

Sanna Liuha

Three Different Approaches to  
Cognitive Fatigue in Patients with  
a Mild Form of Multiple Sclerosis:

Objective Cognitive, Subjective  
Cognitive and Neurophysiological



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Editors

Timo Suutama

Department of Psychology, University of Jyväskylä

Pekka Olsbo, Ville Korhakangas

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## ABSTRACT

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Three different approaches to cognitive fatigue in patients with a mild form of multiple sclerosis: Objective cognitive, subjective cognitive and neurophysiological

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The purpose of this study was to evaluate cognitive fatigue in patients with a mild form of multiple sclerosis (MS) from three different approaches: objective cognitive, subjective cognitive and neurophysiological. Objective cognitive fatigue was assessed with tasks demanding sustained attention, processing speed and working memory. Subjective cognitive fatigue was assessed with self-reported values. Neurophysiological assessment included measurements of event-related potentials (ERP), namely contingent negative variation (CNV) and P3. Alongside these measurements, the participants evaluated their quality of life. 20 MS patients and 20 matched healthy controls (HC) participated in the study. The two study groups did not differ from one another in a brief cognitive screening found to be sensitive to cognitive deficits in MS. Neuropsychological tests revealed some signs of objective cognitive fatigue in both study groups and possible signs of MS-related cognitive fatigue. In both study groups, this manifested as declining cognitive performance within the Paced Auditory Serial Addition Task (PASAT), and in the MS patients as longer reaction times during the last task in the study procedure. At the same time as the reaction times were longer, the analysis of ERPs revealed smaller CNV amplitudes in the frontal electrode sites in the MS group. Moreover, the P3 Go latencies were shorter and the P3 No-Go amplitudes were smaller at the Cz. These results for the MS patients indicated atypical preparation processes when focusing attention in the frontal brain area and attenuated resource allocation for No-Go stimuli. The ERP measurements did not reveal signs of objective cognitive fatigue. Both study groups reported cognitive fatigue caused by cognitive strain. After resting for half an hour, the HCs reported better recovery from subjective cognitive fatigue than the MS patients. The objective neuropsychological results were not associated with the ERP measurements. The subjective evaluations of cognitive fatigue were not associated with the objective cognitive or neurophysiological results. Perceived quality of life was rated lower by the MS patients than HCs. The MS patients' quality of life ratings were associated with their ratings of subjective cognitive fatigue. This may affect the MS patients' idea of their working ability. The results indicate that cognitive fatigue is present in healthy people as well as in patients with MS. It seems that objective cognitive and subjective cognitive fatigue are separate symptoms and that subjective cognitive fatigue does not necessarily affect objective cognitive performance. MS seems to slow down recovery from subjective cognitive fatigue.

Keywords: Multiple sclerosis, fatigue, cognition, CNV, P3 , quality of life

**Author's address** Sanna Liuha  
Department of Neurology, Jyväskylä Central Hospital  
Keskussairaalantie 19, 40620 Jyväskylä  
sanna.liuha@ksshp.fi

**Supervisors** Jukka Kaartinen  
Department of Psychology  
University of Jyväskylä

Päivi Hämäläinen  
Neuroliiton Maskun neurologinen kuntoutuskeskus  
Vaihemäentie 10, 21250 Masku

Timo Ahonen  
Department of Psychology  
University of Jyväskylä

Harri Högmander  
Department of Mathematics and Statistics  
University of Jyväskylä

