.02	0.68
Elevator Counting with Distraction	6.5 $\pm$ 3.2	8	7.4 $\pm$ 2.3	0.28	0.33
Dual Task Performance (Vilkkii et al., 1996) (larger percentage dual task impairment)	51.9 $\pm$ 16.8	10	45.3 $\pm$ 10.8	0.09	0.48
Memory and learning					
WMS-R (Wechsler, 1987) / Logical Memory					
Immediate recall	27.3 $\pm$ 6.1	8	31.0 $\pm$ 5.4	0.003	0.64
Delayed recall	23.1 $\pm$ 7.8	12	28.1 $\pm$ 5.0	0.003	0.79
List Learning of 15 Words (Äikiä et al., 1995)					
Total immediate recall	37.3 $\pm$ 7.8	8	41.4 $\pm$ 6.6	0.006	0.57
Delayed recall	7.1 $\pm$ 3.5	12	9.0 $\pm$ 2.6	0.1	0.63
Delayed recognition	27.0 $\pm$ 2.4	5	27.9 $\pm$ 1.8	0.02	0.43
WMS-R (Wechsler, 1987) / Visual Reproduction					
Immediate recall	35.3 $\pm$ 5.4	13	38.8 $\pm$ 2.2	< 0.001*	0.93
Delayed recall	24.9 $\pm$ 14.2	13	34.7 $\pm$ 6.1	0.001*	0.98
Rey Osterrieth Complex Figure Test (Osterrieth, 1944)					
Delayed recall	16.6 $\pm$ 7.0	15	22.0 $\pm$ 4.4	< 0.001*	0.95
Immediate Recall of 20 Objects (Kujala et al., 1994; Portin et al., 1995)	12.1 $\pm$ 2.3	10	13.7 $\pm$ 1.5	0.001*	0.85
Delayed Recall of 20 Objects (Kujala et al., 1994; Portin et al., 1995)	10.6 $\pm$ 3.0	7	11.8 $\pm$ 2.3	0.04	0.45
Visuospatial functions					
WAIS-R (Wechsler, 1981)					
Block Design	32.0 $\pm$ 8.7	6	37.5 $\pm$ 7.2	0.002	0.69
Picture Completion	17.0 $\pm$ 2.2	4	18.3 $\pm$ 1.9	0.003	0.64
Rey Osterrieth Complex Figure Test (Osterrieth, 1944)					
Copy	32.4 $\pm$ 3.6	11	34.4 $\pm$ 1.9	0.003	0.73
Copying time	146.7 $\pm$ 82.0	3	120.0 $\pm$ 49.5	0.04	0.41
Executive functions					
WCST (Nelson, 1976) / Nelson's Modified Version					
Correct responses	38.4 $\pm$ 6.8	0	39.8 $\pm$ 7.1	0.12	0.20
Categories completed	5.2 $\pm$ 1.7	4	5.6 $\pm$ 1.7	0.06	0.24
Perseverative responses	2.4 $\pm$ 3.0	6	1.0 $\pm$ 1.9	< 0.001*	0.58
Semantic Verbal Fluency (animals) (Lezak, 1995)	24.5 $\pm$ 6.6	2	27.7 $\pm$ 6.5	0.02	0.49
Phonologic Verbal Fluency (s-words) (Lezak, 1995)	15.9 $\pm$ 5.5	8	20.5 $\pm$ 5.9	< 0.001*	0.81
Visual Fluency (Korkman et al., 1998)	15.8 $\pm$ 4.6	9	19.2 $\pm$ 4.6	0.001*	0.74
Language functions					
Naming Time of 20 Objects (Kujala et al., 1994; Portin et al., 1995)	35.0 $\pm$ 12.9	20	24.9 $\pm$ 5.7	< 0.001*	1.10
WAIS-R (Wechsler, 1981) / Similarities	27.0 $\pm$ 3.7	6	28.1 $\pm$ 2.3	0.32	0.37
Stroop (Stroop, 1935)					
Word reading time	26.8 $\pm$ 4.8	11	23.8 $\pm$ 3.2	0.001*	0.75
Colour naming time	35.3 $\pm$ 17.5	11	29.4 $\pm$ 5.0	0.002	0.53
Arithmetic functions					
WAIS-R (Wechsler, 1981) / Arithmetic	15.3 $\pm$ 3.5	3	17.1 $\pm$ 3.6	0.008	0.51
Basic Calculations (correct responses in four minutes) (Ministry of Labour, 1969)	34.3 $\pm$ 10.0	7	40.0 $\pm$ 9.3	0.005	0.59

WAIS-R = Wechsler Adult Intelligence Scale-revised; TEA = Test of Everyday Attention; WMS-R = Wechsler Memory Scale-revised; WCST = Wisconsin Card Sorting Test. *Significant after Bonferroni correction ($p < 0.0015$). Effect sizes are indicated by Cohen *d* in which the difference between means is divided by the pooled standard deviation (patients' and controls' common standard deviation).

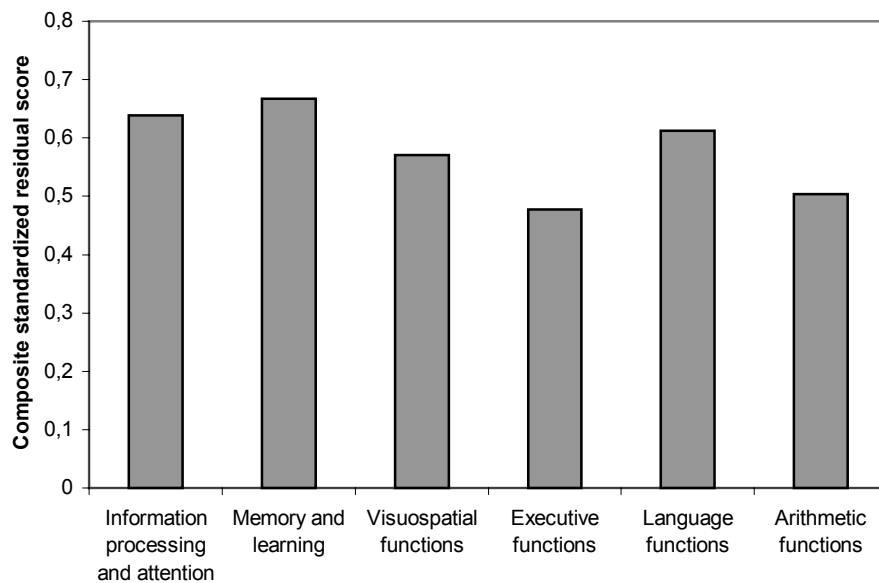


Figure 2. Multiple sclerosis patients' performance in different cognitive domains. Healthy controls' performance is set at 0. Higher values in each domain indicate greater cognitive impairment. It is noteworthy, that several neuropsychological tests included in these cognitive domains, like language functions, were time-related tests in which processing speed is a central component affecting the performance.

MS patients obtained significantly higher scores on the BDI than controls (mean 8.8 ± 7.7 vs. 2.7 ± 4.3 , $p < 0.001$). Applying the fifth percentile of normal scores ($BDI \geq 14.50$) as a cut-off, nine MS patients were classified as depressed. The depressed MS patients failed more tests than did nondepressed patients (mean 11.0 ± 8.9 vs. 6.1 ± 4.5), but this difference was not significant ($p = 0.15$). In addition, nondepressed patients had better PASAT results than their depressed peers (mean 40.2 ± 11.9 vs. 37.0 ± 13.9), but again this difference was not significant ($p = 0.43$). The results remained the same when BDI scores without neurovegetative symptoms were used.

4.1.2 The evolution of cognitive performances (Study III)

The study III aimed at evaluating the longitudinal change in cognitive functioning of RRMS patients. In this study two demographically similar MS groups, cognitively intact and impaired patients, were followed for 1 year. The healthy controls tended to improve their performance in most of the neuropsychological measures. Memory tests were especially sensitive to improvement due to repeated testing. MS patients showed

improvement in fewer neuropsychological tests than controls. Of the 35 cognitive test variables, 19 showed significant improvement within the control group, 8 within cognitively intact MS group, and only 4 within the cognitively impaired MS group (see Table 6). No significant deterioration was found in any of the tests.

As Table 6 indicates, only in the PASAT the mean change between the first and second testing session was significantly different between the three study groups ($p = 0.002$), in all other neuropsychological tests the change between the baseline and the follow-up was similar in all three groups.

Table 6. The raw scores (mean $\pm$ SD) in neuropsychological tests in the follow-up assessment in cognitively impaired, and intact MS patients, and healthy controls, comparisons of changes of the raw scores (mean $\pm$ SD) from baseline to one-year follow-up within the three groups, as well as comparison of the changes between the three groups

Cognitive function and test	1 Impaired MS (<i>n</i> = 19)	Change Raw score within Impaired MS	2 Intact MS (<i>n</i> = 26)	Change Raw score within Intact MS	3 Controls (<i>n</i> = 48)	Change Raw score within controls	<i>P</i> -value for difference between groups
PASAT (Rao et al., 1991a; Kujala et al., 1995) (three-second interstimulus)	33.0 $\pm$ 10.0	-2.5 $\pm$ 5.8	46.0 $\pm$ 10.8	3.4 $\pm$ 5.6 ^b	49.8 $\pm$ 9.0	2.0 $\pm$ 5.1 ^a	0.002 ^{1,2,3}
Information processing and attention							
Trail Making-A (Army, 1944) (time)	51.0 $\pm$ 26.2	-0.2 $\pm$ 27.4	30.2 $\pm$ 7.8	-0.2 $\pm$ 7.1	27.3 $\pm$ 7.4	-0.7 $\pm$ 7.5	0.461
Trail Making-B (Army, 1944) (time)	143.4 $\pm$ 126.8	-17.6 $\pm$ 114.9	68.7 $\pm$ 17.5	4.5 $\pm$ 17.4	61.1 $\pm$ 18.8	5.8 $\pm$ 17.3 ^a	0.255
Stroop (Stroop, 1935) (colour/word interference-time)	68.7 $\pm$ 15.8	-2.1 $\pm$ 7.6	55.2 $\pm$ 13.4	-0.4 $\pm$ 9.0	49.1 $\pm$ 11.3	1.0 $\pm$ 5.2	0.501
WAIS-R (Wechsler, 1981)							
Digit Span	12.6 $\pm$ 2.6	0.6 $\pm$ 2.2	15.0 $\pm$ 2.4	0.2 $\pm$ 2.1	15.8 $\pm$ 3.4	0.8 $\pm$ 2.4 ^a	0.556
Digit Symbol	38.9 $\pm$ 10.8	1.6 $\pm$ 5.6	53.4 $\pm$ 10.7	0.9 $\pm$ 5.5	61.0 $\pm$ 12.2	1.8 $\pm$ 3.4 ^c	0.379
TEA (Robertson et al., 1994)							
Elevator Counting	6.7 $\pm$ 0.7	0.2 $\pm$ 0.5	7.0 $\pm$ 0.2	0.1 $\pm$ 0.3	7.0 $\pm$ 0.0	0.0 $\pm$ 0.2	0.246
Elevator Counting with Distraction	6.0 $\pm$ 3.3	-0.1 $\pm$ 1.2	7.4 $\pm$ 2.7	0.5 $\pm$ 1.5 ^a	7.6 $\pm$ 2.2	0.2 $\pm$ 0.6 ^a	0.309
Dual Task Performance (Vilkkii et al., 1996) (larger percentage dual task impairment)	53.1 $\pm$ 15.5	5.4 $\pm$ 11.0	44.6 $\pm$ 11.7	2.7 $\pm$ 16.3	42.5 $\pm$ 10.1	2.8 $\pm$ 9.7	0.710
Memory and learning							
WMS-R (Wechsler, 1987) / Logical Memory							
Immediate recall	26.3 $\pm$ 5.8	0.8 $\pm$ 4.0	29.3 $\pm$ 8.0	0.8 $\pm$ 4.8	32.1 $\pm$ 6.3	1.1 $\pm$ 4.0	0.936
Delayed recall	22.6 $\pm$ 7.3	2.2 $\pm$ 5.2	26.4 $\pm$ 8.7	1.3 $\pm$ 4.2	29.7 $\pm$ 6.0	1.8 $\pm$ 3.3 ^b	0.748
List Learning of 15 Words (Äikiä et al., 1995)							
Total immediate recall	34.1 $\pm$ 8.5	0.3 $\pm$ 6.8	41.9 $\pm$ 6.6	2.0 $\pm$ 5.8	43.5 $\pm$ 7.7	2.1 $\pm$ 5.6 ^a	0.375
Delayed recall	6.4 $\pm$ 3.3	1.0 $\pm$ 2.0 ^a	8.7 $\pm$ 3.6	0.4 $\pm$ 2.6	9.8 $\pm$ 2.9	0.7 $\pm$ 1.8 ^b	0.826
Delayed recognition	26.2 $\pm$ 2.1	0.4 $\pm$ 2.5	28.5 $\pm$ 1.8	0.5 $\pm$ 1.6	28.2 $\pm$ 1.6	0.3 $\pm$ 1.6	0.501
WMS-R (Wechsler, 1987) / Visual Reproduction							
Immediate recall	30.2 $\pm$ 7.1	-1.4 $\pm$ 4.4	29.3 $\pm$ 8.0	-0.9 $\pm$ 3.9	39.0 $\pm$ 2.4	0.3 $\pm$ 2.6	0.136
Delayed recall	20.3 $\pm$ 13.5	3.6 $\pm$ 6.7 ^a	26.4 $\pm$ 8.7	2.0 $\pm$ 8.5	36.0 $\pm$ 6.6	1.4 $\pm$ 5.0 ^a	0.650
Rey Osterrieth Complex Figure Test (Osterrieth, 1944)							
Delayed recall	12.6 $\pm$ 7.3	0.5 $\pm$ 4.4	20.9 $\pm$ 5.6	1.0 $\pm$ 3.7	23.8 $\pm$ 5.3	1.8 $\pm$ 4.3 ^b	0.483
Immediate Recall of 20 Objects (Kujala et al., 1994; Portin et al., 1995)	12.1 $\pm$ 3.0	0.8 $\pm$ 2.0	13.8 $\pm$ 2.1	1.0 $\pm$ 1.9 ^a	14.1 $\pm$ 1.9	0.4 $\pm$ 1.5 ^a	0.369
Delayed Recall of 20 Objects (Kujala et al., 1994; Portin et al., 1995)	11.1 $\pm$ 2.6	1.5 $\pm$ 2.7 ^a	12.8 $\pm$ 2.9	1.5 $\pm$ 1.8 ^c	12.5 $\pm$ 2.3	0.8 $\pm$ 2.2 ^a	0.330

