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**COGNITIVE FUNCTION AND
NEUROPHYSIOLOGICAL CORRELATES IN
RELAPSING-REMITTING MULTIPLE SCLEROSIS**

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Cognitive Function and Neurophysiological Correlates in Relapsing-Remitting Multiple Sclerosis

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Impaired cognitive function is a frequent consequence of multiple sclerosis (MS). It negatively affects vocational status, treatment adherence, physical independence, competence in activities of daily life, rehabilitation potential, driving safety and quality of life. All papers in this thesis concern cognitive function in relapsing-remitting MS (RRMS), with emphasis on clinical and neurophysiological predictors, moderating factors and the effect of natalizumab (NZ) treatment.

I. The aim of this paper was to identify the strongest clinical predictors for cognitive impairment in RRMS patients. Patients with RRMS (n=72) and healthy control subjects (n=89) underwent comprehensive cognitive testing and clinical assessment. Physical disability (EDSS), fatigue (FSS), somatic and non-somatic components of depression (BDI-S and BDI-NS), disease progression rate (MSSS), and presence of psychotropic medication were included in the analysis. Patients had a mean EDSS of 2.7 and disease duration of 9.3 years. Depression and fatigue estimates were significantly higher in patients than in control subjects ($p < 0.0001$). Cognitive impairment had a prevalence of 30.5% in patients affecting preferentially executive functions, attention and processing speed. EDSS, FSS, BDI-NS and BDI-S were significantly correlated with several cognitive domains and global cognitive function in patients. In regression models, cognitive performance was best predicted by BDI-NS alone or in combination with EDSS. Exclusion of patients with any psychotropic medication did not influence the main findings.

II. The objective of paper II was to explore if cognitive impairment in RRMS is associated with abnormal neural function, and if there is evidence of neural compensatory mechanisms. The study population described in paper I underwent event-related brain potential (ERP) recordings with visual and auditory choice reaction tasks. Patients had *increased* visual P300 amplitude frontally. Auditory and visual P300 amplitude were normal in other brain areas, and response time (RT) was normal. P300 latency was normal except for an increase in auditory latency occipitally. Cognitive performance correlated positively with visual and auditory parietal P300 amplitude in patients ($p < 0.0001$ and $p = 0.009$, respectively) but not in controls. Global cognitive score had a significantly stronger correlation (negative) with RT in patients than in controls (intergroup difference for visual stimulation $p = 0.015$, and for auditory $p = 0.050$). Notably, these associations were not an epiphenomenon of the cognitive impairment in patients, because parietal P300 amplitude and RT were normal. We concluded that patients with low P300 amplitude and long RT were more often cognitively impaired.

III. The aim of paper III was to distinguish different mechanisms for cognitive reserve in RRMS. Thus, we wished to test the cognitive reserve hypothesis in the present study population. This hypothesis predicts that high premorbid intelligence, as may be estimated from years of education and vocabulary knowledge, attenuates the effects of disease burden on cognitive functioning. In this analysis, the normal effects of premorbid intelligence on the test scores need to be accounted for. Thus we compared the strength of the correlation between premorbid intelligence and cognitive performance in patients and controls, respectively. Contrary to the prediction, premorbid intelligence had no stronger effect on cognition in patients than in controls. This finding contrasted against the results in paper II where P300 amplitude and RT did have stronger effect on cognitive function in patients than in controls, *i.e.* showed features of a reserve against cognitive impairment in patients. The strongest neurophysiological (visual P300 amplitude and RT) and clinical (EDSS and BDI-NS) predictors of cognitive function were studied in a hierarchical linear regression model. P300 amplitude and RT explained 34% of the variance in global cognitive function ($p < 0.001$). EDSS and BDI-NS added significantly to explained variance, and the final model accounted for 44% ($p < 0.001$) of the variation. In a separate analysis, we found that the effects of P300 and RT on cognitive function were not moderated by premorbid intelligence.

IV. The objective of paper IV was to evaluate the cognitive effects of NZ treatment, compared to patients on stable first-line treatment and healthy control subjects. Fifteen MS patients (MS-NZ) underwent cognitive testing when starting NZ treatment and were tested again after one year. They were compared with fifteen MS patients on stable interferon beta therapy (MS-C) and twelve healthy control subjects (HC) who also were tested twice with an interval of one year. The effects of NZ on levels of self-reported depression, fatigue, daytime sleepiness and perceived health were also examined. MS patients (MS-NZ and MS-C) had significantly lower baseline cognitive performance compared to HC (global score, $p = 0.002$). At follow-up, both MS-NZ and MS-C had improved significantly in four and five cognitive domains, respectively, and in global cognitive score ($p = 0.013$ and $p < 0.001$, respectively). HC improved significantly in three cognitive domains but not in global score. A regression analysis showed that participants with lower baseline scores had a significantly greater improvement, compared to those with a better initial performance ($p = 0.021$). There were no significant changes in depression, fatigue, daytime sleepiness or perceived health in MS-NZ or MS-C.

Conclusions

Symptoms of depression, especially non-somatic symptoms, and level of physical disability are the most important clinical risk factors for cognitive impairment in RRMS patients.

General factors such as ERP amplitude and RT are limiting for cognitive function in RRMS because P300 amplitude and RT have significantly stronger associations with cognitive performance in patients compared to HC.

High P300 and fast RT reflect a physiological reserve which may be the strongest moderator of cognitive impairment in RRMS. In contrast, premorbid intelligence does not constitute a cognitive reserve in RRMS patients.

The observed increase in frontal P300 amplitude suggests activation of compensatory networks.

There is no evidence of a beneficial effect on cognitive performance after one year of NZ treatment. Retest effects are significant and are important to recognize in studies of cognitive performance.

LIST OF SCIENTIFIC PAPERS

- I. **Sundgren, M.**, Maurex, L., Wahlin, Å., Piehl, F. and Brismar, T. (2013)
Cognitive impairment has a strong relation to nonsomatic symptoms of depression in relapsing-remitting multiple sclerosis.
Archives of Clinical Neuropsychology, 28(2), pp. 144-155.

- II. **Sundgren, M.**, Nikulin, V. V., Maurex, L., Wahlin, Å., Piehl, F. and Brismar, T. (2015)
P300 amplitude and response speed relate to preserved cognitive function in relapsing-remitting multiple sclerosis.
Clinical Neurophysiology, 126(4), pp. 689-697.

- III. **Sundgren, M.**, Wahlin, Å., Maurex, L. and Brismar, T. (2015)
Event related potential and response time give evidence for a physiological reserve in cognitive functioning in relapsing-remitting multiple sclerosis.
Journal of the Neurological Sciences, 356(1-2), pp. 107-112.

- IV. **Sundgren, M.**, Piehl, F., Wahlin, Å. and Brismar, T.
Cognitive function did not improve after initiation of natalizumab treatment in relapsing-remitting multiple sclerosis. A prospective one-year dual control group study.
Manuscript

Paper I-III are reproduced with the permission from the publishers.

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
BDI	Beck Depression Inventory
BDI-NS	Beck Depression Inventory, non-somatic items
BDI-S	Beck Depression Inventory, somatic items
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BVRT-5	Benton Visual Retention Test
CES-D	Center for Epidemiological Studies – Depression scale
CIS	Clinically Isolated Syndrome
CNS	Central nervous system
D-KEFS	Delis-Kaplan Executive Function System
DMT	Disease modifying treatment
EDSS	Kurtzke Expanded Disability Status Scale
EEG	Electroencephalogram
ERP	Event-related potential
ESS	Epworth Sleepiness Scale
fMRI	Functional magnetic resonance imaging
FSMC	Fatigue Scale for Motor and Cognitive functions
FSS	Fatigue Severity Scale
HC	Healthy control group
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MS-C	Multiple sclerosis control group
MS-NZ	Multiple sclerosis natalizumab group
MSSS	Multiple Sclerosis Severity Score
NZ	Natalizumab
n.s.	Non-significant
P150	Event-related potential with largest positive peak in the 130-200 ms interval from visual stimuli
P300	Event-related potential with largest positive peak in the

	200-500 ms interval from visual or auditory stimuli
PH	Perceived health
PPMS	Primary progressive multiple sclerosis
RAVLT	Rey Auditory Verbal Learning Test
RAVLT-recall	Rey Auditory Verbal Learning Test, recall part
RRMS	Relapsing-remitting multiple sclerosis
RT	Response time
S.D.	Standard deviation
SDMT	Symbol Digit Modalities Test
SLDT	Swedish Lexical Decision Test
SPMS	Secondary progressive multiple sclerosis
SRB:1	Synonyms, Reasoning and Block test, part 1 ('Vocabulary')
WAIS-III	Wechsler Adult Intelligence Scale – third edition

1 INTRODUCTION

1.1 MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) primarily affecting persons between 20-40 years of age. MS is a leading cause of neurologic disability among young adults in the developed world. Worldwide, there are more than 2.5 million MS patients [1]. In Sweden, the incidence and prevalence of MS has been estimated to 10.2 and 188.9/100 000/year, respectively, resulting in approximately 17 500 patients, with a female to male ratio of 2.35:1 [2, 3].