**Reviewers** Eija Rosti-Otajärvi  
Tampere University Hospital  
Teiskontie 35, 33521 Tampere

Matti Erkinjuntti  
Turku University Hospital  
Kiinamylynkatu 4-8, 20521 Turku

**Opponent** Eija Rosti-Otajärvi  
Tampere University Hospital  
Teiskontie 35, 33521 Tampere

## TIIVISTELMÄ

Liuha, Sanna

Kolme lähestymistapaa kognitiiviseen uupumukseen lievää MS-tautia sairastavilla potilailla: objektiivinen kognitiivinen, subjektiivinen kognitiivinen ja neurofysiologinen  
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Tämän tutkimuksen tarkoitus oli arvioida kognitiivista uupumusta lievää multippeli skleroosin (MS) muotoa sairastavilla potilailla kolmea eri lähestymistapaa käyttäen: objektiivista kognitiivista, subjektiivista kognitiivista ja neurofysiologista. Objektiivista kognitiivista uupumusta arvioitiin tarkkaavuuden ylläpitoa, reaktionopeutta ja työmuistia mittaavilla tehtävillä. Subjektiivista kognitiivista uupumusta sekä elämänlaatua arvioitiin itsearvioilla. Neurofysiologiset mittaukset käsittivät aivojen sähköisiin herätevästeisiin perustuvia observaatioita. Mittareina olivat kontingentti negatiivinen variaatio (CNV) ja P3. Tutkimukseen osallistui 20 MS-tautia sairastavaa ja 20 verrallistettua tervettä henkilöä. Tutkimusryhmät eivät eronneet kognitiivisesti toisistaan suppeassa arviossa, joka on havaittu herkäksi havaitsemaan MS-potilaiden kognitiivisia suoritusmuutoksia. Tarkemmassa tutkimuksessa ryhmien välillä oli havaittavissa eroja. Neuropsykologisissa testeissä tuli esiin merkkejä objektiivisesta kognitiivisesta uupumuksesta molemmista tutkimusryhmissä ja mahdollisia merkkejä MS-tautiin liittyvää objektiivisesta kognitiivisesta uupumuksesta. Nämä tulivat esiin heikentyvänä suoriutumisenä tehtävän loppua kohti molemmista tutkimusryhmissä sekä MS-potilaiden hitaampina reaktioaikoina viimeisen tutkimustehtävän aikana. Samalla kun MS-potilaiden reaktioajat olivat verrokkeja hitaammat, CNV oli potilaiden aivojen frontaalialuilla amplitudiltaan pienempi kuin verrokeilla. Lisäksi Cz-kanavalla inhibitiota vaativissa ärsykkeissä MS-potilaiden P3 amplitudit olivat verrokkeja pienemmät ja reaktiota vaativissa ärsykkeissä latenssit olivat verrokkeja lyhyemmät. Tulokset tarkoittavat häiriötä tarkkaavuuden kohdentamisen CNV:n ilmaisemassa valmistautumis-prosessissa ja vaimentumista MS-potilaiden voimavarojen kohdentamisessa P3:n reagoimatta jätettäviin ärsykkeisiin. Objektiivisissa mittauksissa saadut tulokset eivät olleet yhteydessä toisiinsa tai subjektiivisiin arvioihin kognitiivisesta uupumuksesta. Elektrofysiologisissa mittauksissa ei tullut esiin objektiiviseen kognitiiviseen uupumukseen viittaavia muutoksia. Tutkimusryhmät arvioivat kognitiivisen kuormituksen aiheuttavan kognitiivista uupumusta, mutta MS-potilaat kokivat toipuvansa siitä terveitä heikommin. MS-potilaat arvioivat elämänlaatunsa terveitä alhaisemmaksi ja matalampi elämänlaatuarvio oli yhteydessä koettuun kognitiiviseen uupumuksen tunteeseen, mikä voi vaikuttaa osaltaan MS-potilaiden kokemukseen työkykyvystään. Tulosten perusteella kognitiivista uupumusta voi esiintyä sekä terveillä että MS-tautia sairastavilla. Objektiivinen kognitiivinen ja subjektiivinen kognitiivinen uupuminen näyttävät olevan toisistaan erillisiä ilmiöitä eikä subjektiivinen kognitiivinen uupuminen vaikuta välttämättä kognitiiviseen suoritustasoon. MS-tauti näyttää kuitenkin hidastavan subjektiivisesta kognitiivisesta uupumuksesta toipumista.

Avainsanat: multippeli skleroosi, uupumus, kognitio, CNV, P3, elämänlaatu



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## FIGURES

FIGURE 1	Distribution of the ERP sites.....	31
FIGURE 2	Procedure of the study protocol.....	32
FIGURE 3	Visual analogue scale for fatigue (VAS-F) evaluations.....	39
FIGURE 4	Health-related quality of life.....	40
FIGURE 5	CNV at F3 site, first part of the CPT .....	42
FIGURE 6	CNV at Fz site, first part of the CPT .....	42
FIGURE 7	CNV at F4 site, first part of the CPT .....	43
FIGURE 8	CNV at F3 site, second part of the CPT .....	43
FIGURE 9	CNV at Fz site, second part of the CPT.....	44
FIGURE 10	CNV at F4 site, second part of the CPT.....	44
FIGURE 11	CNV at F3 site, third part of the CPT .....	45
FIGURE 12	CNV at Fz site, third part of the CPT .....	45
FIGURE 13	CNV at F4 site, third part of the CPT .....	46
FIGURE 14	P3 at Cz site during CPT in No-Go condition; first part of the task .....	51
FIGURE 15	P3 at Cz site during CPT in No-Go condition; second part of the task .....	51
FIGURE 16	P3 at Cz site during CPT in No-Go condition; third part of the task .....	52