Executive functions

WCST / Nelson's Modified Version (Nelson, 1976)							
Correct responses	38.6 ± 6.4	1.3 ± 5.3	40.9 ± 6.6	1.8 ± 3.7 ^a	42.0 ± 4.7	2.2 ± 7.0 ^a	0.651
Categories completed	5.1 ± 1.5	0.2 ± 1.2	5.9 ± 1.7	0.4 ± 1.1	5.8 ± 1.7	0.2 ± 2.1	0.677
Perseverative responses	2.3 ± 3.8	1.0 ± 2.3	0.9 ± 1.1	0.8 ± 1.1 ^b	0.6 ± 1.3	0.4 ± 1.6	0.181
Semantic Verbal Fluency (animals) (Lezak, 1995)	21.6 ± 5.4	-0.4 ± 5.7	27.2 ± 6.0	0.9 ± 5.7	28.7 ± 7.1	1.0 ± 5.8	0.726
Phonologic Verbal Fluency (s-words) (Lezak, 1995)	15.1 ± 6.1	0.8 ± 4.7	19.2 ± 5.7	2.2 ± 3.8 ^b	21.7 ± 6.2	1.2 ± 4.5	0.503
Visual Fluency (Korkman et al., 1998)	14.1 ± 3.0	1.2 ± 3.5	18.7 ± 4.0	0.7 ± 2.7	21.2 ± 5.0	1.9 ± 3.5 ^c	0.105

Visuospatial functions

WAIS-R (Wechsler, 1981)							
Block Design	28.3 ± 7.1	2.6 ± 5.7	37.4 ± 8.2	0.9 ± 4.4	39.2 ± 7.5	1.6 ± 5.8	0.678
Picture Completion	16.6 ± 2.7	0.8 ± 1.4 ^a	18.4 ± 1.8	0.5 ± 1.4	18.9 ± 1.8	0.6 ± 1.5 ^a	0.809
Rey Osterrieth Complex Figure Test (Osterrieth, 1944)							
Copy	30.0 ± 4.1	-0.8 ± 3.4	33.8 ± 2.4	0.2 ± 3.4	34.6 ± 1.5	0.3 ± 1.8	0.907
Copying time	172.2 ± 52.6	26.7 ± 85.8	107.5 ± 30.5	1.1 ± 31.8	96.2 ± 33.9	23.8 ± 31.3 ^c	0.104

Language functions

Naming time of 20 objects (Kujala et al., 1994; Portin et al., 1995)	36.6 ± 15.1	4.2 ± 11.8	25.9 ± 11.9	4.8 ± 8.1 ^b	22.7 ± 5.2	2.2 ± 5.4 ^a	0.405
WAIS-R (Wechsler, 1981) / Similarities	25.5 ± 3.7	-0.1 ± 2.7	28.4 ± 2.8	0.3 ± 1.9	29.2 ± 2.3	1.1 ± 1.9 ^c	0.116
Stroop (Stroop, 1935)							
Word reading time	27.8 ± 4.6	1.0 ± 3.4	25.6 ± 4.2	-0.5 ± 2.7	23.2 ± 3.5	0.7 ± 2.2	0.245
Colour naming time	36.4 ± 7.3	4.7 ± 21.6	31.2 ± 4.4	-0.2 ± 2.7	29.0 ± 6.2	0.4 ± 2.6	0.622

Arithmetic functions

WAIS-R (Wechsler, 1981) / Arithmetic	13.0 ± 4.3	-0.6 ± 3.1	16.8 ± 3.6	0.3 ± 1.7	17.2 ± 3.9	0.1 ± 1.9	0.214
Basic calculations (correct responses in four minutes) (Ministry of Labour, 1969)	31.8 ± 11.3	0.6 ± 3.6	36.5 ± 9.6	0.0 ± 3.9	40.9 ± 8.6	1.2 ± 3.9 ^a	0.473

Background variables

BDI (Beck et al., 1961)	7.8 ± 4.5	3.9 ± 7.6	7.1 ± 6.1	-0.5 ± 3.5	2.8 ± 5.1	0.0 ± 2.7	0.107
15D (Sintonen, 2001)	0.79 ± 0.08	0.03 ± 0.07	0.85 ± 0.1	-0.01 ± 0.06	0.97 ± 0.05	0.0 ± 0.02	0.053
Nervousness Questionnaire	10.6 ± 8.5	-0.1 ± 9.3	13.9 ± 12.3	-2.2 ± 8.1	8.0 ± 8.1	-2.0 ± 5.7 ^a	0.746
EDSS (Kurtzke, 1983)	3.7 ± 1.6	-0.1 ± 0.9	2.2 ± 1.3	0.1 ± 0.8	-	-	0.301

PASAT = Paced Auditory Serial Addition Test; WAIS-R = Wechsler Adult Intelligence Scale-revised; TEA = Test of Everyday Attention; WMS-R = Wechsler Memory Scale-revised; WCST = Wisconsin Card Sorting Test; BDI = Beck Depression Inventory; 15D = Self-reported Quality of Life Questionnaire; EDSS = Expanded Disability Status Scale.

Sign change done when necessary that all values are in same direction; positive values indicate improvement and negative decline during follow-up.

P-value: Comparison of changes from baseline to follow-up between the three groups. In the EDSS comparison of changes from baseline to follow-up between cognitively intact and impaired patients.

^aSignificant change within the group between baseline and the follow-up study at $p < 0.05$.

^bSignificant change within the group between baseline and the follow-up study at $p < 0.01$.

^cSignificant change within the group between baseline and the follow-up study at $p < 0.001$.

4.2 PASAT's sensitivity and specificity (Study I)

Study I also examined PASAT's sensitivity and specificity in detecting MS-related cognitive impairment by using the comprehensive neuropsychological examination as the "gold standard." Special emphasis was placed on psychological factors (depressive symptoms, nervousness, limited cognitive skills) that might confound PASAT interpretation, resulting in misclassification of subjects. The optimum PASAT cut-off point for the presence or absence of cognitive impairment in patients was 40.1, with the sensitivity 74%, and the specificity 65%.

Figure 3 illustrates MS patients' performance on the summary index score and on the PASAT. Five of the 19 patients classified as cognitively impaired according to comprehensive neuropsychological evaluation were classified as cognitively unimpaired by the PASAT. These five misclassified patients had impairment on several cognitive domains, and three of them had impaired performance in language functions. However, no significant differences were found in any of the six cognitive domains between the misclassified ($n = 5$) and the correctly classified ($n = 14$) patients with cognitive impairment. Neither on the BDI (mean 6.0 ± 3.7 vs. 13.8 ± 10.0 , respectively, $p = 0.26$) nor on the nervousness questionnaire (mean 12.8 ± 13.6 vs. 9.6 ± 10.1 , respectively, $p = 0.50$) did the differences between groups reach a statistical significance. None of the five misclassified patients were depressed as assessed by using the fifth percentile of controls' BDI scores ($BDI \geq 14.50$) as a cut-off.

4.3 MS patients' responding patterns on the PASAT (Study II)

Study II aimed at evaluating and comparing the responding strategies of MS patients and healthy controls on the PASAT. As can be seen in Table 7, the MS patients produced significantly fewer correct, more missing, and more erroneous answers on the PASAT than the healthy controls. A significant difference was also found in the dyad score and the percent dyad score between the patients and the controls. Cognitively impaired MS patients had fewer correct and more missing answers on the PASAT than cognitively intact patients, but in the amount of erroneous answers the groups did not differ. A significant difference between cognitively impaired and intact patients occurred also in the dyad scores and percent dyad scores.

Table 7. The mean $\pm$ SD correct, missing, and erroneous answers on the PASAT as well as dyad and percent dyad scores firstly in MS patients and controls and secondly in cognitively impaired and intact MS patients

	MS (<i>n</i> = 45)	Controls (<i>n</i> = 48)	<i>P</i> -value for significance between groups #	Cognitively impaired MS (<i>n</i> = 19)	Cognitively intact MS (<i>n</i> = 26)	<i>P</i> -value for significance between groups *
Correct	39.6 $\pm$ 12.2	47.9 $\pm$ 10.2	< 0.001	35.4 $\pm$ 9.2	42.6 $\pm$ 13.4	0.014
Missing	14.7 $\pm$ 11.9	8.1 $\pm$ 8.6	0.002	18.7 $\pm$ 10.3	11.7 $\pm$ 12.4	0.014
Erroneous	5.8 $\pm$ 3.6	4.0 $\pm$ 3.1	0.022	5.8 $\pm$ 3.4	5.7 $\pm$ 3.9	0.791
Dyad score	27.1 $\pm$ 16.5	39.2 $\pm$ 14.9	0.001	19.7 $\pm$ 13.7	32.5 $\pm$ 16.5	0.012
Percent dyad score	61.8 $\pm$ 25.7	77.9 $\pm$ 20.0	0.001	49.7 $\pm$ 27.3	70.6 $\pm$ 20.7	0.011

#Statistical comparisons are conducted between MS patients and controls.

*Statistical comparisons are conducted between cognitively impaired and intact MS patients.

The responding profile across the PASAT's 60 items revealed that MS patients tended to give fewer correct responses at the end of the series than did the controls (Figure 4). The lack of correct responses in MS patients was mainly due to the increasing amount of missing answers at the end of the series. Same items on the PASAT were difficult for both MS patients and healthy controls, and the number of correct answers was considerably reduced when the sum of the two consecutive digits was over ten.

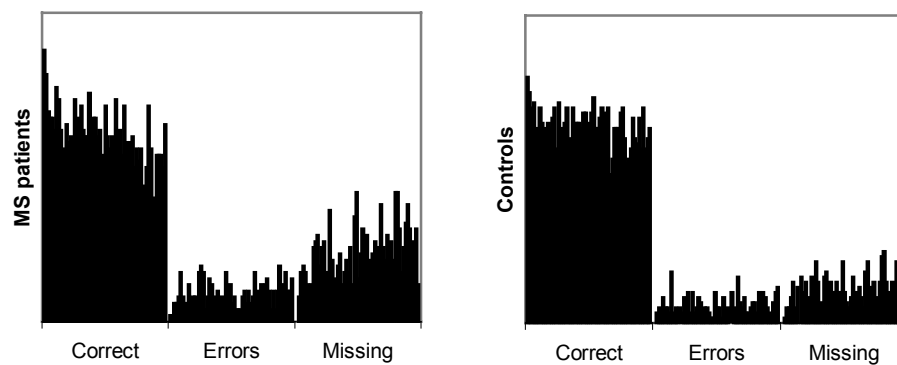


Figure 4. Multiple sclerosis (MS) patients' and controls' profile during the PASAT performance. In correct, erroneous, and missing answers the columns reflect by the amount of persons. The left side always describes the first item, and the right side the last item of the PASAT.

When the responding profile on the PASAT was examined by dividing the performance into six different deciles, the same trend of especially MS patients' declining performance towards the end of the test was seen (Figure 5). MS patients had 7.7 ± 1.1 correct answers on the first 10 items and 5.9 ± 1.0 on the last 10. Controls had 8.5 ± 0.8 correct answers on the first 10 items and 7.7 ± 0.6 on the last 10. Patients experienced an average decline in correct responses of 23.4% and controls 9.4% during the task. The difference between patients and controls in correct answers in the first 10 items was not significant ($p = 0.071$), but in the last 10 items it was significant ($p < 0.001$).

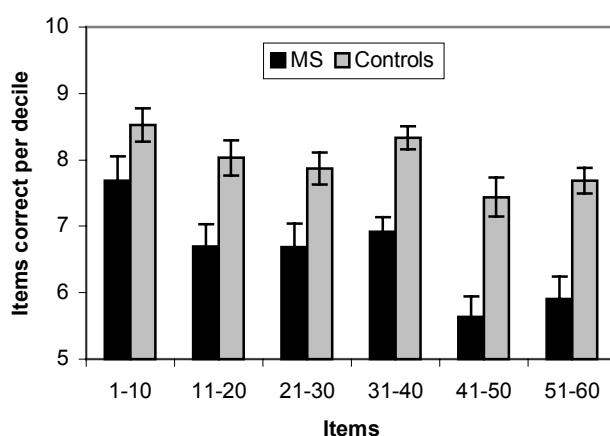


Figure 5. Mean number of items correct (standard error of the mean [SEM]) in each decile of items on the PASAT in multiple sclerosis (MS) patients and healthy controls. Correct responses declined especially in MS patients from beginning to end of the test.

4.4 PASAT's different scoring methods (Study II)

Study II aimed also at evaluating the influence of different scoring methods (standard scoring, dyad score, percent dyad score and a combination thereof) on the PASAT's sensitivity and specificity. ROC curve analyses contrasting the PASAT raw (standard) score, dyad score, and percent dyad score with the summary index to specify the presence or absence of overall cognitive disturbance in MS patient sample are shown in Figure 6. The area under the ROC curve was 0.72 in all scoring methods. The cut-off points, sensitivities, and specificities are given in Table 8.

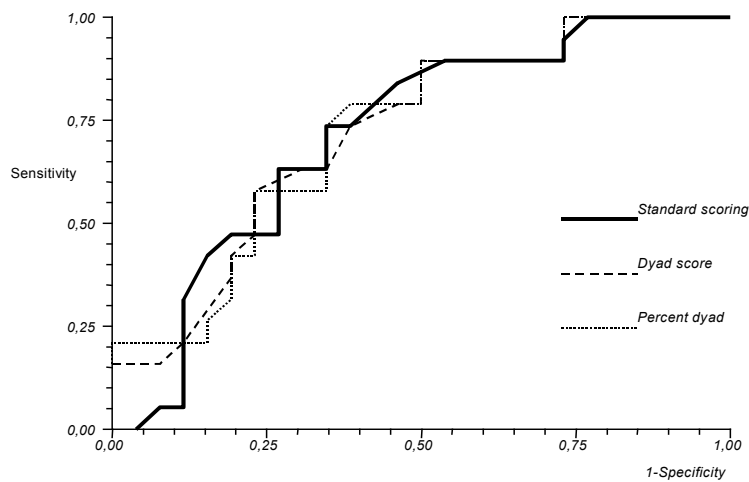


Figure 6. Receiver-operating curve (ROC) for the three PASAT scoring methods (standard scoring, dyad score, and percent dyad score methods) in differentiating between the performance of cognitively impaired and intact multiple sclerosis patients.

As the difference between the MS patients and the controls became most evident at the end of the PASAT series due to the increasing amount of the patients' missing answers, two new scoring methods were derived weighing the last answers. In the first, the missing answers at the last 20 PASAT-items were multiplied by two, and in the second the correct answers at the last 20 PASAT-items were multiplied by two and the result was added to the standard scoring. As is shown in Table 8, the percentage of cases correctly classified as cognitively impaired or unimpaired improved from 67% (dyad score and standard + dyad score) to 73% (the two methods that emphasize the end of the series). In the second new scoring method (standard score + 20 last correct

answers) also the sensitivity and specificity exceeded those of the standard scoring method.

Table 8. Sensitivity, specificity, cut-off points, and accuracy (percentage of cases correctly classified) of different scoring methods of the PASAT in detecting cognitive impairment in relapsing-remitting MS patients ($n = 45$)

Scoring method	Sensitivity %	Specificity %	Cut-off point	Accuracy %
Standard	74	65	40.1	69
Dyad score	89	50	32.1	67
Percent dyad score	79	62	69.8	69
Standard + Dyad score	89	50	76.2	67
The missing answers at the last 20 PASAT-items multiplied by two	68	77	12.0	73
Standard + (the correct answers at the last 20 PASAT-items multiplied by two)	79	69	65.2	73

4.5 PASAT's susceptibility to change (Study III)

The aim of study III was also to clarify the PASAT's susceptibility to long-term change in one-year follow-up. Of the neuropsychological test battery the PASAT was the only test in which the mean change between the first and second testing session was different between the three study groups ($p = 0.002$, see Table 6). In the PASAT, the healthy controls and the cognitively intact MS patients improved their performance, whereas the cognitively impaired patients tended to show a decline. In a pair-wise comparison the impaired group differed significantly from the controls ($p = 0.009$) as well as from the intact group on the PASAT change score ($p = 0.002$). The change score of the controls and the intact group did not differ.