Pathologically, MS is characterized by widespread lesions, or plaques, in the brain and spinal cord, causing a variable degree of inflammation, gliosis and neurodegeneration. The pathogenesis involves both the innate and adaptive immune system leading to widespread focal lymphocytic infiltration. The exact cause of MS is yet unknown. A complex interaction of genetic and environmental factors which triggers an abnormal immune response is suggested [4]. Inflammatory lesions primarily affect the myelin sheath causing inhibition of axonal transmission which eventually leads to irreversible axonal loss. MS is mainly regarded as a demyelinating disease of the white matter in the brain, but involvement of the cortical grey matter is also an important element and not restricted to the progressive stages of the disease [5].

The diagnosis of MS rests on a combination of disease history, clinical signs and defined paraclinical findings [6]. Depending on the disease course, MS patients are separated into three subgroups: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS) [7]. The disease typically presents as RRMS where neurological symptoms evolve sub-acutely and then persist for days or weeks before they gradually remit, however, often leaving some permanent residual neurological symptoms. Neurological deficits depend on the location of the lesions within the CNS but are usually motor, sensory or visual, or a combination of all. The relapse rate is highly variable between patients. The degree of residual symptoms tends to increase with reoccurring relapses. After a variable period of time, most RRMS patients enter a progressive phase where physical disability gradually increases without clear relapses (SPMS). In PPMS, the disease is progressive from start. Importantly, in SPMS and PPMS, neuroinflammation is less pronounced and disease progression is driven mainly by other, less well characterized, mechanisms [4].

During the last 20 years, an increasing number of effective drugs for MS have become available. Disease modifying treatment (DMT) has the ability to reduce the frequency of clinical relapses, the accumulation of neurological disability and the radiological signs of disease activity [8]. To date, the use of DMT is restricted to patients with RRMS. The list of currently approved DMTs in Sweden includes interferon beta (1a and 1b), glatiramer acetat, natalizumab, fingolimod, dimethyl fumarate, teriflunamide and alemtuzumab [9]. Overall, the

basic principle of action for DMTs is inhibition of lymphocyte activity, proliferation and/or migration, thus affecting only the inflammatory component of the disease [8].

1.2 COGNITIVE IMPAIRMENT IN MS

Besides motor, sensory and visual deficits, MS leads to mood and cognitive disturbances. In the last decades, research in MS has increased remarkably. However, at the beginning of this research project, the amount of research dedicated to the cognitive field of MS had not increased equally [10]. Cognitive impairment in MS is frequent, affecting up to 65% of patients in cross sectional studies [14, 15]. It is detectable at all stages and subtypes of the disease [16], including patients with clinically isolated syndrome (CIS) [17]. In RRMS, the prevalence of cognitive dysfunction is estimated to 22-40% [16, 18]. Patients with SPMS or PPMS tend to have an even higher frequency of cognitive impairment [19]. Cognitive impairment in MS usually persists and worsens over time [14, 20]. The need for a deeper understanding of MS-associated cognitive impairment is stressed by its detrimental effects on many activities of daily life such as physical independence, employment, coping, medication adherence, symptom management, rehabilitation potential and driving safety [11]. Self-perception of cognitive performance in MS patients is unreliable and not predictive of objective cognitive functioning [12, 13] and formal testing is therefore necessary.

Cognition is not a uniform entity, but includes many aspects of complex mental functions. Various domains of cognitive functioning can be affected in MS. Reduced performance has been demonstrated in information processing speed, attention, executive functions and memory. Verbal fluency, but not core language abilities, is often reduced in MS. Impaired information processing speed and learning and memory are often considered the major cognitive deficits in MS [21].

While there is an overall consensus about the general profile and importance of cognitive impairment in MS, there is less consensus on clinical risk factors. Previous studies have found a modest or moderate association between cognitive performance and level of physical disability [18, 22, 23], but this relationship is likely to be less pronounced or lacking when the level of physical disability is lower [10]. Cognitive impairment may exist independently of physical disability [24]. A consistent finding in previous studies has been a weak or absent correlation between duration of MS and cognitive impairment [15, 18, 21, 23]. However, an association is likely to emerge when disease duration exceeds 10 years [10]. The speed of clinical disease progression can be measured with the Multiple Sclerosis Severity Score (MSSS) which is an algorithm based on disease duration and level of physical disability [25]. To our knowledge, the MSSS has not previously been evaluated regarding its possible relationship with cognitive performance.

The relationship between depression in MS and cognitive impairment has not been clear [21], but an association has been demonstrated in adequately powered studies [26] and primarily between depression and the cognitive domains of information processing speed and executive functions [27, 28]. Commonly used scales for depression include items rating presence and

severity of somatic symptoms which can be confounded by disease related symptoms in clinical samples such as MS patients. In these depression scales, somatic and non-somatic items can usually be separated but most prior studies have not made this distinction. However, in studies where cognitive performance was correlated with the separate components of depression, a stronger association was reported for the non-somatic symptoms [29, 30].

Fatigue is a common symptom in patients and an association with decreased information processing speed has been reported [31]. However, several other studies did not find subjective fatigue to be associated with cognitive impairment [32, 33].

A concomitant use of CNS-active psychotropic medication against depression, fatigue, pain and insomnia is often present in MS patients. These drugs may have effects, negative or positive, on cognitive performance. In studies on cognitive functioning in MS patients, information regarding the use of psychotropic medication is frequently lacking.

1.3 IMAGING AND COGNITIVE IMPAIRMENT IN MS

Magnetic resonance imaging (MRI) is the most commonly used paraclinical tool to investigate MS pathology and to monitor disease evolution. Cognitive deficits in MS has been related to a disconnection syndrome caused by involvement of white matter tracts [34]. However, most studies have shown a modest or moderate association between visible lesions and cognitive impairment in MS [35]. The overall effect of lesion volume on cognitive impairment is limited and lesion assessment alone is not considered adequate to assess and monitor cognitive function in MS patients [35].

With disease progression, white matter abnormalities change from predominantly focal and periventricular to more subtle and diffuse. Such changes are accompanied by an increase in the extent of demyelination within the grey matter [36]. Some grey matter atrophy is found early in the disease course but becomes prominent in SPMS [37] and the rate of brain atrophy is considered to accelerate around conversion from RRMS to SPMS [38]. As compared to assessment of lesions, measures of global or regional brain atrophy have a more robust association with cognitive performance in MS [39, 40]. However, quantification of brain atrophy has so far not been available in clinical practice. The presence of diffuse damage in the white and grey matter, as identified with experimental and more advanced MRI techniques, are likely to be important for the cognitive impairment [35].

Brain cortical activation can be visualized with functional MRI (fMRI). Several fMRI studies have indicated that cognitive task performance is associated with increased or altered cortical activation patterns in patients with MS [41]. RRMS patients with normal performance in a test of processing speed and working memory activated larger frontal cortical areas compared to healthy control (HC) subjects. In contrast, this increased activity was less pronounced in RRMS patients with a lower cognitive performance [41].

1.4 MODERATING FACTORS OF COGNITIVE IMPAIRMENT

As described, the relationship between measures of disease burden and cognitive outcomes is incomplete and the amount of explained variance in statistical models remains moderate [35, 42]. This phenomenon is not restricted to MS but is seen in other neurological diseases also. For example, higher levels of premorbid intelligence and educational attainment may be factors associated with a slower deterioration in Alzheimer's disease (AD). This has been attributed to a larger 'cognitive reserve', attenuating the effects of the disease process on cognitive functioning [43]. More generally, cognitive reserve can be defined as a brain structure or function that optimizes the individual cognitive performance in the presence of brain pathology or injury. Because direct measurement of cognitive reserve is not available, proxy or surrogate variables are used. Premorbid intelligence, as estimated from years of education or performance in vocabulary tests, is tested as a moderating factor together with other predictors of cognitive outcomes [44, 45]. Cross-sectional studies in populations of mixed sub-groups of MS have reported a moderating effect of premorbid intelligence on the relationship between MRI variables of disease burden and cognitive impairment [46-49]. The effect of cognitive reserve can be assessed in a correlation analysis between premorbid intelligence and cognitive test performance. To support the cognitive reserve hypothesis this correlation needs to be significantly stronger among patients than in healthy individuals [50, 51] (Fig. 1). Previous studies have reported such a finding in MS patients [52, 53]. Cognitive reserve in MS is however still a novel field of research, and the need for replication has been stressed [54].