## TABLES

TABLE 1	Demographic, clinical and cognitive characteristics of the MS and control groups .....	35
TABLE 2	Cognitive performance in RVP, PASAT 2", 3" and CPT.....	36
TABLE 3	Ability to sustain attention in RVP, PASAT 3" & 2" and CPT .....	38
TABLE 4	CNV values during CPT.....	41
TABLE 5	P3 latencies during CPT, Go condition .....	47
TABLE 6	P3 amplitudes during CPT, Go condition .....	48
TABLE 7	P3 latencies during CPT, No-Go condition .....	49
TABLE 8	P3 amplitudes during CPT, No-Go condition.....	50

## CONTENTS

ABSTRACT  
TIIVISTELMÄ  
ACKNOWLEDGEMENTS  
FIGURES AND TABLES  
CONTENTS

1	INTRODUCTION .....	11
1.1	Characteristics of multiple sclerosis.....	11
1.2	Fatigue as a symptom .....	13
1.2.1	Fatigue in neurological diseases .....	13
1.2.2	Fatigue in MS .....	14
1.2.3	Cognitive fatigue in MS research.....	15
1.3	The relationship between objective and subjective fatigue in MS.....	17
1.4	The relationship of fatigue to disability and quality of life .....	19
1.5	The neurophysiological markers of cognitive fatigue in MS .....	20
1.5.1	MRI and fMRI .....	21
1.5.2	Components of event-related potentials.....	22
1.6	Aims and hypotheses .....	25
2	METHODS .....	27
2.1	Participants .....	27
2.2	Evaluation of cognitive status.....	28
2.3	Evaluation of cognitive performance profile.....	28
2.4	Evaluation of subjective cognitive fatigue .....	29
2.5	The 15-D generic questionnaire of quality of life.....	30
2.6	Collection and evaluation of neurophysiological data .....	30
2.7	Procedure .....	31
2.8	Statistical analyses .....	32
3	RESULTS .....	34
3.1	Results on cognitive status, mood and demographic variables .....	34
3.2	Cognitive performance profiles.....	35
3.2.1	Rapid visual perception .....	35
3.2.2	Paced auditorial serial addition task 2" and 3" .....	37
3.2.3	Continuous Performance Task.....	37
3.2.4	Ability to sustain attention by response time variability, coefficient of variation, dyad scores and percent dyad scores .	37
3.3	Results for subjective cognitive fatigue .....	38
3.4	Results for ratings of quality of life.....	39
3.5	Results of the ERPs .....	40
3.6	Associations between the neuropsychological data, subjective evaluations and neurophysiological data .....	53

4	DISCUSSION .....	54
4.1	Neuropsychological variables measuring objective cognitive fatigue.....	54
4.2	Subjective cognitive fatigue.....	58
4.3	Neurophysiological measures .....	59
4.4	Correlation between neuropsychological variables, subjective cognitive fatigue estimations and neurophysiological measures.....	61
4.5	Strengths and weaknesses of the present study.....	63
4.6	Conclusions .....	64
	YHTEENVETO.....	66
	REFERENCES.....	68

# 1 INTRODUCTION

Fatigue is a nonspecific symptom that can occur in healthy persons as well as in people with an illness. It is reported as a symptom in many neurological diseases, for example Parkinson's disease, myasthenia gravis, chronic fatigue syndrome and multiple sclerosis. Usually the term "fatigue" refers to a perceived lack of physical or mental energy or stamina that impairs a person's ability to function normally (Miller, 1998). Fatigue is experienced as a feeling of tiredness before, during or after a task. A similar feeling can be induced by poor muscular condition, depression or the use of certain medications (Chaudhuri & Behan, 2004). Multiple sclerosis (MS) is a debilitating neurological disease that occurs in young people. It often has important consequences for cognition, motor abilities and quality of daily life. Previous research has reported that these factors are often affected by the same common symptom, namely fatigue. One type of fatigue is cognitive fatigue. In the literature, cognitive fatigue refers to the inability to sustain a constant level of performance during a cognitive task or to a decline in performance during a cognitive task or over time in repeated cognitive tasks (Bruce, Bruce, & Arnett, 2010; Krupp & Elkins, 2000; Kujala, Portin, Revonsuo, & Ruutiainen, 1995; Schwid et al., 2003). The purpose of this study was to evaluate different aspects of fatigue in patients with a mild form of MS, with special focus on cognitive fatigue. This was done by objective neuropsychological assessment, subjective evaluations and electrophysiological electroencephalogram measurements.