In regression analyses none of the background variables, namely the change-BDI ($p = 0.836$), the change-15D ($p = 0.800$), or the change-Nervousness Questionnaire ($p = 0.784$) explained the change in the PASAT score. Additionally, no significant correlation was found between the longitudinal change in the patients' EDSS score and the change in the PASAT (whole patient group, $p = 0.402$, intact group, $p = 0.529$, impaired group, $p = 0.890$).

4.6 Reliability and practice effects of the PASAT (Study IV)

Study IV was carried out firstly to investigate PASAT's intra- and interrater reliability and secondly, to evaluate whether the short-term practice effects differ on the PASAT between MS patients and healthy controls. The third purpose of the study was to evaluate the performance variability on the PASAT in the repeated measures. PASAT's ICC for session 3 vs. session 4, the primary measure of intrarater reliability, was 0.90 (95% CI = 0.75-0.96). The ICC for session 4 vs. session 5 (interrater reliability), was 0.87 (95% CI = 0.68-0.95). Improvement was found on the PASAT across the weekly repeated testing sessions ($p < 0.001$) and this took place in both groups as the interaction (PASAT x group) did not reach statistical significance ($p = 0.559$, Figure 7A).

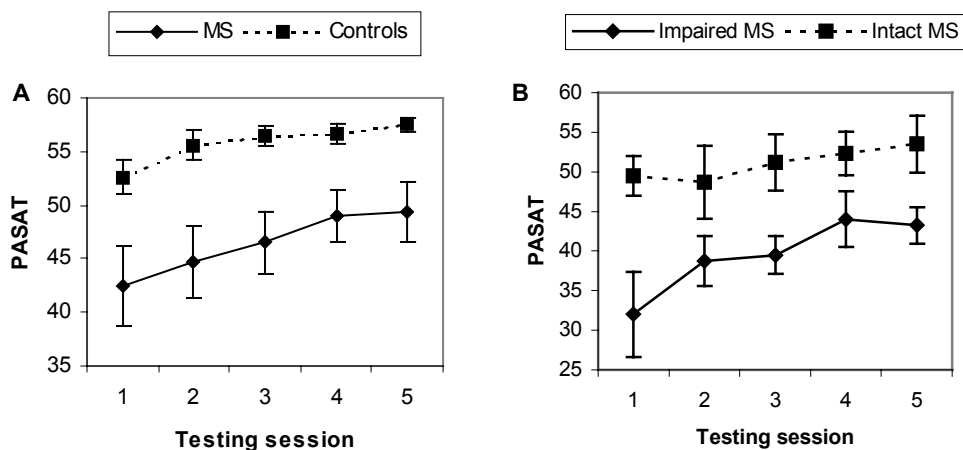


Figure 7. The mean change in raw scores of PASAT in MS patients and controls (A) and in cognitively impaired ($n = 4$) and intact ($n = 6$) MS patients (B) in repeated testing sessions (mean, SEM). Sessions 1 to 4 took place in one week's interval, sessions 4 and 5 on the same day.

The mean variability on the PASAT was 18% (range 3.3-56.7%) for the patients and 12.3% (range 3.3-23.3%) for the controls. As figure 8 illustrates, the variability appeared more noticeable among those patients, whose PASAT score was initially below 50 points than among those, who initially scored above 50. As a group the MS patients improved their performance on the PASAT steadily over the first four sessions but no longer between the session 4 and 5, whereas among the controls the most noticeable change on the PASAT scores was observed between the session 1 and 2 with less change after that (Figure 7A). In the patient group the most noticeable improvement

occurred between the session 1 and 2 in cognitively impaired patients while the improvement was more steady over sessions among cognitively intact patients (Figure 7B). In pair-wise comparisons contrasting patients' each repeated measurement to the fifth testing session, the PASAT showed significant difference for the testing session 1 ($p = 0.009$) and 2 ($p = 0.007$).

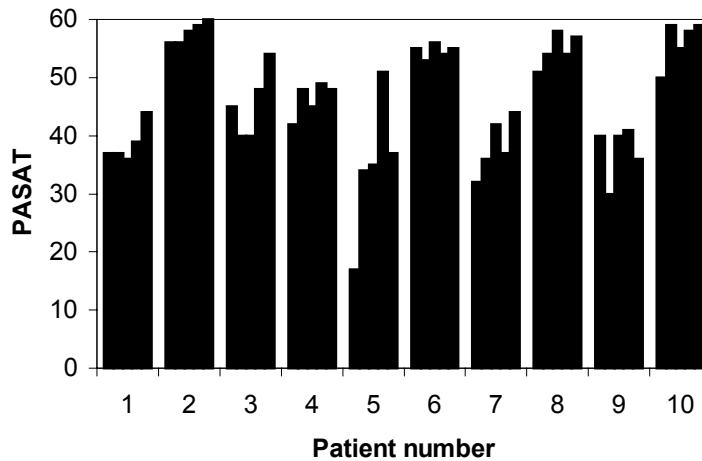


Figure 8. MS patients' individual performance profile on the PASAT during the five testing sessions (raw scores). The farthermost left bar in the blocks illustrates always the first testing session and the farthermost right bar the fifth testing session on each of the 10 patient.

5 DISCUSSION

5.1 The frequency, characteristics, and evolution of cognitive deficits among relapsing-remitting MS patients

Cognitive dysfunction is a common finding among MS patients. In the present study, 42% of relapsing-remitting MS patients were classified as cognitively impaired by a comprehensive neuropsychological test battery. However, the sample of the present study consisted of only noninstitutionalised patients with relapsing-remitting MS. Had the sample included institutionalised patients and all MS types, the frequency of cognitive dysfunction would probably have been higher. The relatively mild stage of the disease can also be seen in the EDSS scores, where 40 of 45 patients scored 5 or below at baseline and could hence walk without assistance at least 200 meters. The results are nevertheless in agreement with previous findings, which have reported cognitive dysfunction rates of about 50% for all MS patients (Rao, 1995; Fischer, 2001; Bagert et al., 2002; Bobholz, 2003). It was found that depressive features (as assessed by BDI scores with or without neurovegetative symptoms) had no statistically significant influence on cognitive functions. MS patients differed from healthy controls in every cognitive domain studied, but significant inter-individual variation was seen. Slowed information processing speed in addition to deficits in memory, learning, and attention have been proposed as key cognitive deficits in MS (Demaree et al., 1999; Archibald & Fisk, 2000; Fischer, 2001; Bobholz, 2003). This finding was replicated in the present study. In this study the formed cognitive domains (e.g. language functions) included many time-related neuropsychological tests, in which processing speed is a central component affecting the performance. Thus, cognitive slowness may have affected several cognitive functions. Probably therefore the relative difference between different cognitive domains was not as notable as generally recognized in MS (e.g. Fischer et al. 1994; Fischer, 1999, 2001; Benedict et al., 2006a).

In line with the findings of Hohol et al. (1997) no clear cognitive changes emerged in the MS group of the present study during one-year follow-up. All patients in this study were at a relatively mild stage of the disease and almost all of them received

betainterferon treatment which may have slowed the progression of cognitive decline. Disease-modifying therapies have previously been shown to inhibit inflammation factors and decrease cerebral lesion formation, and consequently probably delay the development of cognitive impairment (Bagert et al., 2002; Feinstein, 2004; Fischer et al., 2000). Methodological limitations in existing studies of pharmacological therapies has been recognized however and therefore definite conclusions about the effects of these kind of medications on cognitive performances are difficult to draw (Amato, et al. 2006b; Montalban & Rio, 2006). It is generally accepted that once cognitive dysfunction develops in a patient with MS, it does not remit. However, as pathological changes within the cerebral white and grey matters progress, both neurological and cognitive deficits are likely to emerge and increase. Neuropsychological deficits may remain stable over time (Jennekens-Schinkel et al., 1990; Mariani et al., 1991; Hohol et al., 1997; Kujala et al., 1997; Sperling et al., 2001; Piras, 2003; Camp et al., 2005), are not likely to improve but may progress instead (Feinstein et al., 1992; Amato et al., 1995; Kujala et al., 1997; Amato et al., 2001; Zivadinov et al., 2001a; Haase et al., 2004). Part of the discrepancies in the previous studies may be due to the differences in patient samples. Kujala et al. (1994, 1997) previously recommended the use of cognitively homogeneous patient groups, because if patients with varying amounts of initial cognitive impairment are grouped together, the results may be subdued and mild deterioration may not become evident during a short follow-up time. If one subgroup of patients is more physically and cognitively impaired than another after almost the same disease duration (in the present study the impaired group had slightly but not statistically significantly longer disease duration), so it implies that they have a more severe or more rapidly progressing illness. In clinical trials for example, the evaluation of the effect of immunomodulatory drugs to cognition may be problematic if the study groups are heterogeneous and include patients with both intact and impaired cognitive performance. By dividing patients into more homogeneous subgroups, as was done in the present study, it is possible to follow separately the evolution of cognitive decline in those patients who may be more susceptible to progressive cognitive deterioration, and those with more benign course. In the present study, the patients who were initially more impaired showed also more elevated scores in the depression scale, and there was a statistical trend for a difference compared to the intact MS patient group, although it

did not reach full statistical significance. In this case, the depression may have been a subtle marker for initial cognitive decline. The BDI scores tended to improve slightly in the cognitively impaired group during the follow-up, which may have then counteracted the insidious cognitive decline.

When the same or even alternative form of the same neuropsychological test is repeated, learning often occurs. In the present study among healthy controls most of the neuropsychological tests used were vulnerable to practice effects. This was especially noticeable in the memory tests, maybe in part because of the same versions of the tests were used. With the use of alternative test forms this problem has remained minor. When making clinical decisions based on the neuropsychological test results in repeated measurements among patient populations, the knowledge about the normal practice effects in tests should, thus, guide interpretations. The healthy controls tended to perform better at follow-up in more numerous cognitive tests (in 19 tests out of the 35) compared with the cognitively intact (in 8 tests) and especially with the cognitively impaired (in 4 tests) MS patients. Therefore, although the mean change in neuropsychological tests was not significantly different between the groups (except in one test, in the PASAT), a trend was seen where the MS patients were less able to improve their performance. This finding indicates that the patients were either less able to benefit from practice than the healthy controls or that the practice effect in patients was masked by a subtle decline.

5.2 Validity of the PASAT

5.2.1 PASAT's sensitivity and specificity in MS-related cognitive dysfunction

Since the pattern of cognitive impairment in MS at the individual level is heterogeneous and probably widespread, no single measurement can identify all cognitively impaired patients. The PASAT is a test mainly measuring aspects of attention and speed of information processing and it may overlook other types of deficits. In the present study, the PASAT failed to detect one-quarter of the patients who were actually cognitively impaired according to a comprehensive neuropsychological battery. However, PASAT's

overall sensitivity in detecting cognitive impairment compared with that of a comprehensive neuropsychological examination in MS patients was quite high being 74%. This indicates that the key cognitive aspects of MS-related cognitive decline were detected by the PASAT-3.

PASAT's specificity to cognitive impairment among MS patients was clearly lower than its sensitivity being 65%. This means that patients can be evaluated as cognitively impaired by the PASAT although comprehensive neuropsychological examination shows them to be intact. The PASAT has also previously been described as a highly sensitive but non-specific test (Tombaugh, 2006). One possible explanation for this is the wide network of neural systems shown to be activated during the PASAT performance (Lockwood et al., 2004; Mainero et al., 2004; Audoin et al., 2005; Forn et al., 2008). Two recent studies (Deloire et al., 2006; Younes et al., 2007) have also reported the sensitivity and specificity values for the PASAT-3: the sensitivity was 11% and 35% respectively, and specificity 100% in both of these studies. The used cut-off points for the PASAT in these studies were the lowest second percentile of patients' and the lowest fifth percentile of controls' performance, respectively. Therefore, the cut-off points were considerably lower than in the present study (in which the optimum cut-off scores were used), which probably is the main reason for the low sensitivity and high specificity. Also the determination of cognitive impairment varies across studies and may partly explain the discrepancies in the study findings.

Level of depressive symptoms did not explain the PASAT results in the present study. Instead, the patients who performed worse than expected on the PASAT had more difficulty in arithmetic tasks than those whose PASAT performance was consistent with comprehensive neuropsychological examination. The PASAT performance cannot be regarded as independent of mathematical ability, a conclusion already drawn previously (Gronwall & Wrightson, 1981; Sherman et al., 1997; Chronicle & MacGregor, 1998; Tombaugh et al., 2004; Wills & Leathem, 2004), although contradictory findings (Lockwood et al., 2004) and alternative explanations such as PASAT's primary relationship to working memory, and only secondarily to mathematical skills (Gow & Deary, 2004) exist. Interpretation of tests used in the present study to evaluate mathematical operations (WAIS-R Arithmetics and basic calculations) is many-faceted, because both tests are actually assessing characteristics

beyond single-digit math, including, e.g. higher level math, working memory, and processing speed. Therefore it can, at most, be suggested that the PASAT may include same constructs as those present in the Arithmetic subtest of the WAIS-R and basic calculations.

Moreover, subjects' tendencies for test anxiety and thought-blocking nervousness may be one reason for false-positive PASAT ratings. However, because in the present study only a brief scale was used to assess nervousness, results about the impact of self-reported nervousness on the PASAT performance can be interpreted only as indicative. They are nevertheless in line with most of previous findings and cautions suggesting the PASAT as a stressful and emotionally demanding task (Roman et al., 1991; Lezak, 1995; McCaffrey et al., 1995; Holdwick & Wingenfeld, 1999; Fos et al., 2000; Aupperle et al., 2002; Diehr et al., 2003; Strauss et al., 2006). When used for follow-up purposes, examinees may have a negative view of the PASAT, which in turn may cause frustration and nervousness. Therefore, it is essential to pay particular attention to the presentation of the test to the examinees. Encouragement and a supportive atmosphere should be emphasized. The test anxiety and poor mathematical ability may be interrelated and influence the PASAT performance, as thought-blocking nervousness may be due to poor mathematical skills and previously learned anxiety for arithmetic tasks.