It is important to recognize the pervasive effects of education on cognitive test performance in normal healthy individuals [55]. Premorbid intelligence may be of clinical importance even if it does not retard the speed of cognitive decline. Let us assume that there is a certain level where the cognitive decline becomes critical for work abilities and activities of daily life (Fig. 2). For individuals with high premorbid intelligence at disease onset, it takes longer to reach this critical level than for those with low premorbid intelligence. This difference may be thought of as a 'reserve' but is not meant with 'cognitive reserve'.

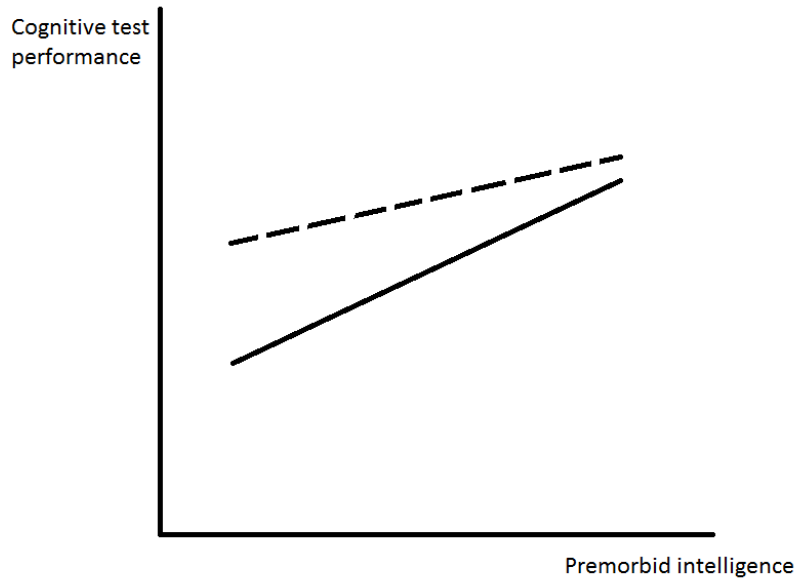


Fig. 1. Schematic illustration of the cognitive reserve hypothesis. The correlation between premorbid intelligence (*e.g.* educational attainment) and cognitive performance should be significantly stronger in the clinical sample (black solid line) than in the normal healthy sample (black interrupted line).

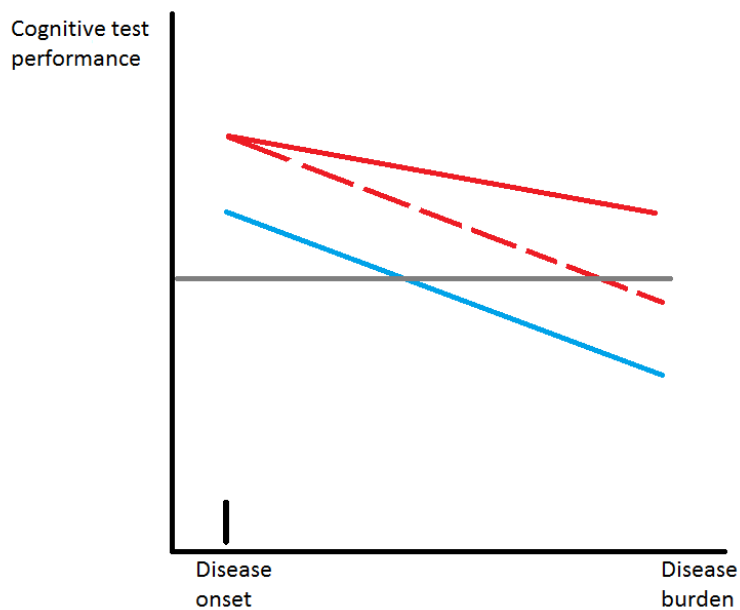


Fig. 2. Schematic illustration of the cognitive reserve hypothesis in a longitudinal analysis. The decline in cognitive performance should be slower in patients with high premorbid intelligence (red solid line) than in patients with low premorbid intelligence (blue solid line). Note that even in the absence of this phenomenon, patients with high premorbid intelligence (red interrupted line) will reach a level of clinical impairment (grey solid line) at a later stage and thus still benefit from a higher premorbid intelligence.

1.5 NEUROPHYSIOLOGICAL ASSESSMENT OF BRAIN FUNCTION

1.5.1 Event-related potentials

All mental functions are mediated through highly complex neuronal activity within the CNS. This is associated with electrical activity causing voltage fluctuations on the scalp which can be recorded in the electroencephalogram (EEG). Specific fluctuations can be elicited in the EEG in response to standardized discrimination tasks involving sensory stimuli (events). Event-related potentials (ERPs) can be elicited when a subject differentiates between two different stimuli and responds to the target with a button press. The stimuli are usually auditory (different sounds) or visual (different visual patterns on a screen). The tasks are not difficult to perform but require the participant's attention. ERP recordings are non-invasive and have an excellent temporal but moderate spatial resolution [56].

Different testing paradigms exist. In the odd-ball design, the subject is instructed to respond only to a predefined infrequent target stimulus in a train of frequent non-target stimuli. In a choice-reaction task design, the subject responds to both of the different stimuli, with a left or right hand button press. Each stimulus (visual or auditory) generates a small electrical signal which is recorded in the EEG. In order to distinguish this signal from the background spontaneous EEG activity, it is necessary to perform an averaging of repeated events. The ERPs appear as a series of positive and negative voltage fluctuations (components), which can be quantified with regard to amplitude and latency [56].

Three main models have been proposed for the mechanisms how ERPs are generated [57]. According to the evoked model, ERPs are created when silent neurons are activated by the stimulus. Another model suggests a resetting mechanism where neurons with ongoing oscillatory activity undergo sudden transition to a specific phase due to the stimulus. A third model proposes that the stimulus induces high frequency oscillations which in turn are correlated with low frequency activity and a baseline shift. The subsequent signal averaging cancels the high frequency component, leaving the baseline shifts in the EEG.

ERPs are classified in a standardized manner after polarity (N, negative or P, positive) and approximate peak latency. The most widely studied ERP is the large positively deflecting component peaking around 300 ms after the stimulus event and before the motor response (P300). P300 is generated over widespread bilateral cortical regions and dominates over centro-parietal scalp regions [58, 59]. There is general agreement that P300 is not a unitary phenomenon but rather represents distributed neural activity that comprises several functionally distinct and mutually overlapping subcomponents. *E.g.*, in easy tasks subcomponents of the P300 add together, whereas in more difficult conditions they diverge leading to a reduced amplitude [60]. Furthermore, a more frontally dominating component can be elicited depending on the nature of the stimulus paradigm [61]. The P300 component is commonly regarded as the neural origin of the cognitive processes related to volitional detection behavior and the P300 amplitude increases in proportion to the amount of attentional capacity invested in the event categorization [60]. The amplitude of P300 is also

dependent on the nature and presentation of the given stimulus. Character and appearance probability (such as inter-stimulus interval) of the targets influence the amplitude [61]. P300 latency is considered to measure the time required to detect and evaluate a given stimulus [62]. Any brain disorder affecting cognitive processes may reduce amplitude and increase latency of the P300 [63].

Early ERP components, appearing <200 ms after a stimulus, are commonly regarded as sensory or exogenous in nature with no relation to cognitive processes. However, an association between early components and cognitive function has been described in diabetes mellitus [64].

1.5.2 Event-related potentials and MS

Previous research with ERP assessments in MS patients is heterogeneous due to discrepancies in sample size, clinical characteristics, cognitive testing and EEG electrode numbers [65, 66]. Most previous ERP-studies have included mixed samples of MS-patients, including both patients with RRMS and those with progressive subtypes of the disease, making inferences or generalizations regarding subgroups of MS difficult. These studies have generally reported reduced amplitude and increased latency of the P300 component [65, 66]. Larger effects on P300 are seen in the SPMS and PPMS, compared to RRMS [67]. Some studies report normal P300 amplitudes in MS patients, despite reduced cognitive test performance [68, 69]. In CIS patients with reduced cognitive performance, P300 amplitude and latency are normal [70].

Few studies have combined MRI and ERP recordings in MS. P300 latency has been reported to be increased and to be correlated with MRI lesions [71]. In another study, P300 to auditory and visual stimuli were normal in three groups of MS patients stratified after degree and distribution of MRI lesions [72]. In MS, early ERP components were found to be both normal [69, 71] and abnormal [73-76].

1.5.3 Response time

Performance in time-dependent cognitive tests is often reduced in MS patients. The response time (RT) of auditory and visual target detection can be assessed during ERP recordings but is frequently lacking in studies with MS patients. RT in ERP stimulation tasks has been reported to be slower [72, 75] or normal [77] but the studies differ with regard to MS patient characteristics and type and difficulty of stimuli. Fast RT is associated with better cognitive abilities in healthy individuals [78]. Similarly, a relationship between RT and measures of processing speed has been reported in RRMS patients [79]. They found that RT in choice reaction tasks was a more sensitive measure of impaired information processing in RRMS as compared to a simple RT task.