## 1.1 Characteristics of multiple sclerosis

MS is a chronic inflammatory, progressive and degenerative disease of the central nervous system. MS is characterized by demyelination, axonal loss (Petzold et al., 2005) and grey matter atrophy (Filippi, Valsasina, & Rocca, 2007). Common manifestations include cognitive impairment, affective disorders, impairment of cranial nerves, impairment of sensory or motor pathways,

impairment of cerebellar pathways and impairment of bladder, bowel and sexual functions (Houtchens, Lublin, Miller, & Houry, 2012), depending on the location and size of the inflammatory foci, i.e., plaques (Tienari, 2014). A plaque consists of a discrete region of demyelination with relative preservation of axons. Individual lesions are generally small but may become confluent, forming large plaques. Plaques develop in a perivenular distribution and are seen most frequently in the periventricular white matter, brainstem and spinal cord. In the plaque, myelin which provides insulation for electrical impulses traveling along axons is destroyed, resulting in myelin debris found in clumps or within lipid-laden macrophages (Houtchens et al., 2012).

The most characteristic clinical course of MS is the occurrence of relapses where acute or subacute clinical dysfunction occurs and reaches its peak over a period ranging from days to several weeks. Relapses are followed by a remission stage during which the symptoms and signs usually resolve, either partially or completely (Houtchens et al., 2012). The cause of MS is unknown but it appears to have an autoimmune origin. Different subtypes of MS can be differentiated from one another according to the way the disease progresses. According to one definition, MS has four different subtypes, namely relapsing-remitting, secondarily progressive, primarily progressive and progressive relapsing (Houtchens et al., 2012).

The relapsing-remitting form of the disease is characterized by clearly defined relapses from which the patient usually recovers fully or with residual deficit on recovery. In secondary progressive MS, the course of the disease is initially relapsing-remitting, but is followed by progression with or without occasional relapses, minor remissions and plateaus. The primary progressive form of the disease progresses steadily from onset and may include occasional plateaus and temporary minor improvements. Progressive relapsing MS is characterized by progression from the onset of the disease. It also has clear acute relapses with or without full recovery. In between relapses, continuing progression of the disease is typical (Houtchens et al., 2012). These phenotypes were used in the present study.

The mean and median onset age of the disease is between ages 29 to 32. The peak age of onset is approximately five years earlier for women than for men. MS is also more common in women than in men. The onset of MS can occur as late as the seventh decade and in a small proportion of patients onset occurs before age 18 (Houtchens et al., 2012). Thus far, no curative medication exists for the disease. The course of the disease is individual and it is estimated to shorten life expectancy by seven years (Tienari, 2014). Onset of the disease at an early age seems to be a favorable factor for life expectancy, whereas onset at a later age carries a less favorable prognosis (Houtchens et al., 2012).

Despite the lack of a curative treatment for the disease, treatments for acute relapses and disease-modifying treatments and medications for controlling symptoms such as spasticity are available. Acute relapses are typically treated with corticosteroids or plasma exchange. The disease-modifying medications can be divided into first-line, second-line and third-line

medications. Unless the activity of the disease demands more drastic measures, care is usually started with first-line medications. First-line medications comprise betainterferons, dimethylfumarate, glatiramer acetate and teriflunomide. Second-line medications include fingolimod and natalizumab. Mitoxantrone is used to treat the disease as a third-line medication (Remes et al., 2015). Some medications, of which amantadine and modafinil are the most commonly prescribed, are used to treat MS-related fatigue, but the effect of these pharmacological interventions seems to be weak and inconclusive (Asano & Finlayson, 2014).

MS is the most common neurological disease causing invalidity among young people in Finland. The prevalence of MS in Finland is around 130/100 000 inhabitants, but considerable different regional differences exist. MS is more common in the western part of Finland than in eastern and southern parts of the country. Epidemiological studies have shown that the prevalence of MS has increased and that local differences have continued to increase. Currently, over 7000 persons have diagnosed MS in Finland and the disease is twice as common in women as in men (Remes et al., 2015; Tienari, 2016).

According to previous studies, cognitive impairment is present in 40–65% of MS patients (Amato et al., 2010; Hämäläinen & Rosti-Otajärvi, 2016). The most vulnerable cognitive functions are memory, attention, information-processing speed, executive functions and visuospatial perception Chiaravalloti & DeLuca, 2008; Langdon, 2011). Of these, processing speed seems to be especially vulnerable (DeLuca et al., 2004). In a Finnish follow-up study, newly diagnosed MS patients showed deficits in attention and information-processing speed already at an early stage of the disease (on average < 3 months from diagnosis) and the same domains continued to decline over the 6.1-year follow-up, although overall cognitive functioning remained rather stable (Hankomäki, Multanen, Kinnunen, & Hämäläinen, 2014).