5.2.2 MS patients' responding patterns on the PASAT

The present study demonstrates, and thus replicates many previous findings (Litvan et al., 1988b; DeLuca et al., 1993; Kujala et al., 1995; Diamond et al., 1997; Archibald & Fisk, 2000; Fisk & Archibald, 2001; Balzano et al., 2006; Solari et al., 2007) suggesting that MS patients show significantly poorer performance on the PASAT compared with demographically similar healthy controls. Gronwall (1977) reported that all examinees tend to make fewer errors and omissions during the first third of a PASAT trial than at the end of the series. In the present study the performance profile of MS patients and healthy controls was compared within the PASAT's 60 items, and it was found that especially the MS patients had a trend of decreasing amount of correct answers towards the end of the PASAT series. The healthy controls had quite an even performance

throughout the task. Additionally, there was no difference between patients and controls in the amount of correct answers in the first 10 items on the PASAT, but a significant difference in the last 10 items. MS patients thus seem less able to maintain the complex attention, processing speed and high performance level under pressure than healthy controls. As recently suggested (Schwid et al., 2002; Schwid et al., 2003; Nagels et al., 2008) cognitive fatigue may interfere with MS patients' performance during the PASAT task and also the PASAT-3 is long enough to bring forth this effect. The PASAT-3 therefore seems a useful tool in clinical trials where the cognitive efficiency of the patients can be an important indicator of the disease process. However, the finding is not completely consistent, because in a recent study of Solari et al. (2007) no indication of increasing difference with time attributable to fatigue was found in MS patients' PASAT performance.

The reduction of correct answers among patients was less due to increasing amount of errors than it was due to the increasing amount of omissions towards the end of the PASAT series. The same phenomenon was seen when cognitively impaired and intact MS patients were compared: the impaired patients had more omissions than the intact patients, while the amount of erroneous answers did not differ between the groups. Also in previous studies MS patients have found to have more omissions, but not more errors than healthy controls in their PASAT performance (Kujala et al., 1995; Solari et al., 2007). Therefore, cognitively impaired MS patients may be more likely to react to the task by leaving an item unanswered than by guessing and producing wrong answers. The mechanism may be that they compensate their deficits by using slower processing rates and therefore do not have enough time to respond. Already in the 1950's Sampson noticed the same phenomenon in the Visual Paced Serial Addition Task (VPSAT) (Sampson, 1956); examinees tended to react to the increase in the pacing rates with a disproportionately high increase in omissions instead of an increase in errors.

Consistent with previous findings (Kujala et al., 1995; Fisk & Archibald, 2001; Snyder & Cappelleri, 2001; Snyder et al., 2001; Solari et al., 2007) MS patients were found to give fewer correct two consecutive answers (dyads) on the PASAT than did the healthy controls. Also, cognitively impaired MS patients tended to have a lower percentage of correct responses accounted by dyads (49.7%) than did the cognitively intact patients (70.6%). This is in accordance with Snyder et al. (2001) and Coe et al.

(2005), suggesting that probably the strategy of cognitively impaired MS patients is to reduce task demands by skipping items intermittently in order to "chunk" the presented information into more manageable portions. The present study showed that also the brief and slow paced PASAT-3 version is sufficient to expose the MS patients' decreasing amount of correct answers toward the end of the PASAT series, and also the effect of cognitively impaired MS patients' skipping strategy.

5.2.3 The effect of different scoring methods on PASAT's sensitivity and specificity

The different PASAT scoring methods (standard scoring, dyad score, percent dyad score) were also compared in calculating PASAT's sensitivity and specificity in disease-associated cognitive impairment. Previously the dyad score has been found to better correlate with MRI-visible white-matter sclerotic lesions (Snyder & Cappelleri, 2001) and be more accurate in discriminating between MS disease courses (Snyder et al., 2001) than the standard scoring method. In the present study, it was found that the dyad score was slightly more sensitive, but at the same time slightly less specific, than the standard scoring in detecting the presence of cognitive impairment in a MS patient sample. The payoffs between differing sensitivity and specificity should be taken into account when considering which scoring method to use. In drug trials with repeated testing sensitivity can perhaps be favoured above specificity, whereas in clinical diagnostics the reverse may be true. Possibly with faster task presentation rates the difference between standard and dyad scoring methods would be more notable, as demonstrated recently (Gonzalez et al., 2006), but at least with the three-second inter-stimulus version, the benefit achieved by using the dyad score method seems to remain marginal. Neither in the PASAT-2 nor the PASAT-3 did the sensitivity improve by using the dyads in one recent study (Younes et al., 2007).

Due to the differences in sensitivity and specificity of the different scoring methods the possible benefit of combining these scoring methods may be worth investigating. Also, because the MS patients' tendency to fading performance at the end of the PASAT has been noted both in the present study and studies by others (Schwid et al., 2002; Schwid et al., 2003; Nagels et al., 2008), the benefits gained by taking this into

account in scoring should be explored. In this study the combination of standard and dyad score methods did not improve the results. Instead it was found that the accuracy of the PASAT in detecting cognitive impairment improved slightly when the answers at the end of the PASAT series were separately taken into account in the scoring. In all, however, the alternate scoring methods involving PASAT dyad score and its modifications did not yield significantly different findings.

5.2.4 PASAT's susceptibility to change in longitudinal setting

In the present study, it was found that the change on the PASAT during the follow-up time was different among the three study groups: the cognitively impaired MS patients showed a declining trend and differed from the healthy controls and the cognitively intact patients, who showed improvement. The change in the EDSS scores had no relationship to the change in the PASAT. Background variables such as change in mood, subjective quality of life, or nervousness did not explain the change either. The cognitively impaired patients whose PASAT performance showed a declining trend during 1 year reported even lower BDI scores at the follow-up compared with the baseline; the difference, however, was not significant. Additionally, the healthy controls reported significantly more anxiety and nervousness during the second testing session but were still able to improve their PASAT performance. As the observed difference in the PASAT change cannot be interpreted to be due to confounding factors, it can be suggested that the decline in the PASAT among impaired patients is due to disease progression.

To conclude, the criterion-related validity of the PASAT can be supported by the finding of the present study, that the PASAT offered a satisfactory sensitivity in detecting the presence of MS-related cognitive impairment. The divergent validity of the PASAT was supported by the finding that the test discriminated MS patients from healthy controls much like the other neuropsychological test did. The present finding of PASAT's susceptibility to detect change in longitudinal follow-up supported PASAT's validity for change. Lower specificity, association to arithmetic skills and to confounding factors such as test anxiety, nervousness, and fatigue as well as MS

patients' skipping strategy on the task and PASAT's practice effects (which are discussed in details in the next paragraph) reduced on their behalf its validity.

5.3 Reliability of the PASAT

In this study, the PASAT showed a intrarater reliability of 0.90 and a interrater reliability of 0.87, first excellent and second good (Strauss et al., 2006). These findings are in accordance with the previously reported high reliability values of the task: the internal consistency of the four PASAT trials has been excellent, split-half reliability varying from 0.90 (Crawford et al., 1998) to 0.96 (Egan, 1988) for original PASAT task. The reported test-retest reliability levels have varied from 0.90 for the children's PASAT version (Dyche & Johnson, 1991) to 0.93 - 0.97 for the original PASAT (McCaffrey et al., 1995) and to 0.92-0.94 for the three seconds version (Solari et al., 2005; Nagels et al., 2008). For the PASAT-3 the previously reported interrater reliability has been 0.96 (Solari et al., 2005).

The present study demonstrates and thus replicates many previous findings about significant practice effects of the PASAT in repeated testing (Bever et al., 1995; Johnson et al., 1997; Cohen et al., 2000; Fischer et al., 2000; Patzold et al., 2002; Beatty et al., 2003; Barker-Collo, 2005; Nagels et al., 2008). Clear improvement across the five sessions was seen both in the performance of the controls' as well as that of the patients'. Among patients, continuous improvement from the first PASAT testing session up to the fourth one was seen, whereas for the controls and for the subgroup of cognitively impaired patients the most significant change occurred at the beginning, from session one to session two. Originally Gronwall (1977) has concluded that there is a significant practice effect between the first and the second administration of the PASAT, but after this further practice produces only negligible improvement, a finding later supported by many (see review Tombaugh, 2006). Previously it has been suggested that three pre-baseline sessions may be needed for the PASAT-3 to compensate for the practice (Solari et al., 2005). In the present study the pair-wise comparisons suggest two pre-baseline measures for the PASAT, but the sample sizes were small and the true number of administrations needed to counteract the practice

effect may be even higher. Because the practice effects have been found to be insensitive to the duration of the test-retest interval (Baird et al., 2007) recent research has suggested that the two PASAT pre-baseline administrations can even be combined in one test session thereby reducing the required number of visits (Baird et al., 2007; Nagels et al., 2008).

The clinical implications of the results concern the appropriateness of using the PASAT in serial administrations in which scores can be unstable due to the practice effects. To separate the practice effects from the treatment effects, the use of control group is recommended in clinical trials. If the cognitive performance is comparable in the study groups, practice effects occur equally both in the treated and untreated groups. When sample sizes are small or change within individual patients is examined, the issue of practice effects still remains a serious one. In clinical settings, employing multiple pre-baseline measurements and using alternative forms might be appropriate.

Bever et al. (1995) showed PASAT's variability to vary from 22% (PASAT-3) to 26% (PASAT-2). In the present study, the variability between testing sessions on the PASAT-3 was more prominent among the MS patients (18%) than the healthy controls (12.3%). There were noticeable individual differences however, with an extreme example of variability of 56.7% between the testing sessions. This particular patient reported nervousness and distress related to the PASAT, which may have been reflected in test performance. The difference in variability between MS patients and controls may be partly due to the fluctuating nature of MS symptoms and partly to the ceiling effects of controls' performance on the test. More variability in cognitive tests has previously been found in MS patients with greater cognitive impairment (Bever et al., 1995). This notion is supported also by the results of the present study. Not only did the controls show less variability than the patients, but also within the patient group the individual variability on the PASAT performance seemed more prominent among those MS patients with lower PASAT scores compared with those with higher scores.

5.4 Methodological considerations

Certain methodological issues should be addressed when evaluating the results of these studies. The patient sample of the present study consisted of a homogeneous group of 45 noninstitutionalised patients out of the about 400 MS patients in health care district of Seinäjoki with definite relapsing-remitting MS in clinical remission at the time of the evaluations. The general characteristics of the sample follow those of wider MS populations. Firstly, the study group consisted of 33 women and 12 men, reflecting the known preponderance of women in MS. Secondly, the age at the onset of MS (34.6 years) follows the general incidence peak age of the disease and subjects under 20 or over 60 years of age were not included in the study to avoid possible influence of developmental factors or aging to cognitive performance. The patients had, however, relatively mild stage of the disease as can be seen in the EDSS scores (baseline 2.9 ± 1.6 , follow-up 2.8 ± 1.6 , study IV 2.5 ± 1.6). Therefore, the results of the current studies with mild stage of the disease and RRMS disease course are not fully applicable to all MS patients, especially to those with more disabling form of the disease or other disease courses.

Recent research has drawn attention to the need to divide the study samples into cognitively homogeneous groups to gain a better understanding of the nature and evolution of the deficits evident in individual patients (Kujala et al., 1994; Grossman et al., 1995; Ryan et al., 1996; Kujala et al., 1997; Camp et al., 2005; Hoffmann et al., 2007). This method was chosen here. Similarly to Kujala et al. (1997) the present study represents the rare longitudinal studies which have adapted the approach and therefore it sheds new light to the discussion about the evolution of MS-related cognitive decline.

The technique used in identifying cognitively impaired patients was adapted from Rao et al. (1984, 1991a) to correct for individual differences in premorbid cognitive ability. It is widely known that age, education, and sex may influence the performance on cognitive tests. Therefore, instead of using conventional *z*-scores, standardized residual scores which take into account the effect of these background variables, were applied to determine the primary cognitive capacity for each of the examinees.

The comprehensive neuropsychological examination was used as a “gold standard” to assess PASAT’s sensitivity and specificity in MS-related cognitive impairment. This assumes that the comprehensive neuropsychological examination in itself is a valid method to reflect the MS-related cognitive dysfunction. Because the used neuropsychological test battery was constructed based on the previous neuropsychological findings in multiple sclerosis and was designed to assess a wide range of cognitive abilities, it was supposed to describe accurately the cognitive decline that can be detected by psychometric neuropsychological methods.

Grouping of cognitive tests into the domains can be based on e.g. factor analysis, clinical experience, or theory. In the present study the test variables were grouped using clinical experience and Lezak’s (Lezak, 1995) theory as a guiding principle. By calculating Cronbach’s alpha for all six domains, the internal consistency and reliability of classification were confirmed. Neuropsychological tests are obviously multifactorial in nature, all of them measuring several cognitive processes. Therefore, also the used cognitive domains based on these tests are multidimensional, and partly overlapping constructs. For the purposes of this study it was necessary to have a single index, sumindex, of the numerous neuropsychological test variables. Such an index is a crude simplification of the complex nature of cognitive functions and loses information, so it was analysed only along with the composite scores and raw scores. The arithmetic functions were separated from the language or information processing and attention domains because the purpose was to examine the influence of mathematical ability on the PASAT performance independently. However, WAIS-R Arithmetic subtest is not solely a measure of arithmetic’s, but also taps components such as attention, freedom of distractibility (Lezak, 1995; Tombaugh, 2006) and working memory (Gow & Deary, 2004). Therefore an additional method for assessing basic calculation was included.

In the present longitudinal study, methodological strengths include the absence of drop-outs, the same examiner of all the subjects both in baseline and in follow-up studies, the use of a control group, extensive and clinically relevant neuropsychological test battery, and the homogeneity of the patient groups in respect to their cognitive status, physical impairment, and disease course. Still, there are some weaknesses too. The follow-up time was short, only 1 year. Although the battery of neuropsychological tests was quite comprehensive, it can never be totally exhaustive. To enable the

completion of the assessments in one session, more tests were not included however. Furthermore, in some of the statistical analyses the sample sizes were small, which may have reduced the power of the statistical comparisons. Results of the present study were, however, in line with the previous findings obtained with larger samples.

The version used affects the PASAT performance, and the results of the present study can only be applied to the PASAT-3. It also has to be taken into account that the Finnish number words are much longer than in English (three syllable word ‘kah-dek-san’ for ‘eight’ for instance). Therefore, the results of this study may not be directly comparable to studies on PASAT in other languages or cultures.

5.5 Clinical implications

The present study, together with previous findings, shows that cognitive impairment is a common disease manifestation in MS. In the present study, the frequency of cognitive dysfunction among RRMS patients was 42%. However, the cognitive status of a MS patient is difficult to evaluate without formal neuropsychological assessment and therefore deficits remain often under-recognized. The cognitive dysfunction of individual MS patient can be highly variable in regards to the characteristics, severity, and evolution of the deficits, a finding verified also in this study. No single pattern of cognitive dysfunction can be identified and therefore, a comprehensive neuropsychological examination is needed to detect MS-associated cognitive impairment.