1.6 TREATMENT OF COGNITIVE DYSFUNCTION IN MS

There is no proven effective rehabilitation program or symptomatic treatment for MS-related cognitive dysfunction. Symptomatic drug treatment to ameliorate cognitive impairment in

MS patients has been investigated. A randomized clinical trial with donepezil (an acetyl cholinesterase inhibitor approved for AD) was negative [80]. Furthermore, the evidence from trials using central stimulants is weak or non-existing [81]. Many studies have reported some cognitive improvement in MS patients following cognitive rehabilitation programs. However, the evidence reported in the literature remains inconclusive, mainly due to methodological weaknesses [82, 83].

All approved DMTs reduce the accumulation of brain damage as measured by MRI and thus should have the potential to slow or restore cognitive function in patients. However, data is not abundant regarding the specific effects of DMTs on cognitive functioning in MS. Most studies report an improvement or less deterioration in patients receiving DMTs. However, the interpretation of data in clinical trials with DMTs is complicated because cognitive performance is usually a secondary outcome measure and cognitive testing is often restricted to a single test [81]. Natalizumab (NZ) is one of the more potent DMTs available. Studies regarding its effect on cognitive outcome in RRMS have reported beneficial effects, however often lacking control groups [84-91].

2 AIMS OF THE THESIS

2.1 GENERAL AIM

The general aim of this thesis was to identify clinical risk factors and neurophysiological correlates of cognitive impairment in RRMS patients, and to study the effect of NZ treatment on cognitive functioning.

2.2 SPECIFIC AIMS

The aim of paper I was to identify the strongest clinical risk factors for cognitive impairment in RRMS patients. Physical disability, depression and fatigue are known to be interrelated in MS and may all influence cognitive function. The comparison included the importance of the disease progression speed *vs.* physical disability, the somatic *vs.* non-somatic component of depression, and the possible confounding effect of psychotropic medication (*e.g.* antidepressants).

The aim of paper II was to explore if cognitive impairment in RRMS patients is associated with abnormal neuronal function, if there is evidence of neural compensatory mechanisms and if the association between cognitive function and ERP variables is different in patients compared to HC subjects.

The aim of paper III was to distinguish how different factors influence cognitive function in RRMS. In particular, we tested if cognitive impairment in RRMS is influenced by premorbid intelligence, how much of the variance in cognitive function is explained by clinical and neurophysiological predictors, and if the associations of P300 and RT with cognitive performance are moderated by premorbid intelligence.

The aim of paper IV was to examine the effects of the first year of NZ treatment, compared with a control receiving standard DMT, on cognitive functioning in RRMS patients. A second objective was to study the effects on measures of depression, fatigue, daytime sleepiness and perceived health.

3 SUBJECTS AND METHODS

3.1 SUBJECTS

RRMS is the largest subgroup of MS and the only one in which DMTs are approved. The degree of cognitive impairment may vary depending on subgroup [19]. For these reasons, only RRMS patients were included in this research project.

The thesis is based on the results from two sets of data. Dataset 1 (paper I, II and III) is a cross-sectional analysis including RRMS patients (n=72) and HC subjects (n=89). The patients were recruited at the Department of Neurology at the Karolinska University Hospital in Stockholm (Solna) between April 2006 and May 2011. The HC subjects were recruited randomly by the aid of the Swedish population registry (Statistiska centralbyrån).

Dataset 2 (paper IV) is a longitudinal analysis including RRMS patients (n=30) and HC subjects (n=12), tested twice with an interval of one year. The participants in dataset 2 were recruited between February 2010 and June 2012. The HC subjects in paper IV were chosen from the HC subjects of dataset 1.

3.2 CLINICAL INSTRUMENTS

All patients and control subjects were clinically evaluated. The instruments used for the different groups are indicated in the list below.

The Kurtzke Expanded Disability Status Scale (EDSS) [92] was used to assess physical disability in patients. This scale has been designed specifically for MS patients and is the most frequently and widely used scale to rate physical disability.

Multiple Sclerosis Severity Score (MSSS) [25] was used to rate disease severity. The MSSS is an algorithm relating the score on EDSS with disease duration.

Beck Depression Inventory (BDI) [93] was used to assess symptoms of depression in patients and HC subjects in all papers. BDI is a widely used self-report questionnaire for scoring depressive symptoms, and it is recommended for use in populations with MS [94, 95]. The BDI score was also separated into its non-somatic (BDI-NS, items 1-13), and its somatic part (BDI-S, items 14-21).

Center for Epidemiologic Studies - Depression (CES-D) [96] is a scale for self-assessment of depressive symptoms given to patients in paper IV, in addition to the BDI. CES-D is widely used and has good accuracy for predicting clinical depression in MS [97].

Fatigue Severity Scale (FSS) was used for the assessment of subjective fatigue in patients and controls in all papers. The nine item FSS is the most widely used scale to rate fatigue in MS, showing high reliability, validity and internal consistency [98].

Fatigue Scale for Motor and Cognitive functions (FSMC) [99] is a scale for rating subjective fatigue and it is designed specifically for the use in MS patients. It was given to patients in paper IV.

Epworth Sleepiness Scale (ESS) [100] was used to measure daytime sleepiness in patients in paper IV.

Perceived health (PH) was evaluated with the first item from the Health Related Quality of Life Short Form (SF-12®) [101]. It was scored on a Likert scale (1 to 5) where 1 is “excellent” and 5 is “poor”. PH was evaluated in patients in paper IV.

The scores from CES-D and FSMC may be divided and reported as four (CES-D) or two (FSMC) subscales [96, 99]. However, due to the limited sample size in paper IV and in order to reduce the number of comparisons, we included only the total scores. For the same reasons, only the total BDI score was reported in paper IV.

The HC subjects in paper IV (n=12) had received the BDI and FSS at their first test session (dataset 1) but not the CES-D, FSMC, ESS and PH. Thus, they were only given the BDI and FSS at the second evaluation.

3.3 COGNITIVE EXAMINATION

Patients and controls underwent a comprehensive cognitive evaluation covering six cognitive domains (memory, verbal ability, attention, executive functions, visual perception and organization and processing speed). The included tests were available in Swedish and could be administered, after sufficient training, by a non-neuropsychologist. All participants were tested in a distraction-free and quiet environment. Several tests measure more than one cognitive ability and were thus included in more than one cognitive domain. The grouping of tests and subtests into cognitive domains was theoretical and decided after discussion among the authors of paper I (Table 1). The included tests are listed below.

Benton Visual Retention Test (BVRT-5) (Form C, Administration A) [102]. The task is to memorize and reproduce visual patterns. Domains: memory, visual perception and organization.

Rey Auditory Verbal Learning Test (RAVLT and RAVLT-recall) [103]. The task is to learn and recall a list of words. Domain: memory.

Vocabulary from the Synonyms, Reasoning and Block Test, part 1 (SRB:1) [104, 105]. The task is to identify correct synonyms. Domain: verbal ability. In paper III, the SRB:1 is treated as a surrogate marker for premorbid intelligence [55].

Controlled Oral Word Association Test from the Delis-Kaplan Executive Function System (D-KEFS) [106]. The task is to verbally produce, in 60 sec, as many words as possible, beginning with a specific letter. Domains: verbal ability, executive functions, processing speed.

Color-Word Interference Test from D-KEFS [106]. The test consists of four timed subtests. Condition 1 (color naming), condition 2 (word reading), condition 3 (inhibition) and condition 4 (inhibition and switching). Domains: attention (Condition 1 and 2), executive functions (Condition 1, 2, 3 and 4).

Trail Making Test from D-KEFS [106]. The test consists of five timed subtests. Condition 1 (visual scanning), condition 2 (number sequencing), condition 3 (letter sequencing), condition 4 (number-letter sequencing) and condition 5 (motor speed). Domains: attention (Condition 1, 2, 3 and 5), executive functions (Condition 1, 2, 3, 4 and 5).

Block Design Test from the Wechsler Adult Intelligence Scale - third edition (WAIS-III) [107]. The timed task is to reproduce patterns using a set of cubes. Domain: visual perception and organization.

Digit Span Test (Forward and Backward) from WAIS-III [107]. The task is to verbally repeat, forward or backward, series of digits. Domains: attention (Forward, Backward and Total), executive functions (Backward).

Digit Symbol Coding Test from WAIS-III [107]. The task is to fill in as many correct symbols as possible in 120 sec. Domains: visual perception and organization, processing speed.

Symbol Search Test from WAIS-III [107]. The task is to correctly complete as many symbol comparisons as possible in 120 sec. Domains: visual perception and organization, processing speed.

Additionally, premorbid verbal IQ was assessed by the Swedish Lexical Decision Test (SLDT) [108] in all HC subjects and in patients in paper IV. The total number of cognitive test scores was twenty. However, RAVLT and RAVLT-recall were not part of dataset 1 because they were not initially included in the patients' study protocol. Besides test grouping into domains, a global score was calculated and included in all papers. The total number of cognitive test sessions in the present thesis was 218.