## **1.2 Fatigue as a symptom**

### **1.2.1 Fatigue in neurological diseases**

Fatigue is a common symptom in many neurological diseases. Patients with traumatic brain injury frequently report mental fatigue as a symptom of their condition (Dikmen, Ross, Machamer, & Temkin, 1995; LaChapelle & Finlayson, 1998; Ponsford, Olver, & Curran, 1995). Patients with traumatic brain injury have also shown increased reaction times and deficits in accuracy on tasks demanding sustained or divided attention. These deficits have been related to subjective estimations of mental fatigue (Belmont, Agar, & Azouvi, 2009; Ziino & Ponsford, 2006). Belmont et al. (2009) also studied the possible effect of time on task on a computerized sustained selective attention task but did not find a greater deterioration in reaction times from the first half of the test to the end.

With myasthenia gravis, patients' increase in subjective mental fatigue has been associated with poorer performance in cognitive measures of information processing speed, fluency, learning and memory (Paul, Cohen, & Gilchrist, 2002). Although patients reported higher levels of mental fatigue prior to demanding cognitive strain than healthy controls, these estimates were not associated with their cognitive performance. The same patients estimated a significant increase in their level of mental fatigue during cognitive strain, whereas no such a change was observed among healthy controls. This change was associated with cognitive performance (Paul et al., 2002).

In chronic fatigue syndrome, fatigue is the most debilitating symptom. The literature includes findings of cognitive impairment in the spatial working memory and in sustained attention among patients reporting high levels of mental fatigue. These deficits were not found in patients reporting low levels of mental fatigue or in non-fatigued participants. Performance in the sustained attention task was impaired only in the last third of the test, when the reaction times of the patients with a high level of mental fatigue increased significantly when compared to their performance in the earlier parts of the test (Capuron et al., 2006). Chronic fatigue syndrome patients have also exhibited significantly greater activity in the parietal cingulate, inferior frontal and superior temporal cortices, cerebellum and cerebellar vermis during a fatiguing cognitive task but no differences in cognitive performance compared to healthy controls. This increased brain activity has been related to higher estimations of mental fatigue during assessments (Cook, O'Connor, Lange, & Steffener, 2007).

In Parkinson's disease patients, one study (Abe, Takanashi, & Yanagihara, 2000) found an association between the Fatigue Severity Scale score, depression scale (estimated with the Self-assessed Depression Scale) and reduced frontal lobe perfusion with a trend toward an association between reduced frontal lobe perfusion and reduced performance on the Wisconsin Card Sorting task. Findings of a relationship between a lower Mini-Mental State Examination score and increased complaints of fatigue have also been reported (Alves, Wentzel-Larsen, & Larsen, 2004). Mentis et al. (2003) noticed that to achieve similar performance with healthy controls in trial-and-error learning, the Parkinson patients activated four times as much neural tissue.

Patients with different neurological conditions commonly report fatigue as a symptom. Previous research has found an association between cognitive deficits and subjective fatigue. Attention and processing speed seem especially to be involved. However, the results on the association between objective cognitive fatigue and subjective fatigue remain conflicting.

### **1.2.2 Fatigue in MS**

As already mentioned, a considerable number of MS patients report fatigue as a symptom (Bakshi, 2003; Freal, Kraft, & Coryell, 1984; Krupp, Alvarez, LaRocca, & Scheinberg, 1998), and it is often considered to be one of the most debilitating symptoms, greatly affecting quality of life (Opara, Jaracz, & Broła, 2010). Fatigue is variously defined in the literature. The Multiple Sclerosis Council for



Clinical Practice Guidelines defines it as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities” (Miller, 1998). Schwid, Covington, Segal and Goodman (2002) defined fatigue as a three-component phenomenon, differentiating motor fatigue, cognitive fatigue and lassitude or subjective fatigue. Motor fatigue can be measured as a decline in motor performance, for example in strength during sustained muscle contractions, cognitive fatigue as an analogous decline in cognitive performance during tasks requiring sustained attention, and lassitude as the subjective sense of reduced energy.