There is an evident need of effective diagnostic, follow-up as well as clinical trial methods to evaluate these widespread, individual, and possibly progressive MS-related cognitive deficits. The PASAT has now been used for many years as a measure of processing speed, divided attention, and working memory (Lezak, 1995; Strauss et al., 2006). These cognitive deficits, especially the reduced information processing efficiency, are the key characteristics of MS-related cognitive dysfunction (Fischer, 2001; Benedict & Bobholz, 2007), as demonstrated also in this study. The evidence from the present study, together with previous findings, indicates that the PASAT is moderately sensitive to neurocognitive deficits of MS. To compensate for their

difficulties in the PASAT cognitively impaired MS patients left an item unanswered rather than guessed and produced an erroneous answer. Additionally, towards the end of the task MS patients' performance had a tendency to fade as noticed also by others (Schwid et al., 2002, 2003; Nagels et al., 2008). Therefore, the reduced cognitive efficiency and fatigue seen in MS patients can be objectively demonstrated in their PASAT performance. The PASAT was the only neuropsychological test that showed a difference in the follow-up between the study groups and was susceptible to cognitive decline observed in the cognitively impaired patients. PASAT's intra- and interrater reliability were on an excellent level. Moreover, the PASAT can be considered to have general advantages in regards to its test characteristics; it is brief, not dependent on sensorimotor functions (excluding dysarthria), has alternate forms, and yields both quantitative and qualitative data. Therefore, the PASAT can be recommended to be used as a part of a comprehensive test battery in MS patients' neuropsychological evaluation in single and in follow-up examinations for clinical and research settings and also as a sole measure of cognition in clinical trials.

However, the PASAT has also its unique set of limitations, which may make it less appropriate in certain circumstances or with certain patients. *Firstly*, patient's premorbid mathematical skills can affect the PASAT performance. Therefore, the PASAT should be used with caution if prior difficulties with mathematics are suspected. In addition to arithmetical requirements, PASAT's probable relationship to IQ and education suggests that the test may best be suited for individuals with average to above-average intellectual status (Tombaugh, 2006). *Secondly*, the PASAT can be a demanding, frustrating, and aversive task and therefore the performance was affected by test anxiety, nervousness, and thought-blocking tendencies. *Thirdly*, the task may induce fatigue. All these factors can lead to an excessively poor performance level regardless of patient's cognitive status. *Fourthly*, cognitively impaired MS patients may take advantage of the skipping strategy on the PASAT, which makes the task easier and circumvents its working memory and processing speed demands. *Fifthly*, in serial administrations the PASAT has significant practice effects and especially among patients with greater cognitive impairment the variability in performance profiles between trials can be prominent, which both make the scores unstable. In clinical trials, the use of a control group and in clinical settings, the employment of alternative forms

and multiple pre-baseline measurements can reduce the disadvantages of practice effects. And *lastly*, a one trial version, such as the PASAT-3, may suffer from ceiling or floor effects, which were observed in some subjects' individual PASAT performances and may make the PASAT-3 less appropriate for individuals with exceptionally low or high intellectual status.

The advantages and disadvantages in using the PASAT among MS patients based on the findings of the present study as well as the previous ones are summarized in Table 9.

Table 9. The use of the PASAT-3 among MS patients: main advantages and disadvantages based on the findings of the present study. Those marked *italics* are the findings of the previous studies.

Advantages	Disadvantages
1) Sensitivity	1) Lower specificity
2) Differentiates between MS patients and healthy controls as well as between cognitively impaired and intact MS patients	2) Vulnerable to effects of premorbid mathematical skills
3) MS patients' fatigue effect may be objectively demonstrated as fading performance towards the end of the performance	3) Vulnerable to effects of test anxiety and thought-blocking nervousness
4) Susceptible to detect change during follow-up	4) Vulnerable to effects of fatigue
5) Excellent intra- and interrater reliability	5) The task difficulty can be reduced by skipping strategy
-----	6) Practice effects
6) <i>Brief</i>	7) Variability in serial administrations
7) <i>Not dependent on sensorimotor functions</i>	8) Ceiling and floor effects
8) <i>Has alternative forms</i>	-----
9) <i>Yields both quantitative and qualitative data</i>	9) <i>Vulnerable to effects of dysarthria</i>

6 CONCLUSIONS

The main findings of this study were:

1) Cognitive dysfunction is a common finding among MS patients; in the present study 42% of RRMS patients were classified as cognitively impaired compared with demographically similar healthy controls. Most vulnerable cognitive functions are memory, information processing abilities, and attention skills. However, inter-individual variation is significant and the evaluation requires a comprehensive neuropsychological examination. During 1 year follow-up the cognitive performance was relatively stable among RRMS patients on a group level. However, the practice effects in cognitive tests were less pronounced among MS patients than healthy controls, suggesting the patients to be either less able to benefit from practice or that the practice effects were masked by a subtle decline in the patients.

2) The PASAT is a moderately accurate neuropsychological test in detecting MS-related cognitive impairment. The observed sensitivity to cognitive impairment was 74% and the specificity was 65%. Compared to comprehensive neuropsychological assessment 69% of patients were correctly classified as cognitively impaired or unimpaired. Misclassification of cognitive impairment was associated with self-reported nervousness and poor arithmetic skills.

3) The cognitively impaired MS patients' responding pattern on the PASAT was to leave an item unanswered rather than guess and to produce erroneous answer to compensate for their difficulties in the task. This skipping strategy may reduce and alter the demands of the task. Furthermore, towards the end of the task MS patients' performance had a tendency to fade. Therefore, the reduced cognitive efficiency and fatigue seen in MS patients can be objectively demonstrated in their PASAT performance.

4) Calculating the dyad score or the percent dyad score did not essentially increase the specificity of the PASAT compared with the standard scoring method, but the overall

accuracy improved slightly when the answers at the end of task series were weighted. Using the new, modified score, 73% of the patients were correctly classified as cognitively impaired or unimpaired.

5) The PASAT was the only neuropsychological test in the comprehensive test battery that showed a difference in the follow-up between the study groups and detected the cognitively impaired MS patients' decline. Therefore, the PASAT is a sensitive measure to show clinical change in MS patients' cognitive status.

6) The intra- and interrater reliability of the PASAT is excellent. However, the PASAT is prone to a considerable practice effect, which is a serious problem and has to be taken into account e.g. by using a control group, using alternative forms of the test or employing multiple pre-baseline measurements.

7 ACKNOWLEDGEMENTS

This study was carried out at the University of Helsinki, Department of Psychology, the Seinäjoki Central Hospital, Department of Neurology, and the Tampere University Hospital, Department of Neurology and Rehabilitation, during years 2002-2008. I wish to express my deep gratitude to all of these institutes for the opportunity to do this research which has been a great challenge for me. I am greatly indebted to Keijo Koivisto, MD, the Head of the Department of Neurology, Seinäjoki Central Hospital, for introducing me to fascinating and challenging field of MS research by offering me the initial study idea and for his contributions to this study.

I am mostly indebted to my excellent supervisors, Docent Laura Hokkanen, PhD and Docent Päivi Hämäläinen, PhD. I am deeply grateful for both of them for their insightful and patient guidance throughout these years and for sharing their expertise with me. I sincerely can say that I have been extremely lucky to have supervisors like you, I truly appreciate your thorough work! Furthermore, throughout this study they have provided me with encouragement and empathy both at moment of success and disappointment. Somehow, they always managed to convince me to keep on at it.

Professor Veijo Virsu, PhD, and all the members of his seminar group deserve my heartfelt thanks. I am most grateful to Pertti Keskivaara, MA, for his valuable support on statistical methodology.

I would like to thank my extremely skilled official reviewers Professor Ralph Benedict, PhD and Docent Iiro P. Jääskeläinen, PhD for their excellent comments on the manuscript. All the anonymous referees who have given me valuable comments and suggestions concerning the papers of this study are acknowledged. I am also grateful to Professor Jyrki Launes, MD, PhD, and Docent Juhani Ruutiainen, MD, PhD, for their beneficial comments concerning the earliest versions of the papers.

My colleagues in Seinäjoki Central Hospital deserve a special thank you. I wish to express my deepest thanks to Kari Vihriälä, MA, the Head of the Department of Psychology, Seinäjoki Central Hospital, who has always supported me in all my endeavours both in clinical work and research. Mervi Ranta, Lic.Psych, deserve my special thanks for her kind assistance in reliability evaluations and especially for her guidance to the world of clinical neuropsychology during these many years. Warmest thanks to Seija Pohto, MA, for her constant support, sincere friendship and discussions covering many aspects of clinical and theoretical issues as well as the issues far outside the world of neuropsychology.

I sincerely thank the Study nurse Seija Ahlbäck from Seinäjoki Central Hospital, Department of Neurology for countless advices concerning the practical arrangements of the study. Also, the staff of Scientific Library of Seinäjoki Central Hospital were immensely helpful in finding the information I needed for the study.

Thanks to several colleagues in Tampere University Hospital during the past years – Minna Wäljas, Lic.Psych, Marjatta Musikka-Siirtola, Lic.Psych, Tiia Saunamäki, Lic.Psych, Pia Helin, Lic.Psych, Sanna Maijala, MA, Mari Laihosalo, MA, Susanna Mustalahti, MA, Eija-Inkeri Ruuskanen, MA, Heidi Losoi, MA, Riikka Kilpinen, MA, and many others – who have by their presence created a pleasant, inspiring, and supportive working atmosphere. Special thanks to Docent Mervi Jehkonen, PhD, for her extremely valuable comments and advices concerning the study and especially for her

contagious enthusiasm towards the research. In fact, the whole staff of the Seinäjoki Central Hospital, Department of Psychology and Neurology and Tampere University Hospital, Department of Neurology and Rehabilitation should be acknowledged. I wish to express my sincere gratitude to my colleagues around different centers of Finland for inspiring discussions in the field of neuropsychology.

I am grateful to all the patients, their relatives, and controls, who kindly participated in this study and thus made it possible. This work was financially supported by EVO grants, Seinäjoki Central Hospital and Finnish Cultural Foundation, which are gratefully acknowledged.

I wish to express my sincere gratitude to all my dear friends for support and understanding. My true thanks belong to my parents Raija and Jouko who have always given me their warmest love and care and sincerely supported me in everything I have done in my life. Heartfelt thanks also to my sister, Arja and her family, who have always been a source of support and joy for me.

Most importantly, I could not have done this without the unbelievable support of my dear husband Jukka. I thank him for his firm support and tenderness during these years and at the same time keeping my feet on the ground. He has stood by me for a long time by sharing every moments of ups and downs; I am assured that he will also truly share my satisfaction for the completion of the present work. Finally, I dedicate this thesis to our precious children Venla and Ville, who both were born during these hectic years with thesis project. I hope that this work encourages you in your lives to strive patiently for whatever you feel is worth effort. You remind me every day of what really is important in life.

Tampere, December 2008

A handwritten signature in black ink, reading 'Eija Rosti-Otajärvi'. The script is cursive and elegant, with the first name 'Eija' being particularly prominent.

Eija Rosti-Otajärvi

8 REFERENCES

- Amato, M. P., Ponziani, G., Pracucci, G., Bracco, L., Siracusa, G., & Amaducci, L. (1995). Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. *Archives of Neurology*, 52, 168-172.
- Amato, M. P., Ponziani, G., Siracusa, G., & Sorbi, S. (2001). Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. *Archives of Neurology*, 58, 1602-1606.
- Amato, M. P., & Zipoli, V. (2003). Clinical management of cognitive impairment in multiple sclerosis: a review of current evidence. *The International MS Journal*, 10, 72-83.
- Amato, M. P., Portaccio, E., Goretti, B., Zipoli, V., Ricchiuti, L., De Caro, M. F., et al. (2006a). The Rao's Brief Repeatable Battery and Stroop Test: normative values with age, education and gender corrections in an Italian population. *Multiple Sclerosis*, 12, 787-793.
- Amato, M. P., Zipoli, V., & Portaccio, E. (2006b). Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. *Journal of Neurological Sciences*, 245, 41-46.
- Archibald, C. J., & Fisk, J. D. (2000). Information processing efficiency in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, 22, 686-701.
- Army Individual Test. Manual of directions and scoring.* (1944). Washington, D.C.: War Department, Adjutant General's Office.
- Arnett, P. A., Higginson, C. I., Voss, W. D., Wright, B., Bender, W. I., Wurst, J. M., et al. (1999). Depressed mood in multiple sclerosis: relationship to capacity-demanding memory and attentional functioning. *Neuropsychology*, 13, 434-446.
- Audoin, B., Ibarrola, D., Ranjeva, J. P., Confort-Gouny, S., Malikova, I., Ali-Cherif, A., et al. (2003). Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of MS. *Human Brain Mapping*, 20, 51-58.
- Audoin, B., Ibarrola, D., Au Duong, M. V., Pelletier, J., Confort-Gouny, S., Malikova, I., et al. (2005). Functional MRI study of PASAT in normal subjects. *Magma*, 18, 96-102.
- Aupperle, R. L., Beatty, W. W., Shelton Fde, N., & Gontkovsky, S. T. (2002). Three screening batteries to detect cognitive impairment in multiple sclerosis. *Multiple Sclerosis*, 8, 382-389.
- Baddeley, A. (1986). *Working memory*. Oxford: Oxford University Press.
- Bagert, B., Camplair, P., & Bourdette, D. (2002). Cognitive dysfunction in multiple sclerosis: natural history, pathophysiology and management. *CNS Drugs*, 16, 445-455.
- Baird, B. J., Tombaugh, T. N., & Francis, M. (2007). The effects of practice on speed of information processing using the Adjusting-Paced Serial Addition Test (Adjusting-PSAT) and the Computerized Tests of Information Processing (CTIP). *Applied Neuropsychology*, 14, 88-100.
- Balzano, J., Chiaravalloti, N., Lengenfelder, J., Moore, N., & DeLuca, J. (2006). Does the scoring of late responses affect the outcome of the paced auditory serial addition task (PASAT)? *Archives of Clinical Neuropsychology*, 21, 819-825.
- Barbizet, J., & Cany, E. (1968). Clinical and psychometrical study of patient with memory disturbances. *International Journal of Neurology*, 7, 44-54.
- Barker-Collo, S. L. (2005). Within session practice effects on the PASAT in clients with multiple sclerosis. *Archives of Clinical Neuropsychology*, 20, 145-152.
- Barr, W. B. (1997). Receiver operating characteristic curve analysis of Wechsler memory scale - revised scores in epilepsy surgery candidates. *Psychological Assessment*, 9, 171-176.
- Basso, M. R., Beason-Hazen, S., Lynn, J., Rammohan, K., & Bornstein, R. A. (1996). Screening for cognitive dysfunction in multiple sclerosis. *Archives of Neurology*, 53, 980-984.
- Beatty, W. W., Goodkin, D. E., Monson, N., & Beatty, P. A. (1989). Cognitive disturbances in patients with relapsing remitting multiple sclerosis. *Archives of Neurology*, 46, 1113-1119.
- Beatty, W. W., & Goodkin, D. E. (1990). Screening for cognitive impairment in multiple sclerosis. An evaluation of the Mini-Mental State Examination. *Archives of Neurology*, 47, 297-301.
- Beatty, W. W., Goodkin, D. E., Hertsgaard, D., & Monson, N. (1990). Clinical and demographic predictors of cognitive performance in multiple sclerosis. Do diagnostic type, disease duration, and disability matter? *Archives of Neurology*, 47, 305-308.
- Beatty, W. W., Paul, R. H., Wilbanks, S. L., Hames, K. A., Blanco, C. R., & Goodkin, D. E. (1995). Identifying multiple sclerosis patients with mild or global cognitive impairment using the Screening Examination for Cognitive Impairment (SEFCI). *Neurology*, 45, 718-723.