<i>Cognitive domain</i>	<i>Cognitive tests</i>
Memory	Benton Visual Retention Test Rey Auditory Verbal Learning Test Rey Auditory Verbal Learning Test – recall
Verbal ability	Controlled Oral Word Association Test Vocabulary Test
Attention	Color-Word Interference Test, condition 1 and 2 Digit Span Test, Forward Digit Span Test, Backward Digit Span Test, Total Trail Making Test, condition 1,2,3 and 5
Executive functions	Color-Word Interference Test, condition 1-4 Controlled Oral Word Association Test Digit Span Test, Backward Trail Making Test, condition 1-5
Visual perception and organization	Benton Visual Retention Test Block Design Test Digit Symbol Coding Test Symbol Search Test
Processing speed	Controlled Oral Word Association Test Digit Symbol Coding Test Symbol Search Test
Global score	All tests, including subtests

Table 1. Cognitive tests and cognitive domains

3.4 NEUROPHYSIOLOGICAL INVESTIGATIONS

3.4.1 Recordings

All patients and HC subjects underwent a neurophysiological investigation which was conducted in a separately located EEG room, designated for research subjects, at the Department of Neurophysiology at the Karolinska University Hospital (Solna). The investigation was usually performed within a few days from the cognitive and clinical evaluations and in many cases it was performed on the same day. EEG was recorded with a 23-channel EEG amplifier (Nervus Digital Equipment Cephalon, Copenhagen, Denmark). The EEG silver cap electrodes were placed over both hemispheres according to the 10–20 International System. The participants first underwent a standardized resting EEG followed

by auditory and visual choice reaction tasks. The collected neurophysiological data were auditory and visual ERPs in the two modalities.

The specific procedures regarding test-response epochs, recording reference, ground electrode, inter-stimulus intervals, eye movements monitoring, sampling rate, post processing of signals and artifact rejection are detailed in paper II.

3.4.2 Auditory ERPs

Auditory ERPs were recorded during an auditory choice reaction task where the participants were seated with their eyes closed and were instructed to press response keys with their left and right index finger upon hearing low and high pitch signals, respectively. The signals were delivered through a loud speaker device at 65 dB and with a duration of 100 ms. Auditory ERP data were obtained by averaging trials with low and high pitch, respectively. P300 was identified as the largest positive peak in the interval 200-500 ms.

3.4.3 Visual ERPs

Visual ERPs were recorded with a visual choice reaction task using Kanizsa images of an illusory square or a non-square (Fig. 3). The subjects were seated in front of a screen (distance 150 cm), and instructed to press with their right or left index finger, according to given instructions, when an illusory square or a non-square was presented. Visual ERP data were obtained by averaging trials with illusory squares and non-squares, respectively. P300 was identified as the largest positive peak in the interval 200-500 ms. P150 was identified as the largest positive peak in the interval 130-200 ms.

3.4.4 Response time

Response time (RT) was measured simultaneously with the ERP recordings in the auditory and visual experiment, respectively. RT was recorded from the onset of the stimulus to the time for response (button press). RT data were obtained by averaging trials of auditory stimuli (to both auditory targets) and visual stimuli (to both visual targets), respectively.



Fig. 3. Images for the visual choice reaction task. Kanizsa illusory square (left panel) and non-square (right panel).

3.5 CALCULATIONS AND STATISTICS

3.5.1 Normalization

The cognitive test scores were normalized (z-scored) in order to adjust for the normal effects of age, sex and education. First a linear regression model of the effects of age on each cognitive test score, respectively, was calculated in the HC subjects separately for men and women. The residuals were then used to study the normal effect of education (years in school and higher education) in a second linear regression model and a final set of residuals was obtained.

The regression lines obtained in the healthy control group for each test score, respectively, were used on the patient data to adjust for the effects of age separately for men and women and education, and the final residuals were obtained for each subject and test. Z-scores were calculated by dividing the final residuals with the standard deviation (S.D.) of the final residuals in the healthy controls. In this way the tests scores obtained the same weight and the cognitive domain scores could be calculated from the mean scores of the included tests. For each participant, a global score was constructed as the average of the z-scores obtained for all tests.

ERP variables and RT were normalized to adjust for the normal effects of age and sex, following the same linear regression procedures described for the cognitive scores. Mean ERP parameter values were calculated for illusory squares and non-squares, and for low and high pitch signals, respectively. These calculations resulted in z-scored parameter values in each electrode position. Similarly, RT parameter values were also z-scored.

3.5.2 Missing data

In dataset 1, missing or excluded cognitive data were replaced with the mean value for each score in patients and controls, respectively. In dataset 2, missing data were not replaced. Only complete data, with both a baseline and follow-up value, entered the paired *t*-test analysis.

3.5.3 Group comparisons, correlations and regression analyses

Values were given as mean \pm S.D. Significance level was $p < 0.05$. Differences in means between groups were tested using *t*-test. Correlation analyses were performed with ranked data (Spearman's correlation). Multiple regression analysis was performed with robust linear regression. Paper III includes both parametric and non-parametric correlations, as indicated. In paper IV, baseline group differences were analyzed with ANOVA or Chi-square test. Other group comparisons at baseline were made with *t*-test or with Wilcoxon rank sum test in case of non-normal distributed data. Paired *t*-test was used to analyze changes in data between the first and second examination.

3.5.4 Multiple comparisons

To reduce the number of comparisons, cognitive test results were only analyzed on domain levels and as a global cognitive score. The included regression analyses have primarily used

global score as the dependent variable. In paper I, only clinical variables with a significant effect on the global score were considered to be significant. In paper II the number of comparisons was reduced by grouping electrode positions in five brain regions: frontal (F3, F4, F7, F8, Fz, Fp1, Fp2 and Fpz), central (C3, C4 and Cz), parietal (P3, P4 and Pz), temporal (T3, T4, T5 and T6) and occipital (O1, O2 and Oz). In the correlation analyses between cognitive performance and ERP variables (amplitude and latency), electrode data from responses to both targets were analyzed together in the auditory and visual modality, respectively. The Bonferroni procedure was used to correct for multiple independent comparisons. In paper II, the cumulative binomial distribution was used for multiple dependent comparisons because simultaneously recorded EEG electrode data from different locations are not independent from each other [109].

3.6 ETHICAL CONSIDERATIONS

All subjects were informed about the nature and purpose of the study before consenting to participate. The protocol was approved by the regional ethics committee (Regionala etikprövningsnämnden i Stockholm). The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

4 RESULTS

4.1 PAPER I

Sundgren, M., Maurex, L., Wahlin, Å., Piehl, F. and Brismar, T. (2013) Cognitive impairment has a strong relation to nonsomatic symptoms of depression in relapsing-remitting multiple sclerosis. *Arch Clin Neuropsychol*, 28(2), pp. 144-55.

RRMS patients (n=72) and HC subjects (n=89) were evaluated with a large cognitive test battery and an extensive clinical assessment. The clinical variables of interest were disease duration, physical disability (EDSS), disease severity (MSSS), fatigue (FSS), depression (BDI, BDI-NS, BDI-S) and presence of psychotropic medication (*e.g.* antidepressants). There were no significant differences between patients and HC in age (mean 37.9 and 38.2, respectively) or years of education (mean 13.8 and 14.1, respectively). In patients, mean disease duration was 9.3 years, EDSS 2.7 and MSSS 4.1. As expected, patients had significantly more symptoms of depression and fatigue compared to HC ($p < 0.0001$). In patients, 31.9% had a BDI score ≥ 10 indicating an increased risk of depression. Patients had a high level of subjective fatigue as 52.8% had an FSS score ≥ 5 .

Patients had significantly lower cognitive performance than control subjects (global score -0.71, $p < 0.0001$), affecting preferentially executive functions (-0.92), attention (-0.88), processing speed (-0.64), and visual perception and organization (-0.49). Cognitive impairment, defined as z-score < -1.5 in two or more cognitive domains, had a prevalence of 30.5%. Cognitive performance in patients had significant negative correlations (non-parametric) with several of the clinical variables. *E.g.*, global cognitive score correlated with EDSS ($r = -0.36$), FSS ($r = -0.31$) and BDI-NS ($r = -0.32$). BDI-NS had stronger correlation with cognitive function than BDI-S. Disease duration and MSSS had no or little association with cognitive impairment. In HC subjects, cognitive performance did not correlate with FSS, BDI-NS or BDI-S.