Chaudhuri and Behan (2000) adopted the terms peripheral and central fatigue to describe the phenomenon. Peripheral fatigue refers to limited ability to sustain a specified force or work rate during exercise or physical activity while mental tasks show no deterioration. This kind of fatigue can be seen in patients with neuromuscular or peripheral circulatory disorders. Evidence of peripheral fatigue has also been found among MS patients (e.g., Andreasen et al., 2009). Problems in initiating and/or sustaining attention during mental tasks and physical activities, especially those requiring self-motivation indicate central fatigue. This is common, for example, in patients with progressive neurological disorders such as Huntington’s disease, Parkinson’s disease and MS (Chaudhuri & Behan, 2000). In MS, fatigue is reported to affect up to 80% of patients (Bakshi, 2003) and is considered a persistent symptom of the disease. In a follow-up study with a mean follow-up of 18 months, as many as 86.8% of the MS patients reporting themselves as fatigued at the onset of the study remained so at the end of the follow-up period (Tellez et al., 2006).

Kluger, Krupp and Enoka (2013) suggested distinguishing between fatigue, defined as the subjective perception of tiredness, and fatigability, defined as objectively measurable changes in performance. Furthermore, in defining the phenomenon, Genova et al. (2013) differentiated state and trait components of fatigue. On this definition, state fatigue is a transient condition, and thus changes over time. It can also fluctuate due to both internal and external factors. Trait fatigue is a more permanent state in an individual and thus unlikely to change significantly over time. Both components can be observed in MS patients.

### **1.2.3 Cognitive fatigue in MS research**

The literature reports several definitions and ways to operationalize cognitive fatigue. In patients with MS, a decline in performance has been found during a single test and during sustained cognitive effort, and difficulties in sustaining a stable level of cognitive performance have been observed during tests demanding sustained attention (Bruce et al., 2010; Krupp & Elkins, 2000; Kujala et al., 1995; Schwid et al., 2003). These findings have been interpreted as signs of cognitive fatigue.

Kujala et al. (1995) evaluated the mechanisms of cognitive decline in MS with a group of cognitively intact and a group of cognitively mildly deteriorated MS patients alongside healthy controls, using tests demanding

attentional skills. The cognitively intact MS patients exhibited a decline in reaction times towards the end of a vigilance test. Schwid et al. (2003) found a decline in the performance of MS patients during the Paced Auditory Serial Addition Task (PASAT), which demands attention and processing speed. Rosti, Hämäläinen, Koivisto and Hokkanen (2006) reported similar results in Finnish patients using the 60-item series of PASAT, finding a deteriorating trend in the performance of MS patients while the performance of the controls remained more stable throughout the test. Also Rosti-Otajärvi et al. (2015) used PASAT and found a declining performance profile in MS patients having relapsing-remitting and progressive form of the disease. There are also findings of a partial decline in cognitive performance profiles over a single testing session in repeated neuropsychological tests (Krupp & Elkins, 2000).

Bruce et al. (2010) suggested the analysis of response time variability (RTV) during a sustained cognitive task as an alternative way to measure cognitive fatigue in patients with MS. They suggested that cognitive fatigue may not cause a linear decline in cognitive performance but instead occasional lapses in attention. During these lapses, additional effort may be required to gather the necessary mental reserves to efficiently and consistently perform a designated task. In their study, Bruce et al. (2010) found that the MS patients exhibited increased RTV and response latency when compared to healthy controls.

Bodling, Denney and Lynch (2012) also noticed higher individual variability among MS patients when compared to healthy controls. The participants were assessed with a series of reaction time tests. A coefficient of variation (CoV) was calculated, which is a measure of inconsistency. CoV was used to avoid the confounding effect of group differences in mean reaction time on individual variability, as greater means are commonly associated with higher standard deviations (Hultsch et al., 2000). CoV was calculated by dividing the standard deviation of each individual by their mean reaction time. It was not considered, however, if this higher individual inconsistency was a sign of cognitive fatigue. This could have been done by assessing perceived cognitive fatigue and evaluating whether the CoV scores were associated with the subjective cognitive fatigue evaluations.

It has been suggested that cognitive fatigue can be evaluated in a single test by assessing the individual's performance profile. Previous findings have indicated that in the PASAT test, for example, MS patients tend to give significantly fewer series of two or more correct consecutive responses than healthy controls (Fisk & Archibald, 2001; Kujala et al., 1995; Snyder, Cappelleri, Archibald, & Fisk, 2001). Instead they seem to skip items intermittently, thereby making the demands of the test more manageable. This may reflect the difficulty of sustaining attention and meeting the demands of the test. By analyzing test performance with the dyad score method suggested by Snyder et al. (2001), it is possible to measure how adequately the test is performed and the degree to which correct responses reflect performance in relation to the intended demands of the task (Fisk & Archibald, 2001). The dyad score method

involves counting only the total number of two consecutive correct responses (dyads). The percent dyad score is the proportion of total correct responses accounted for by the dyads.