- Beatty, W. W. (1999). Assessment of cognitive and psychological functions in patients with multiple sclerosis: considerations for databasing. *Multiple Sclerosis*, 5, 239-243.
- Beatty, W. W., Goretta, B., Siracusa, G., Zipoli, V., Portaccio, E., & Amato, M. P. (2003). Changes in neuropsychological test performance over the workday in multiple sclerosis. *Clinical Neuropsychologist*, 17, 551-560.
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, 4, 561-571.
- Beglinger, L. J., Gaydos, B., Tangphao-Daniels, O., Duff, K., Kareken, D. A., Crawford, J., et al. (2005). Practice effects and the use of alternate forms in serial neuropsychological testing. *Archives of Clinical Neuropsychology*, 20, 517-529.
- Benedict, R. H., Fischer, J. S., Archibald, C. J., Arnett, P. A., Beatty, W. W., Bobholz, J., et al. (2002). Minimal neuropsychological assessment of MS patients: a consensus approach. *Clinical Neuropsychologist*, 16, 381-397.
- Benedict, R. H., Munschauer, F., Linn, R., Miller, C., Murphy, E., Foley, F., et al. (2003). Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Multiple Sclerosis*, 9, 95-101.
- Benedict, R. H., Weinstock-Guttman, B., Fishman, I., Sharma, J., Tjoa, C. W., & Bakshi, R. (2004a). Prediction of neuropsychological impairment in multiple sclerosis. *Archives of Neurology*, 61, 226-230.
- Benedict, R. H., Cox, D., Thompson, L. L., Foley, F., Weinstock-Guttman, B., & Munschauer, F. (2004b). Reliable screening for neuropsychological impairment in multiple sclerosis. *Multiple Sclerosis*, 10, 675-678.
- Benedict, R. H. (2005). Effects of using same- versus alternate-form memory tests during short-interval repeated assessments in multiple sclerosis. *Journal of the International Neuropsychological Society*, 11, 727-736.
- Benedict, R. H., Zivadinov, R., Carone, D. A., Weinstock-Guttman, B., Gaines, J., Maggiore, C., et al. (2005). Regional lobar atrophy predicts memory impairment in multiple sclerosis. *American Journal of Neuroradiology*, 26, 1824-1831.
- Benedict, R. H. B., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., et al. (2006a). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, 12, 549-558.
- Benedict, R. H. B., Jared, M. B., Dwyer, M. G., Abdelrahman, N., Hussein, S., Weinstock-Guttman, B. et al. (2006b). Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Archives of Neurology*, 63, 1301-1306.
- Benedict, R. H., & Bobholz, J. H. (2007). Multiple sclerosis. *Seminars in Neurology*, 27, 78-85.
- Benton, A. L., & Hamsher, K. (1976). *Multilingual Aphasia Examination*. Iowa: University of Iowa.
- Bever, C. T., Jr., Grattan, L., Panitch, H. S., & Johnson, K. P. (1995). The Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis: a preliminary serial study. *Multiple Sclerosis*, 1, 165-169.
- Blinkenberg, M., Rune, K., Jensen, C. V., Ravnborg, M., Kyllingsbaek, S., Holm, S., et al. (2000). Cortical cerebral metabolism correlates with MRI lesion load and cognitive dysfunction in MS. *Neurology*, 54, 558-564.
- Bobholz, J. & Rao, S. (2003). Cognitive dysfunction in multiple sclerosis: a review of recent developments. *Current Opinion in Neurology*, 16, 283-288.
- Bongioanni, P., Mosti, S., Romano, M. R., Lombardo, F., Moscato, G., & Meucci, G. (2000). Increased T-lymphocyte interleukin-6 binding in patients with multiple sclerosis. *European Journal of Neurology*, 7, 291-297.
- Brassington, J. C., & Marsh, N. V. (1998). Neuropsychological aspects of multiple sclerosis. *Neuropsychology Review*, 8, 43-77.
- Brittain, J. L., La Marche, J. A., Reeder, K. P., Roth, D. L., & Boll, T. J. (1991). Effects of age and iq on paced auditory serial addition task (PASAT) performance. *The Clinical Neuropsychologist*, 5, 163-175.
- Caine, E. D., Bamford, K. A., Schiffer, R. B., Shoulson, I., & Levy, S. (1986). A controlled neuropsychological comparison of Huntington's disease and multiple sclerosis. *Archives of Neurology*, 43, 249-254.
- Calabrese, P. (2006). Neuropsychology of multiple sclerosis-an overview. *Journal of Neurology*, 253, 10-15.

- Camp, S. J., Stevenson, V. L., Thompson, A. J., Ingle, G. T., Miller, D. H., Borrás, C., et al. (2005). A longitudinal study of cognition in primary progressive multiple sclerosis. *Brain*, 128, 2891-2898.
- Carone, D. A., Benedict, R. H. B., Munschauer, F. E., Fishman, I., & Weinstock-Guttman, B. (2005). Interpreting patient/informant discrepancies of reported cognitive symptoms in MS. *Journal of the International Neuropsychological Society*, 11, 574-583.
- Casetta, I., & Granieri, E. (2000). Prognosis of multiple sclerosis: environmental factors. *Neurological Sciences*, 21, 839-842.
- Charcot, J.-M. (1877). *Lectures on the Diseases of the Nervous System delivered at La Salpêtrière*. London: New Sydenham Society.
- Chipchase, S. Y., & Lincoln, N. B. (2001). Factors associated with carer strain in carers of people with multiple sclerosis. *Disability and Rehabilitation*, 23, 768-776.
- Chronicle, E. P., & MacGregor, N. A. (1998). Are PASAT scores related to mathematical ability? *Neuropsychological Rehabilitation*, 8, 273-282.
- Cohen, J. A., Fischer, J. S., Bolibrush, D. M., Jak, A. J., Kniker, J. E., Mertz, L. A., et al. (2000). Intrarater and interrater reliability of the MS functional composite outcome measure. *Neurology*, 54, 802-806.
- Cohen, J. A., Cutter, G. R., Fischer, J. S., Goodman, A. D., Heidenreich, F. R., Jak, A. J., et al. (2001). Use of the multiple sclerosis functional composite as an outcome measure in a phase 3 clinical trial. *Archives of Neurology*, 58, 961-967.
- Cohen, J. A., Cutter, G. R., Fischer, J. S., Goodman, A. D., Heidenreich, F. R., Kooijmans, M. F., et al. (2002). Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology*, 59, 679-687.
- Coo, H., Hopman, W. M., Edgar, C. M., McBride, E. V., & Brunet, D. G. (2005). The Paced Auditory Serial Addition Test: to what extent is it performed as instructed, and is it associated with disease course? *Multiple Sclerosis*, 11, 85-89.
- Crawford, J. R., Obonsawin, M. C., & Allan, K. M. (1998). PASAT and components of WAIS-R performance: convergent and discriminant validity. *Neuropsychological Rehabilitation*, 8, 255-272.
- Cutter, G. R., Baier, M. L., Rudick, R. A., Cookfair, D. L., Fischer, J. S., Petkau, J., et al. (1999). Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain*, 122, 871-882.
- De Stefano, N., Matthews, P. M., Filippi, M., Agosta, F., De Luca, M., Bartolozzi, M. L., et al. (2003). Evidence of early cortical atrophy in MS: relevance to white matter changes and disability. *Neurology*, 60, 1157-1162.
- Deary, I. J., Langan, S. J., Hepburn, D. A., & Frier, B. M. (1991). Which abilities does the pasat test? *Personality and Individual Differences*, 12, 983-987.
- Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *California Verbal Learning Test: manual*. New York: Psychological Corporation.
- Deloire, M. S., Bonnet, M. C., Salort, E., Arimone, Y., Boudineau, M., Petry, K. G., et al. (2006). How to detect cognitive dysfunction at early stages of multiple sclerosis? *Multiple Sclerosis*, 12, 445-452.
- Deloire, M. S., Salort, E., Bonnet, M., Arimone, Y., Boudineau, M., Amieva, H., et al. (2005). Cognitive impairment as marker of diffuse brain abnormalities in early relapsing remitting multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, 76, 519-526.
- DeLuca, J., Johnson, S. K., & Natelson, B. H. (1993). Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. *Archives of Neurology*, 50, 301-304.
- DeLuca, J., Johnson, S. K., Beldowicz, D., & Natelson, B. H. (1995). Neuropsychological impairments in chronic fatigue syndrome, multiple sclerosis, and depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 58, 38-43.
- DeLuca, J., Chelune, G. J., Tulskey, D. S., Lengenfelder, J., & Chiaravalloti, N. D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of Clinical and Experimental Neuropsychology*, 26, 550-562.
- DeLuca, J. (2005). Fatigue, cognition, and mental effort. In J. DeLuca (Ed.), *Fatigue as a window to the brain* (pp. 37-58). Cambridge: Massachusetts Institute of Technology.
- Demaree, H. A., DeLuca, J., Gaudino, E. A., & Diamond, B. J. (1999). Speed of information processing as a key deficit in multiple sclerosis: implications for rehabilitation. *Journal of Neurology, Neurosurgery and Psychiatry*, 67, 661-663.

- Demaree, H. A., Gaudino, E., & DeLuca, J. (2003). The relationship between depressive symptoms and cognitive dysfunction in multiple sclerosis. *Cognitive Neuropsychiatry*, 8, 161-171.
- D'Esposito, M., Onishi, K., Thompson, H., Robinson, K., Armstrong, C., & Grossman, M. (1996). Working memory impairments in multiple sclerosis: evidence from a dual-task paradigm. *Neuropsychology*, 10, 51-56.
- Diamond, B. J., DeLuca, J., Kim, H., & Kelley, S. M. (1997). The question of disproportionate impairments in visual and auditory information processing in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, 19, 34-42.
- Diehr, M. C., Cherner, M., Wolfson, T. J., Miller, S. W., Grant, I., & Heaton, R. K. (2003). The 50 and 100-item short forms of the Paced Auditory Serial Addition Task (PASAT): demographically corrected norms and comparisons with the full PASAT in normal and clinical samples. *Journal of Clinical and Experimental Neuropsychology*, 25, 571-585.
- Diehr, M. C., Heaton, R. K., Miller, W., & Grant, I. (1998). The Paced Auditory Serial Addition Task (PASAT): norms for age, education, and ethnicity. *Assessment*, 5, 375-387.
- Drew, M., Tippet, L. J., Starkey, N. J., & Isler, R. B. (2008). Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: A descriptive study. *Archives of Clinical Neuropsychology*, 23, 1-19.
- Dujardin, K., Deneve, C., Ronval, M., Krystkowiak, P., Humez, C., Destee, A., et al. (2007). Is the paced auditory serial addition test (PASAT) a valid means of assessing executive function in Parkinson's disease? *Cortex*, 43, 601-606.
- Dyche, G. M., & Johnson, D. A. (1991). Development and evaluation of CHIPASAT, an attention test for children: II. Test-retest reliability and practice effect for a normal sample. *Perceptual and Motor Skills*, 72, 563-572.
- Egan, V. (1988). PASAT: observed correlations with iq. *Personality and Individual Differences*, 9, 179-180.
- Feinstein, A., Kartsounis, L. D., Miller, D. H., Youl, B. D., & Ron, M. A. (1992). Clinically isolated lesions of the type seen in multiple sclerosis: a cognitive, psychiatric, and MRI follow up study. *Journal of Neurology, Neurosurgery and Psychiatry*, 55, 869-876.
- Feinstein, A. (2004). The neuropsychiatry of multiple sclerosis. *Canadian Journal of Psychiatry*, 49, 157-163.
- Feinstein, A. (2006). Mood disorders in multiple sclerosis and the effects on cognition. *Journal of Neurological Sciences*, 245, 63-66.
- Feinstein, A. (2007). *The clinical neuropsychiatry of multiple sclerosis*. New York: Cambridge University Press.
- Feldner, M. T., Leen-Feldner, E. W., Zvolensky, M. J., & Lejuez, C. W. (2006). Examining the association between rumination, negative affectivity, and negative affect induced by a paced auditory serial addition task. *Journal of Behavior Therapy and Experimental Psychiatry*, 37, 171-187.
- Felver-Gant, J. C., Bruce, A. S., Zimmerman, M., Sweet, L. H., Millman, R. P., & Aloia, M. S. (2007). Working memory in obstructive sleep apnea: construct validity and treatment effects. *Journal of Clinical Sleep Medicine*, 3, 589-594.
- Fischer, J. S., Frederick, W. F., Aikens, J. E., Ericson, G. D., Rao, S. M., & Shindell, S. (1994). What do we really know about cognitive dysfunction, affective disorders, and stress in multiple sclerosis? A Practitioner's guide. *Journal of Neurological Rehabilitation*, 8, 151-164.
- Fischer, J. (1999). Assessment of neuropsychological function. In R. Rudick & D. Goodkin (Eds.), *Multiple Sclerosis Therapeutics* (pp. 31-47). London: Martin Dunitz Ltd.
- Fischer, J. S., Priore, R. L., Jacobs, L. D., Cookfair, D. L., Rudick, R. A., Herndon, R. M., et al. (2000). Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. *Annals of Neurology*, 48, 885-892.
- Fischer, J. (2001). Cognitive impairment in multiple sclerosis. In S. D. Cook (Ed.), *Handbook of Multiple Sclerosis* (3rd ed., pp. 233-256). New York: Marcel Dekker, Inc.
- Fischer, J. (2003). Assessment of neuropsychological function in multiple sclerosis. In J. A. Cohen & R. A. Rudick (Eds.), *Multiple Sclerosis therapeutics* (2nd ed., pp. 37-60). London: Martin Dunitz Ltd.
- Fisk, J. D., & Archibald, C. J. (2001). Limitations of the Paced Auditory Serial Addition Test as a measure of working memory in patients with multiple sclerosis. *Journal of the International Neuropsychological Society*, 7, 363-372.

- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189-198.
- Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C. A., Kartsounis, L. D., Thompson, A. J., et al. (1997). Executive function in multiple sclerosis. The role of frontal lobe pathology. *Brain*, 120, 15-26.
- Forn, C., Barros-Loscertales, A., Escudero, J., Belloch, V., Campos, S., Parcet, M. A., et al. (2006). Cortical reorganization during PASAT task in MS patients with preserved working memory functions. *Neuroimage*, 31, 686-691.
- Forn, C., Ventura-Campos, N., Belenguer, A., Belloch, V., Parcet, M. A., & Avila, C. (2008). A comparison of brain activation patterns during covert and overt paced auditory serial addition test tasks. *Human Brain Mapping*, 29, 644-50.
- Fos, L. A., Greve, K. W., South, M. B., Mathias, C., & Benefield, H. (2000). Paced Visual Serial Addition Test: an alternative measure of information processing speed. *Applied Neuropsychology*, 7, 140-146.
- Ge, Y., Grossman, R. I., Udupa, J. K., Babb, J. S., Mannon, L. J., & McGowan, J. C. (2002). Magnetization transfer ratio histogram analysis of normal-appearing gray matter and normal-appearing white matter in multiple sclerosis. *Journal of Computer Assisted Tomography*, 26, 62-68.
- Ghaffar, O., & Feinstein, A. (2007). The neuropsychiatry of multiple sclerosis: a review of recent developments. *Current Opinion in Psychiatry*, 20, 278-285.
- Gonzalez, R., Miller, S. W., Carey, C. L., Woods, S. P., Rippeth, J. D., Schweinsburg, B. C., et al. (2006). Association between dyads and correct responses on the Paced Auditory Serial Addition Task (PASAT). *Assessment*, 13, 381-384.
- Gow, A. J., & Deary, I. J. (2004). Is the PASAT past it? Testing attention and concentration without numbers. *Journal of Clinical and Experimental Neuropsychology*, 26, 723-736.
- Granieri, E., Casetta, I., Tola, M. R., & Ferrante, P. (2001). Multiple sclerosis: infectious hypothesis. *Neurological Sciences*, 22, 179-185.
- Gronwall, D. M. (1977). Paced auditory serial-addition task: a measure of recovery from concussion. *Perceptual and Motor Skills*, 44, 367-373.
- Gronwall, D., & Wrightson, P. (1981). Memory and information processing capacity after closed head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, 44, 889-895.
- Grossman, M., Robinson, K. M., Onishi, K., Thompson, H., Cohen, J., & D'Esposito, M. (1995). Sentence comprehension in multiple sclerosis. *Acta Neurologica Scandinavica*, 92, 324-331.
- Haase, C. G., Tinnefeld, M., Lienemann, M., Ganz, R. E., & Faustmann, P. M. (2003). Depression and cognitive impairment in disability-free early multiple sclerosis. *Behavioural Neurology*, 14, 39-45.
- Haase, C. G., Tinnefeld, M., Daum, I., Ganz, R. E., Haupts, M., & Faustmann, P. M. (2004). Cognitive, but not mood dysfunction develops in multiple sclerosis during 7 years of follow-up. *European Neurology*, 52, 92-95.
- Heaton, R. K. (1981). *Wisconsin Card Sorting Test Manual*. Odessa: Psychological Assessment Resources.
- Heaton, R. K., Nelson, L. M., Thompson, D. S., Burks, J. S., & Franklin, G. M. (1985). Neuropsychological findings in relapsing-remitting and chronic-progressive multiple sclerosis. *Journal of Consulting and Clinical Psychology*, 53, 103-110.
- Henry, J. D., & Beatty, W. W. (2006). Verbal fluency deficits in multiple sclerosis. *Neuropsychologia*, 44, 1166-1174.
- Hoffmann, S., Tittgemeyer, M., & von Cramon, D. Y. (2007). Cognitive impairment in multiple sclerosis. *Current Opinion in Neurology*, 20, 275-280.
- Hohol, M. J., Guttmann, C. R., Orav, J., Mackin, G. A., Kikinis, R., Khoury, S. J., et al. (1997). Serial neuropsychological assessment and magnetic resonance imaging analysis in multiple sclerosis. *Archives of Neurology*, 54, 1018-1025.
- Holdwick, D. J., & Wingenfeld, S. A. (1999). The subjective experience of PASAT testing: does the PASAT induce negative mood? *Archives of Clinical Neuropsychology*, 14, 273-284.
- Holland, N. J., Murray, T. J., & Reingold, S. C. (2007). *Multiple sclerosis: a guide for the newly diagnosed* (3rd ed.). New York: Demos Medical Publishing, LLC.
- Hoogervorst, E. L., van Winsen, L. M., Eikelenboom, M. J., Kalkers, N. F., Uitdehaag, B. M., & Polman, C. H. (2001). Comparisons of patient self-report, neurologic examination, and functional impairment in MS. *Neurology*, 56, 934-937.

- Hooper, H. E. (1958). *The Hooper Visual Organization Test Manual*. Los Angeles, California: Western Psychological Services.
- Houtchens, M. K., Benedict, R. H., Killiany, R., Sharma, J., Jaisani, Z., Singh, B., et al. (2007). Thalamic atrophy and cognition in multiple sclerosis. *Neurology*, 69, 1213-1223.
- Jennekens-Schinkel, A., Laboyrie, P. M., Lanser, J. B., & van der Velde, E. A. (1990). Cognition in patients with multiple sclerosis after four years. *Journal of Neurological Sciences*, 99, 229-247.
- Johnson, D. A., Roethig-Johnston, K., & Middleton, J. (1988). Development and evaluation of an attentional test for head injured children-I. Information processing capacity in a normal sample. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 29, 199-208.
- Johnson, S. K., Lange, G., DeLuca, J., Korn, L. R., & Natelson, B. (1997). The effects of fatigue on neuropsychological performance in patients with chronic fatigue syndrome, multiple sclerosis, and depression. *Applied Neuropsychology*, 4, 145-153.
- Kalkers, N. F., de Groot, V., Lazerou, R. H., Killestein, J., Ader, H. J., Barkhof, F., et al. (2000). MS functional composite: relation to disease phenotype and disability strata. *Neurology*, 54, 1233-1239.
- Kalkers, N. F., Bergers, E., Castelijns, J. A., van Walderveen, M. A., Bot, J. C., Ader, H. J., et al. (2001a). Optimizing the association between disability and biological markers in MS. *Neurology*, 57, 1253-1258.
- Kalkers, N. F., Bergers, L., de Groot, V., Lazerou, R. H., van Walderveen, M. A., Uitdehaag, B. M., et al. (2001b). Concurrent validity of the MS Functional Composite using MRI as a biological disease marker. *Neurology*, 56, 215-219.
- Kalmar, J. H., Bryant, D., Tulskey, D., & DeLuca, J. (2004). Information processing deficits in multiple sclerosis: does choice of screening instrument make a difference? *Rehabilitation Psychology*, 49, 213-218.
- Kidd, D., Barkhof, F., McConnell, R., Algra, P. R., Allen, I. V., & Revesz, T. (1999). Cortical lesions in multiple sclerosis. *Brain*, 122, 17-26.
- Korkman, M., Kirk, U., & Kemp, S. (1998). *NEPSY - A developmental neuropsychological assessment: Manual*. San Antonio TX: Psychological Corporation.
- Kotterba, S., Orth, M., Eren, E., Fangerau, T., & Sindern, E. (2003). Assessment of driving performance in patients with relapsing-remitting multiple sclerosis by a driving simulator. *European Neurology*, 50, 160-164.
- Krupp, L. B., Sliwinski, M., Masur, D. M., Friedberg, F., & Coyle, P. K. (1994). Cognitive functioning and depression in patients with chronic fatigue syndrome and multiple sclerosis. *Archives of Neurology*, 51, 705-710.
- Krupp, L. B. (2001). Assessment and treatment of fatigue in multiple sclerosis. In L. Kappos, J. Kesselring, E. W. Radu & K. Johnson (Eds.), *Multiple sclerosis: tissue destruction and repair* (pp. 177-182). London: Martin Dunitz Ltd.
- Krupp, L. B. (2004). *Fatigue in multiple sclerosis: a guide to diagnosis and management*. New York: Demos Medical Publishing Inc.
- Kujala, P., Portin, R., Revonsuo, A., & Ruutinen, J. (1994). Automatic and controlled information processing in multiple sclerosis. *Brain*, 117, 1115-1126.
- Kujala, P., Portin, R., Revonsuo, A., & Ruutinen, J. (1995). Attention related performance in two cognitively different subgroups of patients with multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, 59, 77-82.
- Kujala, P., Portin, R., & Ruutinen, J. (1996a). Memory deficits and early cognitive deterioration in MS. *Acta Neurologica Scandinavica*, 93, 329-335.
- Kujala, P., Portin, R., & Ruutinen, J. (1996b). Language functions in incipient cognitive decline in multiple sclerosis. *Journal of Neurological Sciences*, 141, 79-86.
- Kujala, P., Portin, R., & Ruutinen, J. (1997). The progress of cognitive decline in multiple sclerosis. A controlled 3-year follow-up. *Brain*, 120, 289-297.
- Kurtzke, J. F. (1970). Neurologic impairment in multiple sclerosis and the disability status scale. *Acta Neurologica Scandinavica*, 46, 493-512.
- Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*, 33, 1444-1452.
- Langdon, D. W., & Thompson, A. J. (1999). Multiple sclerosis: a preliminary study of selected variables affecting rehabilitation outcome. *Multiple Sclerosis*, 5, 94-100.

- Lejuez, C. W., Kahler, C. W., & Brown, R. A. (2003). A modified computer version of the paced auditory serial addition task (PASAT) as a laboratory-based stressor: Implications for behavioral assessment. *Behavior Therapist*, 26, 290-292.
- Lengenfelder, J., Bryant, D., Diamond, B. J., Kalmar, J. H., Moore, N. B., & DeLuca, J. (2006). Processing speed interacts with working memory efficiency in multiple sclerosis. *Archives of Clinical Neuropsychology*, 21, 229-238.
- Lensch, E., Matzke, M., Petereit, H. F., Scherer, P., Schramm, S., & Calabrese, P. (2006). Identification and management of cognitive disorders in multiple sclerosis-a consensus approach. *Journal of Neurology*, 253, 129-31.
- Leong, F. T. L., & Austin, J. T. (1996). *The psychology research hand book: a guide for graduate students and research assistants*. Thousand Oaks: Sage Publications, Inc.
- Levin, H. S., Mattis, S., Ruff, R. M., Eisenberg, H. M., Marshall, L. F., Tabaddor, K., et al. (1987). Neurobehavioral outcome following minor head injury: a three-center study. *Journal of Neurosurgery*, 66, 234-243.
- Lezak, M. D. (1995). *Neuropsychological assessment*. 3rd ed. New York: Oxford University Press.
- Lincoln, N. B., & Radford, K. A. (2008). Cognitive abilities as predictors of safety to drive in people with multiple sclerosis. *Multiple Sclerosis*, 14, 123-128.
- Litvan, I., Grafman, J., Vendrell, P., Martinez, J. M., Junque, C., Vendrell, J. M., et al. (1988a). Multiple memory deficits in patients with multiple sclerosis. Exploring the working memory system. *Archives of Neurology*, 45, 607-610.
- Litvan, I., Grafman, J., Vendrell, P., & Martinez, J. M. (1988b). Slowed information processing in multiple sclerosis. *Archives of Neurology*, 45, 281-285.
- Lockwood, A. H., Linn, R. T., Szymanski, H., Coad, M. L., & Wack, D. S. (2004). Mapping the neural systems that mediate the Paced Auditory Serial Addition Task (PASAT). *Journal of the International Neuropsychological Society*, 10, 26-34.
- Lublin, F. D., & Reingold, S. C. (1996). Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*, 46, 907-911.
- Mahler, M. E. (1992). Behavioral manifestations associated with multiple sclerosis. *The Psychiatric Clinics of North America*, 15, 427-438.
- Mainero, C., Caramia, F., Pozzilli, C., Pisani, A., Pestalozza, I., Borriello, G., et al. (2004). fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. *Neuroimage*, 21, 858-867.
- Maor, Y., Olmer, L., & Mozes, B. (2001). The relation between objective and subjective impairment in cognitive function among multiple sclerosis patients-the role of depression. *Multiple Sclerosis*, 7, 131-135.
- Mariani, C., Farina, E., Cappa, S. F., Anzola, G. P., Faglia, L., Bevilacqua, L., et al. (1991). Neuropsychological assessment in multiple sclerosis: a follow-up study with magnetic resonance imaging. *Journal of Neurology*, 238, 395-400.
- Marrie, R. A., Chelune, G. J., Miller, D. M., & Cohen, J. A. (2005). Subjective cognitive complaints relate to mild impairment of cognition in multiple sclerosis. *Multiple Sclerosis*, 11, 69-75.
- McCaffrey, R. J., Cousins, J. P., Westervelt, H. J., Martynowicz, M., Remick, S. C., Szebenyi, S., et al. (1995). Practice effects with the NIMH AIDS abbreviated neuropsychological battery. *Archives of Clinical Neuropsychology*, 10, 241-250.
- McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H. P., Lublin, F. D., et al. (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology*, 50, 121-127.
- McDonald, W. I., & Ron, M. A. (1999). Multiple sclerosis: the disease and its manifestations. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 354, 1615-1622.
- Miller, D. M., Rudick, R. A., Cutter, G., Baier, M., & Fischer, J. S. (2000). Clinical significance of the multiple sclerosis functional composite: relationship to patient-reported quality of life. *Archives of Neurology*, 57, 1319-1324.
- Ministry of Labour, Employment Office (1969). *Arithmetics, NI/K*. Helsinki: Psykologien Kustannus.
- Montalban, X., & Rio, J. (2006). Interferons and cognition. *Journal of the Neurological Sciences*, 245, 137-140.
- Nagels, G., D'Hooghe M, B., Kos, D., Engelborghs, S., & De Deyn, P. P. (2008). Within-session practice effect on paced auditory serial addition test in multiple sclerosis. *Multiple Sclerosis*, 14, 106-111.

- Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex*, 12, 313-324.
- O'Connor, P. (2002). Key issues in the diagnosis and treatment of multiple sclerosis. An overview. *Neurology*, 59, S1-S3.
- O'Jile, J. R., Ryan, L. M., Betz, B., Parks-Levy, J., Hilsabeck, R. C., Rhudy, J. L., et al. (2006). Information processing following mild head injury. *Archives of Clinical Neuropsychology*, 21, 293-296.
- Osterrieth, P. A. (1944). Le test de copie d'une figure complexe. *Archives de Psychologie*, 30, 206-356.
- Ozakbas, S., Ormeci, B., & Idiman, E. (2005). Utilization of the multiple sclerosis functional composite in follow-up: relationship to disease phenotype, disability and treatment strategies. *Journal of Neurological Sciences*, 232, 65-69.
- Patzold, T., Schwengelbeck, M., Ossege, L. M., Malin, J. P., & Sindern, E. (2002). Changes of the MS functional composite and EDSS during and after treatment of relapses with methylprednisolone in patients with multiple sclerosis. *Acta Neurologica Scandinavica*, 105, 164-168.
- Peyser, J. M., Rao, S. M., LaRocca, N. G., & Kaplan, E. (1990). Guidelines for neuropsychological research in multiple sclerosis. *Archives of Neurology*, 47, 94-97.
- Piras, M. R., Magnamo, I., Canu, E. D. G., Paulus, K. S., Satta, W. M., Soddu, A., Conti, M., Achene, A., Solinas, G., Aiello, I. (2003). Longitudinal study of cognitive performance in multiple sclerosis: neuropsychological, neuroradiological, and neurophysiological findings. *Journal of Neurology, Neurosurgery and Psychiatry*, 74, 878-885.
- Polman, C. H., Reingold, S. C., Edan, G., Filippi, M., Hartung, H. P., Kappos, L., et al. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Annals of Neurology*, 58, 840-846.
- Polman, C. H., Thompson, A. J., Murray, T. J., Bowling, A. C., & Noseworthy, J. H. (2006a). *Multiple Sclerosis - the guide to treatment and management* (6th ed.). New York: Demos Medical Publishing, LLC.
- Polman, C. H., O'Connor, P. W., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D. H., et al. (2006b). A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *New England Journal of Medicine*, 354, 899-910.
- Portin, R., Saarijarvi, S., Joukamaa, M., & Salokangas, R. K. (1995). Education, gender and cognitive performance in a 62-year-old normal population: results from the Turva Project. *Psychological Medicine*, 25, 1295-1298.
- Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., et al. (1983). New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*, 13, 227-231.
- Poser, C. M., & Brinar, V. V. (2002). Multiple sclerosis 2001. *Clinical Neurology and Neurosurgery*, 104, 165-167.
- Prevey, M. L., Delaney, R. C., Cramer, J. A., & Mattson, R. H. (1998). Complex partial and secondarily generalized seizure patients: cognitive functioning prior to treatment with antiepileptic medication. VA Epilepsy Cooperative Study 264 Group. *Epilepsy Research*, 30, 1-9.
- Rao, S. M., Hammeke, T. A., McQuillen, M. P., Khatri, B. O., & Lloyd, D. (1984). Memory disturbance in chronic progressive multiple sclerosis. *Archives of Neurology*, 41, 625-631.
- Rao, S. M., Leo, G. J., Haughton, V. M., St Aubin-Faubert, P., & Bernardin, L. (1989). Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology*, 39, 161-166.
- Rao, S. M., & Society, C. F. S. G. o. t. N. M. S. (1990). *A manual for the Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis*. New York: National Multiple Sclerosis Society.
- Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991a). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*, 41, 685-691.
- Rao, S. M., Leo, G. J., Ellington, L., Nauertz, T., Bernardin, L., & Unverzagt, F. (1991b). Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology*, 41, 692-696.
- Rao, S. M. (1995). Neuropsychology of multiple sclerosis. *Current Opinion in Neurology*, 8, 216-220.
- Rao, S. M. (2004). Cognitive function in patients with multiple sclerosis: impairment and treatment. *International Journal of MS Care*, 1, 9-22.
- Raven, J. C. (1960). *Guide to the Standard Progressive Matrices*. London: H. K. Lewis.
- Robertson, I., Ward, T., Ridgeway, V., & Nimmo-Smith, I. (1994). *The Test of Everyday Attention: Manual*. Suffolk UK: Thames Valley Test Company.