Importantly, several of the clinical variables associated with cognitive impairment in patients were intercorrelated. *E.g.*, FSS was strongly correlated with EDSS, BDI-NS and BDI-S ($p < 0.0001$). However, MSSS was not associated with FSS or BDI. Multiple regression analysis was performed to separate the effects of the clinical risk factors on cognitive function in patients. BDI-NS had stronger effect than other clinical variables, including BDI (total) and BDI-S, on cognitive function in all cognitive domains except verbal ability which had no significant predictor. The strongest relationship was between BDI-NS and executive functions ($p < 0.0001$, adjusted $r^2 = 0.223$) and visual perception and organization ($p < 0.0001$, adjusted $r^2 = 0.198$). Because depression may be secondary to the level of physical disability, we also performed a hierarchical regression analysis with EDSS as the first predictor. The model EDSS + BDI-NS resulted in higher adjusted r^2 values, as compared to BDI-NS as the single predictor, in two cognitive domains. A model with EDSS + FSS was not significant in any cognitive domain. The regression analyses were repeated after exclusion of the RRMS

patients (n=25) that were receiving any psychotropic medication. However, the results were similar.

4.2 PAPER II

Sundgren, M., Nikulin, V. V., Maurex, L., Wahlin, Å., Piehl, F. and Brismar, T. (2015) P300 amplitude and response speed relate to preserved cognitive function in relapsing-remitting multiple sclerosis. *Clin Neurophysiol*, 126(4), pp. 689-97.

The study population described in paper I also underwent a neurophysiological investigation with ERP and RT assessments.

Visual ERP

Patients had a significant decrease in P150 amplitude and increase in P150 latency in the frontal region compared to controls. Patients displayed an *increase* in the P300 amplitude in the frontal region. *E.g.*, in the Fpz electrode position the P300 amplitude (illusory square stimulation) was 8.9 ± 3.9 and 7.4 ± 3.3 μV in patients and controls, respectively ($p < 0.03$). There were no differences between patients and controls regarding visual P300 amplitudes over any other brain region. Visual P300 latency was normal in patients.

Auditory ERP

The auditory P300 amplitude in response to both targets was normal in patients. There was a small but significant increase of auditory P300 latency in five, mainly occipital electrodes, in the low and high pitch stimulation ($p = 0.002$).

ERP and correlation with cognitive function

The P150 amplitude and latency were not related to cognitive function in patients or control subjects. Contrary, there were consistent and significant correlations between cognitive function and P300 amplitude of both stimulation modalities in patients, in contrast to HC. In the linear correlation analysis between parietal visual P300 amplitude and global cognitive function the correlation coefficient was 0.44 ($p < 0.0001$) in patients and 0.11 (n.s.) in controls. The strongest correlations (non-parametric) were seen for visual P300 in the parietal region (global score, $r = 0.51$, $p < 0.0001$). P300 amplitude in other brain regions also had significant correlations with cognitive function, however less strong compared to the parietal P300. Auditory P300 amplitude correlated significantly with cognitive function in patients, albeit less so than visual. In HC subjects cognitive performance had a weak correlation ($p < 0.05$) with visual P300 amplitude in the central region, but not in any other brain region and not with auditory P300 amplitude. The correlation analyses were repeated after exclusion of the patients with ongoing psychotropic medication (n=25), as specified in paper I, and the main findings were similar.

Visual P300 latency in patients was not correlated with global score in patients and controls. Auditory P300 latency showed a *positive* correlation with three cognitive domains and the

global score. This correlation was strongest in the central region (global score, $r= 0.32$, $p=0.007$). There was no correlation between auditory P300 latency and cognitive performance in controls. Our finding differed from the findings by Whelan *et al.* (2010) (*see Errata*) who described a negative correlation similar to the association between P300 latency and cognitive performance in dementia disorders where the latency is increased [63]. Our patients had normal auditory P300 latency in the central region. A possible explanation for the present finding is that the P300 often has multiple intra-component peaks in the normal interval [61]. A selective reduction of the later components would make the peak latency appear earlier.

Visual and auditory RT

Visual RT was 0.47 ± 0.08 and 0.45 ± 0.07 seconds and auditory RT was 0.62 ± 0.15 and 0.60 ± 0.15 seconds, in patients and controls, respectively (n.s.).

RT and correlation with cognitive function

In linear correlation analysis, visual RT correlated significantly with global cognitive function in patients (-0.53 , $p<0.001$) and in controls (-0.21 , $p<0.001$). Auditory RT correlated significantly with global score in patients (-0.40 , $p<0.001$) and in controls (-0.15 , $p=0.02$). Similar to the results regarding P300, the intergroup difference in strength of correlation was significant.

In patients, RT correlated significantly with the global score and all cognitive domains except memory (*e.g.*, visual RT and global score, $r= -0.52$, $p<0.001$). In control subjects, significant correlations between RT and cognitive function were only present for visual RT, and the strongest association was observed for global score (-0.44 , $p<0.001$).

Subsequently we tested if the identified neurophysiological predictors were associated with the previously identified strongest clinical risk factors, but there were no significant correlations.

4.3 PAPER III

Sundgren, M., Wahlin, Å., Maurex, L. and Brismar, T. (2015) Event related potential and response time give evidence for a physiological reserve in cognitive functioning in relapsing-remitting multiple sclerosis. *J Neurol Sci*, 356(1-2), pp. 107-112.

In paper III, we tested the cognitive reserve hypothesis in our sample of RRMS patients, using demographic data regarding participants' formal education and level of vocabulary knowledge (SRB:1). The results were compared to the findings in paper II.

Global cognitive function had a significant positive correlation with education in both patients ($r= 0.102$, $p=0.007$) and controls ($r= 0.085$, $p=0.001$). Similarly, global score correlated with vocabulary knowledge in patients ($r= 0.29$, $p=0.004$) and controls ($r= 0.23$, $p=0.0003$). The differences in strength of correlation between groups were however not

significant. Similarly, no intergroup differences were detected when the same correlation analyses were performed for each of the cognitive domains.

The neurophysiological variables with the strongest association with global cognitive function in patients (visual RT and visual parietal P300 amplitude) and the strongest clinical predictors (EDSS and BDI-NS), were entered into a hierarchical multiple linear regression model where P300 and RT were Block 1, EDSS Block 2 and BDI-NS Block 3. The neurophysiological variables (Block 1) explained most of the variance (adjusted $r^2 = 0.335$). The clinical predictors (Block 2 and 3) added significant variance, and the final model had an adjusted r^2 of 0.444 ($p < 0.001$). The regression analysis was repeated for the separate cognitive domains as the dependent variable, respectively. P300 and RT explained most of the variance (16-29%) in five of six domains. Memory was not predicted by P300 or RT or any of the clinical predictors.

A possible moderating effect of premorbid intelligence on the association between P300/RT and cognitive function was tested in hierarchical regression models with global score and the six cognitive domains as dependent variables, respectively. Education (years) and vocabulary knowledge, respectively, were tested in Block 1 and P300 and RT, respectively, were tested in Block 2. The interactions education*P300, education*RT, vocabulary*P300 and vocabulary*RT were entered in Block 3, respectively. However, none of the interactions were found to be significant.

4.4 PAPER IV

Sundgren, M., Piehl, F., Wahlin, Å. and Brismar, T. Cognitive function did not improve after initiation of natalizumab treatment in relapsing-remitting multiple sclerosis. A prospective one-year dual control group study. *Manuscript*

MS patients starting NZ (MS-NZ, $n=15$), MS controls with stable interferon beta therapy (MS-C, $n=15$) and healthy control subjects (HC, $n=12$) performed cognitive testing twice with an intertest interval of one year. The effects of NZ on levels of self-reported depression (BDI, CES-D), fatigue (FSS, FSMC), daytime sleepiness (ESS) and perceived health (PH) were also examined. There were no differences in age, sex, years of education or verbal IQ between the three groups. MS patients (MS-NZ and MS-C) had significantly lower baseline performance in all six cognitive domains and in global cognitive function compared to HC (global score, $p=0.002$). However, there were no significant baseline differences between MS-NZ and MS-C in cognitive performance.

After one year, MS-NZ had improved significantly in memory ($p=0.015$), verbal ability ($p=0.005$), visual perception and organization ($p=0.030$), processing speed ($p=0.003$) and in global score ($p=0.013$). Similarly, MS-C improved significantly in memory ($p=0.016$), attention ($p=0.030$), executive function ($p=0.016$), visual perception and organization ($p < 0.001$), processing speed ($p < 0.001$) and global score ($p < 0.001$). The HC group improved significantly in verbal ability ($p=0.035$), visual perception and organization ($p=0.002$) and processing speed ($p=0.021$), but not in the other three cognitive domains or in global

cognitive score. Due to these results, we hypothesized that the improvements could be secondary to a stronger retest effect in subjects with low baseline test performance. A regression analysis including baseline cognitive z-score and z-score change showed that participants with lower baseline scores had a significantly greater improvement at follow-up, compared to those with a better initial performance (Spearman's rho -0.36, $p=0.021$).

There was no significant change in depression, fatigue, daytime sleepiness or perceived health in MS-NZ or MS-C. HC subjects improved significantly in FSS ($p=0.031$).