Previous research has revealed that increased reaction times are correlated with subjective cognitive evaluations of fatigue, indicating that increased reaction time may also be a possible marker of cognitive fatigue (Neumann et al., 2014; Nepal et al. 2013; Weinges-Evers et al., 2010). Neumann et al. (2014) found that, when rested, patients reporting cognitive fatigue had longer reaction times than healthy controls. After cognitive load, the reaction times increased significantly in the patients but remained unchanged in controls. In another study (Nepal et al., 2013), MS patients with subjective fatigue showed a reduced level of alertness manifested as increased motor reaction time when compared to the performance of healthy controls and patients who did not report fatigue as a symptom of the disease. Furthermore, Weinges-Evers et al. (2010) found that self-reported fatigue scores in the Fatigue Severity Scale (FSS) were an independent predictor of performance in the alertness subtest of the Test of Attentional Performance, as the mean reaction times of fatigued MS patients (FSS scores  $\geq 4$ ) were significantly longer than those of non-fatigued patients.

Previous research has used a variety of methods in an effort to study cognitive fatigue in MS. Most studies have used tasks demanding processing speed, attention and working memory in order to reveal signs of cognitive fatigue. Some studies have focused on deterioration in performance in time on task or over time, whereas others have seen the inability to sustain a stable level of performance as the best indication of cognitive fatigue. The fact that the methods used have varied from one study to another, makes it hard to compare results. It is also hard to say if the first or the latter approach better captures the phenomenon, as no studies have tried out both approaches with the same patient group. Previous research has supported the view that increased reaction times are associated with evaluations of subjective fatigue. This suggests that investigating cognitive fatigue by using a task demanding high processing speed is justified.

### **1.3 The relationship between objective and subjective fatigue in MS**

Subjective fatigue has been defined as a subjective sense of reduced energy (Schwid et al., 2002) and is typically measured with self-report questionnaires (Greim, Benecke, & Zettl, 2007). Several papers have reported on the relationship between objectively measured cognitive fatigue and self-reported subjective fatigue (e.g. Bailey, Channon, & Beaumont, 2007; Beatty et al., 2003; Parmenter, Denney, & Lynch, 2003). In most of these studies, however, the subjective feeling of fatigue has not been evaluated repeatedly during sustained

cognitive effort. Subjective fatigue has referred more to a general feeling of tiredness over a longer period of time. Bruce et al. (2010) showed a significant correlation between cognitive performance and self-reported measures of fatigue when cognitive fatigue was defined as increased variability in response time. However, the course of fatigue was not assessed in this study either; instead subjective fatigue was measured once with the Fatigue Impact Scale (Fisk et al., 1994). The participants were asked to rate how much trouble fatigue had caused them in the past month on a scale from 0 (none) to 4 (extreme). The problem with this study was that the subjective evaluation of fatigue focused more on fatigue as a permanent state rather than fatigue at the moment the neuropsychological assessment was made.

Bailey et al. (2007) evaluated the subjective feeling of fatigue four consecutive times during a neuropsychological testing procedure, but did not find a correlation between cognitive and subjective fatigue. In their study, cognitive fatigue was defined as a decline in performance over time (both within a task and across a session) and subjective fatigue as self-reported ratings of fatigue. A general feeling of subjective fatigue was assessed with the FSS, which is concerned with the effects of subjective fatigue on activities of daily living. Subjective fatigue during cognitive load was assessed with a simple scale developed for the study. In it the participants reported a number between 0 to 8, depending on how tired/fatigued they felt at the time of evaluation. 0 meant not fatigued at all and 8 extremely fatigued. The study did not focus on evaluating the course of subjective cognitive fatigue but more on state fatigue as described by Genova et al. (2013). Cognitive fatigue over time was assessed with two tasks; a working memory task that measures the ability to hold, update, and manipulate information in a temporary memory store and an attention task that measures sustained attention without working memory demand. The percentage of correct responses and mean reaction time served as the variables of interest. One task took 15-20 minutes to complete and the same task was presented twice during the assessment session (Bailey et al., 2007).

The results revealed that the performance of the MS patients declined during the session and over time during the working memory task whereas the performance of the controls remained stable. Processing speed and accuracy were also poorer in the MS group than in the healthy controls. (Bailey et al., 2007). Subjectively, both study groups reported increasing levels of overall fatigue across the assessment sessions; however, this effect was more pronounced in the MS group during the working memory task that demanded more cognitive effort. When the associations between the subjective ratings of fatigue during cognitive load and the cognitive measures were examined in the MS group, the correlations revealed that the subjective ratings of fatigue were not significantly associated with the objective findings of cognitive fatigue (Bailey et al., 2007).