- Rogers, J. M., & Panegyres, P. K. (2007). Cognitive impairment in multiple sclerosis: evidence-based analysis and recommendations. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia*, 14, 919-927.
- Rohowsky-Kochan, C., Molinaro, D., & Cook, S. D. (2000). Cytokine secretion profile of myelin basic protein-specific T cells in multiple sclerosis. *Multiple Sclerosis*, 6, 69-77.
- Roman, D. D., Edwall, G. E., Buchanan, R. J., & Patton, J. H. (1991). Extended norms for the paced auditory serial addition task. *The Clinical Neuropsychologist*, 5, 33-40.
- Rovaris, M., Filippi, M., Falautano, M., Minicucci, L., Rocca, M. A., Martinelli, V., et al. (1998). Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis. *Neurology*, 50, 1601-1608.
- Rudick, R., Antel, J., Confavreux, C., Cutter, G., Ellison, G., Fischer, J., et al. (1996). Clinical outcomes assessment in multiple sclerosis. *Annals of Neurology*, 40, 469-479.
- Rudick, R., Antel, J., Confavreux, C., Cutter, G., Ellison, G., Fischer, J., et al. (1997). Recommendations from the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force. *Annals of Neurology*, 42, 379-382.
- Rudick, R. A., Cutter, G., Baier, M., Fisher, E., Dougherty, D., Weinstock-Guttman, B., et al. (2001). Use of the Multiple Sclerosis Functional Composite to predict disability in relapsing MS. *Neurology*, 56, 1324-1330.
- Ryan, L., Clark, C. M., Klonoff, H., Li, D., & Paty, D. (1996). Patterns of cognitive impairment in relapsing-remitting multiple sclerosis and their relationship to neuropathology on magnetic resonance images. *Neuropsychology*, 10, 176-193.
- Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, 103, 403-428.
- Sampson, H. (1956). Pacing and performance on a serial addition task. *Canadian Journal of Psychology*, 10, 219-225.
- Sartori, E., & Edan, G. (2006). Assessment of cognitive dysfunction in multiple sclerosis. *Journal of Neurological Sciences*, 245, 169-175.
- Scarrabelotti, M., & Carroll, M. (1999). Memory dissociation and metamemory in multiple sclerosis. *Neuropsychologia*, 37, 1335-1350.
- Schweitzer, J. B., Hanford, R. B., & Medoff, D. R. (2006). Working memory deficits in adults with ADHD: is there evidence for subtype differences? *Behavioral and Brain Functions*, 2, 43.
- Schwid, S. R., Covington, M., Segal, B. M., & Goodman, A. D. (2002). Fatigue in multiple sclerosis: current understanding and future directions. *Journal of Rehabilitation Research and Development*, 39, 211-224.
- Schwid, S. R., Tyler, C. M., Scheid, E. A., Weinstein, A., Goodman, A. D., & McDermott, M. P. (2003). Cognitive fatigue during a test requiring sustained attention: a pilot study. *Multiple Sclerosis*, 9, 503-508.
- Schächinger, H., Cox, D., Linder, L., Brody, S., & Keller, U. (2003). Cognitive and psychomotor function in hypoglycemia: response error patterns and retest reliability. *Pharmacology Biochemistry and Behavior*, 75, 915-920.
- Sherman, E. M. S., Strauss, E., & Spellacy, F. (1997). Validity of the paced auditory serial addition test (PASAT) in adults referred for neuropsychological assessment after head injury. *The Clinical Neuropsychologist*, 11, 34-45.
- Sherman, T. E., Rapport, L. J., & Ryan, K. A. (2007). Awareness of deficit in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, 1-11.
- Shucard, J. L., Parrish, J., Shucard, D. W., McCabe, D. C., Benedict, R. H., & Ambrus, J., Jr. (2004). Working memory and processing speed deficits in systemic lupus erythematosus as measured by the paced auditory serial addition test. *Journal of the International Neuropsychological Society*, 10, 35-45.
- Siebert, R. J., & Abernethy, D. A. (2005). Depression in multiple sclerosis: a review. *Journal of Neurology, Neurosurgery and Psychiatry*, 76, 469-475.
- Sintonen, H. (2001). The 15D instrument of health-related quality of life: properties and applications. *Annals of Medicine*, 33, 328-336.
- Sjogren, P., Olsen, A. K., Thomsen, A. B., & Dalberg, J. (2000). Neuropsychological performance in cancer patients: the role of oral opioids, pain and performance status. *Pain*, 86, 237-245.
- Sjogren, P., Thomsen, A. B., & Olsen, A. K. (2000). Impaired neuropsychological performance in chronic nonmalignant pain patients receiving long-term oral opioid therapy. *Journal of Pain and Symptom Management*, 19, 100-108.

- Smith, A. (1973). *Symbol digit modalities test: manual*. Los Angeles: Western Psychological Services.
- Smits, R. C., Emmen, H. H., Bertelsmann, F. W., Kulig, B. M., van Loenen, A. C., & Polman, C. H. (1994). The effects of 4-aminopyridine on cognitive function in patients with multiple sclerosis: a pilot study. *Neurology*, 44, 1701-1705.
- Snyder, P. J., Aniskiewicz, A. S., & Snyder, A. M. (1993). Quantitative MRI correlates and diagnostic utility of multi-modal measures of executive control in multiple sclerosis [Abstract]. *Journal of Clinical and Experimental Neuropsychology*, 15, 18.
- Snyder, P. J., & Cappelleri, J. C. (2001). Information processing speed deficits may be better correlated with the extent of white matter sclerotic lesions in multiple sclerosis than previously suspected. *Brain and Cognition*, 46, 279-284.
- Snyder, P. J., Cappelleri, J. C., Archibald, C. J., & Fisk, J. D. (2001). Improved detection of differential information-processing speed deficits between two disease-course types of multiple sclerosis. *Neuropsychology*, 15, 617-625.
- Solari, A., Radice, D., Manneschi, L., Motti, L., & Montanari, E. (2005). The multiple sclerosis functional composite: different practice effects in the three test components. *Journal of Neurological Sciences*, 228, 71-74.
- Solari, A., Motta, A., Radice, D., & Mendozzi, L. (2007). A shortened version of PASAT-3 is feasible. *Multiple Sclerosis*, 13, 1020-1025.
- Sperling, R. A., Guttmann, C. R., Hohol, M. J., Warfield, S. K., Jakab, M., Parente, M., et al. (2001). Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: a longitudinal study. *Archives of Neurology*, 58, 115-121.
- SPSS. (1989-2003). SPSS for Windows release 12.0.1. SPSS Inc. Chicago, USA.
- Staffen, W., Mair, A., Zauner, H., Unterrainer, J., Niederhofer, H., Kutzelnigg, A., et al. (2002). Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. *Brain*, 125, 1275-1282.
- StatsDirect. (1990-2002). StatsDirect Statistical Software v. 2,2,2 StatsDirect Limited, Ashwell UK.
- Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary* (3rd ed.). Oxford: Oxford University Press.
- Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, 18, 643-662.
- Sumelahti, M. L., Tienari, P. J., Wikström, J., Palo, J., & Hakama, M. (2001). Increasing prevalence of multiple sclerosis in Finland. *Acta Neurologica Scandinavica*, 103, 153-158.
- Sumelahti, M. L., Tienari, P. J., Wikström, J., Salminen, T. M., & Hakama, M. (2002). Survival of multiple sclerosis in Finland between 1964 and 1993. *Multiple Sclerosis*, 8, 350-355.
- Sumelahti, M. L., Tienari, P. J., Hakama, M., & Wikström, J. (2003). Multiple sclerosis in Finland: incidence trends and differences in relapsing remitting and primary progressive disease courses. *Journal of Neurology, Neurosurgery and Psychiatry*, 74, 25-28.
- Tekok-Kilic, A., Benedict, R. H., Weinstock-Guttman, B., Dwyer M. G., Carone, D., Srinivasaraghavan, B., et al. (2007). Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis. *Neuroimage*, 36, 1294-1300.
- Thornton, A. E., & Raz, N. (1997). Memory impairment in multiple sclerosis: a quantitative review. *Neuropsychology*, 11, 357-366.
- Tombaugh, T. N. (1999). *Administrative Manual for the Adjusting-Paced Serial Addition Test (Adjusting-PSAT)*. Ottawa, Ontario: Carleton University.
- Tombaugh, T. N., Rees, L., Baird, B., & Kost, J. (2004). The effects of list difficulty and modality of presentation on a computerized version of the Paced Serial Addition Test (PSAT). *Journal of Clinical and Experimental Neuropsychology*, 26, 257-265.
- Tombaugh, T. N. (2006). A comprehensive review of the Paced Auditory Serial Addition Test (PASAT). *Archives of Clinical Neuropsychology*, 21, 53-76.
- Townsend, L. A., Malla, A. K., & Norman, R. M. (2001). Cognitive functioning in stabilized first-episode psychosis patients. *Psychiatry Res*, 104, 119-131.
- Trapp, B. D., Ransohoff, R., & Rudick, R. (1999a). Axonal pathology in multiple sclerosis: relationship to neurologic disability. *Current Opinion in Neurology*, 12, 295-302.
- Trapp, B. D., Ransohoff, R. M., Fisher, E., & Rudick, R. A. (1999b). Neurodegeneration in multiple sclerosis: relationship to neurological disability. *The Neuroscientist*, 5, 48-57.
- Ward, T. (1997). A note of caution for clinicians using the Paced Auditory Serial Addition Task. *British Journal of Clinical Psychology*, 36, 303-307.

- Wechsler, D. (1981). *Wechsler Adult Intelligence Scale - Revised: Manual*. New York: Psychological Corporation.
- Wechsler, D. (1987). *Wechsler Memory Scale - Revised: Manual*. New York: Psychological Corporation.
- Weersink, E. J., van Zomeren, E. H., Koeter, G. H., & Postma, D. S. (1997). Treatment of nocturnal airway obstruction improves daytime cognitive performance in asthmatics. *American Journal of Respiratory and Critical Care Medicine*, 156, 1144-1150.
- Whitaker, J. N., McFarland, H. F., Rudge, P., & Reingold, S. C. (1995). Outcomes assessment in multiple sclerosis clinical trials: a critical analysis. *Multiple Sclerosis*, 1, 37-47.
- Wiens, A. N., Fuller, K. H., & Crossen, J. R. (1997). Paced Auditory Serial Addition Test: adult norms and moderator variables. *Journal of Clinical and Experimental Neuropsychology*, 19, 473-483.
- Vilkkii, J., Virtanen, S., Surma-Aho, O., & Servo, A. (1996). Dual task performance after focal cerebral lesions and closed head injuries. *Neuropsychologia*, 34, 1051-1056.
- Wills, S., & Leathem, J. (2004). The effects of test anxiety, age, intelligence level, and arithmetic ability on Paced Auditory Serial Addition Test performance. *Applied Neuropsychology*, 11, 180-187.
- Wingenfeld, S. A., Holdwick, D. J., Jr., Davis, J. L., & Hunter, B. B. (1999). Normative data on computerized paced auditory serial addition task performance. *The Clinical Neuropsychologist*, 13, 268-273.
- Younes, M., Hill, J., Quinless, J., Kilduff, M., Peng, B., Cook, S. D., et al. (2007). Internet-based cognitive testing in multiple sclerosis. *Multiple Sclerosis*, 13, 1011-1019.
- Zaffaroni, M., & Ghezzi, A. (2000). The prognostic value of age, gender, pregnancy and endocrine factors in multiple sclerosis. *Neurological Sciences*, 21, S857-860.
- Zarei, M., Chandran, S., Compston, A., & Hodges, J. (2003). Cognitive presentation of multiple sclerosis: evidence for a cortical variant. *Journal of Neurology, Neurosurgery and Psychiatry*, 74, 872-877.
- Zarei, M. (2006). Clinical characteristics of cortical multiple sclerosis. *Journal of Neurological Sciences*, 245, 53-58.
- Zivadinov, R., Sepcic, J., Nasuelli, D., De Masi, R., Bragadin, L. M., Tommasi, M. A., et al. (2001a). A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, 70, 773-780.
- Zivadinov, R., De Masi, R., Nasuelli, D., Bragadin, L. M., Ukmar, M., Pozzi-Mucelli, R. S., et al. (2001b). MRI techniques and cognitive impairment in the early phase of relapsing-remitting multiple sclerosis. *Neuroradiology*, 43, 272-278.
- Zou, K. H., Hall, W. J., & Shapiro, D. E. (1997). Smooth non-parametric receiver operating characteristic (ROC) curves for continuous diagnostic tests. *Statistics in Medicine*, 16, 2143-2156.
- Äikiä, M., Kälviäinen, R., & Riekkinen, P. J. (1995). Verbal learning and memory in newly diagnosed partial epilepsy. *Epilepsy Research*, 22, 157-164.

ORIGINAL PUBLICATIONS

ISSN 0781-8254
ISBN 978-952-10-5105-0 (pbk.)
ISBN 978-952-10-5106-7 (PDF)
<http://ethesis.helsinki.fi>
Helsinki University Printing House
Helsinki 2008