5 CONCLUSIONS

5.1 PAPER I

Symptoms of depression, especially non-somatic symptoms, and level of physical disability are the most important clinical predictors of poor cognitive performance in RRMS patients.

Fatigue is not a predictor when controlling for the effects of depression.

Cognitive performance in RRMS is not related to MSSS or treatment with psychotropic medication.

5.2 PAPER II AND III

P300 and RT have stronger association with cognitive test performance in patients than in healthy controls. In specific, patients with larger P300 amplitude and faster RT had less cognitive impairment than those with lower P300 amplitude and RT. For this reason, P300 amplitude and RT may be markers of a physiological reserve for cognitive functioning in RRMS.

The increase in frontal P300 amplitude in patients may reflect compensatory mechanisms.

The average P300 and RT showed only small differences between patients and controls, and for that reason they are not sensitive markers of brain dysfunction in RRMS.

The proposed physiological reserve may be the strongest moderator of cognitive impairment in RRMS. Physiological reserve and clinical risk factors (physical disability and depression) explain a considerable amount of the variance in cognitive functioning in RRMS. In contrast, premorbid intelligence does not constitute a cognitive reserve in RRMS.

5.3 PAPER IV

There is no evidence of a beneficial effect of NZ treatment on cognitive functioning across one year. Significant improvement may be artificial and due to retest effects.

Adequate control groups are essential when evaluating cognitive functioning in intervention trials in RRMS patients.

6 LIMITATIONS

In dataset 1, memory function was restricted to the BVRT-5. It was not a sensitive test to detect impaired memory in patients, despite being a test of immediate visual memory which is considered to be vulnerable in MS [21]. In dataset 2, the memory domain also included the RAVLT and RAVLT-recall. In paper IV, patients had significantly lower performance in memory, compared to HC.

Reduced eye saccadic initiation time and fine motor control of the hand may negatively interfere with the performance in written cognitive tests in MS, even in patients with low EDSS [110]. This could potentially have influenced performance in time-dependent tests.

Depression was assessed with self-report scales. Thus, only subjective symptoms of depression were evaluated. A clinical diagnosis of depression would have required a deeper psychiatric interview using standardized major depression criteria. However, both BDI and CES-D have shown good diagnostic accuracy for depression in MS patients [97, 111].

Anxiety is related to depression but should be regarded as a separate psychological disorder. However, a separate measure of anxiety symptoms was not included among the clinical instruments.

Disease burden was only assessed with clinical measures. MRI can provide additional information regarding lesion volume and brain atrophy.

In Paper III, the cognitive reserve hypothesis was tested using years of education and vocabulary knowledge as proxies. However, there are other proposed surrogate markers of cognitive reserve that were not included, such as IQ or questionnaires grading the level of premorbid cognitive leisure activities. A test of verbal IQ (SLDT) was given to all healthy control subjects and MS patients entering the longitudinal study, but not to the majority of MS patients in dataset 1.

In Paper IV, the relatively small numbers per group increased the risk of a type-II error regarding change in depression, fatigue, daytime sleepiness and perceived health.

7 DISCUSSION AND FUTURE PROSPECTS

7.1 CLINICAL RISK FACTORS

We identified depression, especially non-somatic symptoms of depression, and physical disability as the strongest clinical predictors of cognitive impairment in RRMS. The separation of the somatic and non-somatic items in the BDI was justified because BDI-NS had a stronger association than BDI-S with cognitive function in patients. Subjective fatigue was common in patients but it was not a significant predictor for cognitive impairment when the effects of EDSS and BDI-NS were included in regression models. Notably, the means of EDSS and BDI were not high (2.7 and 8.8, respectively). In comparison, the level of fatigue was high as more than 50% of patients scored ≥ 5 in the FSS. Our finding that subjective fatigue is not a prominent predictor of cognitive impairment in MS is in agreement with previous reports [32, 33]. Similarly, we replicated the finding that disease duration is not associated with cognitive impairment in MS [15, 18, 21, 23]. Disease progression rate, as measured with MSSS was also not associated with cognitive impairment in patients. Furthermore, MSSS was not associated with depression or fatigue.

In MS studies with cognitive outcome measures, the presence of CNS-active psychotropic drugs with potential effects on cognitive performance is frequently overlooked. However, psychotropic medication was not a confounding factor in our study. It is important to point out that the patients receiving psychotropic medication were heterogeneous with regard to indication, pharmaceutical substances, dosage and possible combinations of drugs.

EDSS is regularly monitored in RRMS patients in contrast to symptoms of depression. The results point at the importance of evaluating depression, especially non-somatic mood symptoms, in RRMS patients with cognitive impairment. As a consequence, clinicians should consider the possibility of reduced cognitive function in clinically depressed patients.

If there is an association between depressive symptoms and cognitive impairment in RRMS, would cognitive function improve if depression is successfully treated? This has not been sufficiently studied [27]. One controlled clinical study reported objective cognitive improvement parallel to improved mood [112], a finding that was not confirmed in a later study [113]. Despite the overall high prevalence of depression in persons with MS [114], there is a lack of well designed clinical trials for the treatment of depression in MS patients [115]. In future such studies, it should be considered that depressed but otherwise physically healthy individuals have an increased risk of cognitive impairment. Cognitive performance is not immediately restored after successful anti-depressive treatment [116, 117], not even when other abilities have returned to normal [118]. This issue relates to the topic regarding cognitive effects of concomitant psychotropic medication, discussed above. In our material, antidepressants were the most common psychotropic medication.

7.2 PHYSIOLOGICAL RESERVE

A major finding was that cognitive performance in RRMS patients is strongly correlated with the strength of the electrical brain signal and time for response in choice reaction tasks. These correlations were absent or weaker in healthy individuals. Importantly, RT and parietal P300 amplitude were normal in patients, and the correlations were not epiphenomena of reduced cognition. Additionally, P300 and RT were not correlated with EDSS. Similarly, in a previous study, auditory and visual P300 amplitude were normal and not significantly different between MS patients stratified according to level and distribution of MRI lesion volume [72]. The results suggest that RRMS patients rely more than healthy individuals on their level of brain attentional resources and behavioral response speed, for their cognitive performance. In other words, high P300 amplitude and fast RT may be protective against cognitive dysfunction in RRMS.

In contrast, years of education and vocabulary knowledge influenced cognitive test performance equally in patients and healthy control subjects. Accordingly, premorbid intelligence did not constitute a cognitive reserve in patients. This is in variance with previous reports [52, 53]. We do not rule out that educational attainment and vocabulary knowledge attenuate the degree of cognitive impairment in MS patients with more advanced or severe disease [53].

A physiological reserve hypothesis can be formulated in the same way as the cognitive reserve hypothesis. Accordingly, patients should have a stronger correlation between the physiological reserve variable and cognitive function than healthy individuals. Our results show that P300 amplitude and RT, in contrast to premorbid intelligence, have this association with cognitive function in RRMS. We suggest that physiological reserve is as a cognition-related neural buffer system that helps patients to compensate for the negative cognitive effects of MS pathology. Importantly, the physiological reserve explained as much as 34% of the variance in global cognitive function in RRMS. The combined effect of physiological reserve, physical disability (EDSS) and depression (BDI-NS) explained 44% of the variance.

The description of a measurable physiological reserve in RRMS is a novel finding and may help identifying RRMS patients at increased risk of cognitive impairment.

Physiological reserve has similarities with the definition of neural reserve proposed by Stern *et al.* [119]. Neural reserve represents the natural inter-individual variability in brain network efficiency and ability to perform a task. Thus, individuals with higher brain network efficiency may be better at coping with brain pathology.

Neural compensation is another concept of cognitive reserve and refers to the process by which individuals suffering from brain pathology use different brain networks, or existing networks differently, to compensate for the disruption imposed by brain disease [44, 45]. In paper II we found a small but significant *increase* in frontal P300 amplitude in RRMS patients. This finding may correspond to an increased, and possibly compensatory, fMRI signal previously described in MS patients performing cognitive tasks [41, 120, 121].

Previous studies have investigated the degree to which premorbid intelligence moderates the association between MRI indices of MS pathology and cognitive impairment [47-49]. The proposed physiological reserve should be tested similarly. Does the level of P300 amplitude and RT moderate the relationship between brain atrophy (or lesion load) and cognitive function in RRMS? Ideally, a physiological reserve hypothesis should be tested in a longitudinal study of sufficient length. Does high P300 amplitude and short RT reduce the risk of cognitive decline associated with MS? Or conversely, are patients with a lower physiological reserve at higher risk for cognitive impairment? Identification of patients with increased risk of cognitive dysfunction has recently been highlighted as an important challenge in MS [35]. MS typically begins at an earlier age than other common CNS disorders. Other concurrent dementing medical conditions are rare at this age and normal age-related cognitive decline is not yet large, which facilitates such studies.

7.3 FUTURE INTERVENTION STUDIES

In the present papers we have compared the findings in the patients with control subjects. In paper IV, it was shown that after one year, NZ therapy did not improve cognitive function as compared with the control group of other MS patients. Presumably, the increased test performance in both MS groups was artificial and due to retest effects that were stronger in patients with a lower baseline performance. The results underscore the importance of including control groups when evaluating cognitive outcomes in intervention trials. Learning or retest effects are seen in several cognitive domains, are largest in young adults, and may be significant also after many years [122]. Retest effects are not restricted to healthy individuals as they have been described in a variety of clinical samples including MS-patients [123-125]. Uncontrolled studies on cognitive function have therefore limited value. Besides the need for control groups, several methods for attenuating or eliminating retest effects have been proposed, such as alternate forms of tests, standardized massed practice and creation of reliable change indices. However, there is no consensus on the best method [126]. Contrary to common belief, alternate forms do not eliminate retest effects [127] and may, if forms are not psychometrically equivalent, introduce irrelevant variance [126]. Including only healthy individuals as controls is not likely to be sufficient, since retest effects cannot be assumed to be equal in magnitude in healthy and clinical samples or in individuals across different ages [122, 128]. Indeed, paper IV showed that the retest effect was larger in patients with a lower baseline performance. Regardless these constraints, these aspects need to be addressed in future studies, especially intervention studies with symptomatic drug treatment or cognitive rehabilitation programs. Targeted enrollment of MS patients with a lower cognitive reserve, thus at increased risk of developing cognitive impairment, has been suggested [129].

Regarding the cognitive outcome of DMT interventions, comparable non-intervention patient control groups can not readily be created, for obvious ethical reasons. If DMT mainly limits progression, rather than restoring function, a future study on cognitive function would probably need to extend over several years because the natural rate of progression of cognitive dysfunction may be slow [14]. Considering the difficulties constructing well

designed controlled clinical DMT trials with cognitive outcomes, are there acceptable alternatives? One option may be large scale observational data, which could be achieved through MS-registries [130]. However, currently only a single cognitive test (symbol digit modalities test, SDMT) is regularly monitored, and additional tests may be needed to better cover the spectrum of cognitive deficits. A three test screening battery, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), has been proposed to monitor MS cognitive performance [131]. The BICAMS, which does not require expert skills to administer, includes two memory tests (verbal and visual, respectively) besides the SDMT. The findings in the present thesis also suggest that inclusion of relevant moderating variables would improve the interpretation of cognitive outcomes following DMT interventions.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Den övergripande problemställningen i denna avhandling är kognitiv nedsättning vid multipel skleros (MS). MS är en kronisk sjukdom som drabbar unga vuxna, företrädesvis i åldern 20-40 år med övervikt för kvinnor. I Sverige finns ca 18 000 personer med MS. Vid sjukdomen uppträder återkommande lokaliserade inflammationer ("plack") inom centrala nervsystemet vilka kan ge upphov till en rad olika neurologiska symptom såsom gång-, kraft-, känsel- och synstörningar. En stor andel av MS-patienterna drabbas även av försämrade kognitiva funktioner. Särskilt ses nedsättning inom processhastighet, minne, uppmärksamhet och flexibilitets- och organisationsförmåga. MS-patienter med kognitiva problem har en ökad risk för arbetslöshet och sämre yrkeskarriär, sämre följsamhet mot ordinerad behandling och sämre upplevd livskvalitet. Inom den största MS-gruppen med s.k. skovvis förlöpande MS (relapsing-remittent MS, RRMS), uppskattas betydande kognitionssnedsättning föreligga hos mellan 22-40%.

Frågeställningarna i avhandlingens delarbeten I-III var: Vilka faktorer och sjukdomsuttryck kan öka risken för att utveckla kognitiv nedsättning vid RRMS? Är det hur länge man haft sjukdomen, grad av neurologiska bortfall, försämringstakten, grad av depression eller abnorm uttrötthet (s.k. fatigue) som är av störst betydelse?

De första delarbetena baseras på en tvärsnittsstudie av patienter med RRMS (n=72) och friska kontrollpersoner (n=89). Patienterna undersöktes kliniskt och fick besvara en rad frågeformulär. Patienter och friska undersöktes med ett kognitivt testbatteri. Hos patienterna var prestationen signifikant sämre jämfört med de friska. Som förväntat hade patienterna också betydligt högre förekomst av depression och fatigue än de friska kontrollerna. Analysen visade att depressionssymptom, ensamt eller i kombination med neurologiska bortfallssymptom, var de starkaste riskfaktorerna för kognitiv försämring vid RRMS. Betydelsen av depressionssymptomen var ännu tydligare om man exkluderade de symptom som berör kroppsliga depressionsuttryck (t.ex. dålig sömn och oro för sitt hälsotillstånd), eftersom dessa kan vara uttryck för själva grundsjukdomen. Våra fynd är viktiga eftersom de belyser att depressionssymptom, även måttliga, är kognitivt betydelsefulla och bör uppmärksammas av behandlande läkare.

Deltagarna testades också med s.k. event-related potentials (ERP) som är en EEG-metod, och samtidigt mättes reaktionstiden. I synnerhet studerade vi styrkan i en specifik ERP-signal (P300). Vi fann att sambandet mellan P300 och kognitiv prestationsförmåga var betydligt starkare i patientgruppen jämfört med friska kontroller. Samma mönster sågs vad gällde reaktionstiden. Detta betyder att patienter som har, eller förmår upprätthålla, en starkare hjärnsignal (eller snabbare reaktionstid) var betydligt mindre benägna att uppvisa kognitiv nedsättning. Detta vittnar om att det finns en fysiologisk kognitiv reservkapacitet som utnyttjas vid RRMS, som kan förhindra eller minimera kognitiv försämring.

Kognitiva reservmekanismer har studerats tidigare, framför allt inom demensforskningen. Medfödda eller förvärvade faktorer har i viss utsträckning visats kunna skydda personers kognitiva funktioner i händelse av en sjukdom som drabbar hjärnan. Hög utbildningsnivå och god s.k. vokabulär kunskap har ansetts vara en sådan faktor, även vid MS. Vi testade denna hypotes på vårt studiematerial. I sådana jämförelser måste man ta hänsyn till att dessa faktorer även påverkar testresultatet hos friska försökspersoner, och testdata måste korrigeras därefter. Vi fann att patienter med högre utbildning och god vokabulär inte hade en mindre grad av kognitiv nedsättning jämfört de patienter som hade lägre utbildning. Hög utbildning och vokabulär kunskap utgjorde därmed ingen kognitiv reserv vid RRMS. Detta till skillnad från hög P300 amplitud och snabb reaktionstid som alltså uppvisade de kännetecken som karaktäriserar en kognitiv reserv. P300 och reaktionstiden kunde i våra beräkningar förklara en stor del av risken att utveckla kognitiv nedsättning vid RRMS. Denna reserv har tidigare inte beskrivits inom MS och kan komma att förbättra möjligheterna att identifiera MS-patienter med högre respektive lägre risk för kognitiv svikt.

Många s.k. bromsmediciner finns idag för behandling av RRMS. En vanlig förstahandsbehandling vid RRMS är interferon-beta men flera alternativ har tillkommit under de senaste åren och som inkluderar behandlingar som i mycket hög utsträckning minskar den inflammatoriska komponenten i sjukdomen. Det har emellertid gjorts få studier som specifikt utvärderar dessa läkemedels effekter på de kognitiva förmågorna. En av de mest effektiva bromsmedicinerna är natalizumab (NZ). Vår hypotes i delarbete IV var att NZ-behandling kunde motverka eller reversera kognitiv försämring vid RRMS. Vi genomförde en longitudinell studie där en grupp RRMS-patienter (n=15) som startade NZ-behandling jämfördes med stabila patienter på förstahandsbehandling (n=15) samt friska kontrollpersoner (n=12). Alla tre grupper testades kognitivt två gånger med ett års mellanrum. I båda MS-grupperna, och i viss utsträckning även också hos de friska kontrollerna, sågs signifikanta förbättringar efter ett år. NZ-behandlade patienter förbättrades inte mer än den andra MS-gruppen. Vi drog slutsatsen att de förbättrade kognitiva testresultaten var s.k. inlärningseffekter. Vi fann också att inlärningseffekten var starkare hos individer med ett sämre första resultat. Tidigare kognitionsstudier på NZ har sällan inkluderat kontrollgrupper och därmed inte observerat denna effekt. Vår slutsats är att NZ inte ger en mätbar kognitiv förbättring efter ett års behandling. Framtida behandlingsstudier bör ha noggrant definierade kontrollgrupper, beakta normala inlärningseffekter, löpa över längre tid samt med fördel även inkludera uppskattningar av deltagarnas kognitiva reservkapacitet.

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