The connection between objective cognitive fatigue and subjective cognitive fatigue has not been widely studied. Only one study so far has been published on objective and subjective cognitive fatigue (Sandry et al., 2014). In

that study, the participants completed neuropsychological tasks in the processing speed and working memory domains with different levels of cognitive load (high vs. low), each consisting of four blocks. Subjective cognitive fatigue was assessed with a visual analog scale at baseline and at multiple time points throughout the experiment. It was discovered that subjective and objective cognitive fatigue symptoms seem to be independent of one another and that cognitive fatigue does not depend on cognitive load. For the processing speed task, subjective cognitive fatigue increased with time more prominently in the MS group than healthy controls. In the working memory domain, however, no differences were observed between the MS group and healthy controls. It was suggested that subjective cognitive fatigue in patients with MS increases as a function of time during sustained cognitive activity.

Many previous studies have failed to find an association between objective cognitive fatigue and subjective fatigue. One reason for this may be that most of these studies have assessed subjective fatigue in more general terms. Most studies have not been especially interested in the subjective feeling of cognitive fatigue caused by cognitive strain, i.e., the feeling that one's performance declines when performing cognitive tasks, but rather on fatigue as a general feeling of tiredness. The development of subjective cognitive fatigue and recovery from it are also under-researched topics.

#### **1.4 The relationship of fatigue to disability and quality of life**

The term "quality of life" has different definitions in the literature. It can refer to an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (The WHOQOL Group, 1995) or it may refer more to health issues, that is, to the overall dimension of health, including aspects of physical health, emotional status and cognition (Wood-Dauphinee, 1999). In the present study, this latter definition of quality of life is used. Previous studies have found significant correlations between the degree of fatigue experienced and higher disability (Colosimo et al., 1995; Kroencke, Lynch & Denney, 2000; Pittion-Vouyovitch et al., 2006) or a substantial reduction in the quality of daily life (Pittion-Vouyovitch et al., 2006; Pittock et al., 2004). In the study by Pittion-Vouyovitch et al. (2006) no definition of the concept "quality of life" was given.

An association between fatigue and depression has been found in some studies (Bakshi et al., 2000; Koch et al., 2009; Pittion-Vouyovitch et al., 2006), but not in others (Krupp et al., 1988; Moller et al., 1994). Pittion-Vouyovitch et al. (2006) reported that MS patients with a high level of depression also showed high scores on the cognitive, physical, social role and psychological subscales of the Fatigue Impact Scale (FIS). The authors considered this association to be problematic and ambiguous, as fatigue can be a symptom of depression. Fatigue also increases depressed mood and, conversely, depression increases fatigue.

Yamout et al. (2013) simultaneously and comprehensively assessed the role of different demographic, clinical, physical, social, economic and psychological parameters in MS patients' perceptions of their quality of life. The data analysis revealed that unemployment, especially, seemed to contribute to poor quality of life and that a low fatigue score on the FSS predicted good quality of life. Other predictors were depression, social support, religiosity, level of education and living area.

Niino et al. (2014) reported an association between depression/apathy, and decreased cognitive function in patients with MS. Cognitive function was assessed with the Brief Repeatable Battery of Neuropsychological tests (BRBNT) and depression with the Beck Depression Inventory Second Edition (BDI-II). The MS patients participating in the study reported more severe fatigue than healthy controls in the Fatigue Questionnaire. Scores on the Expanded Disability Status Scale (EDSS), which evaluates the level of disability caused by MS, also correlated with apathy, depression and cognitive deficits in MS patients. The authors suggested that both fatigue and cognitive deficits affect quality of life for patients with MS.

Among young and middle aged adults, MS is the main reason for disability and limitations in functional abilities (Forbes, While, Mathes, and Griffiths, 2006). The young age of onset of MS also makes it one of the major causes of reduced work capacity due to neurological disease in western society. Of all the symptoms of the disease, the majority of MS patients consider fatigue to be the worst and most handicapping (Flesner, Ek, Landtblom, & Söderhamn, 2008). In a Swedish descriptive cross-sectional study, low fatigue was found to be related to work capacity. Moreover, participants with work capacity showed significantly higher health-related quality of life than those with low or no work capacity (Flesner et al., 2013).

Previous studies have consistently found associations of depression with fatigue and the health-related quality of life of MS patients. If fatigue is seen solely as an outcome of depression, it may affect the way patients are treated. If, however, fatigue is a separate symptom from depression, then it is important that it is not treated as a psychiatric symptom, as such treatment may not be effective if fatigue is caused by neurological changes in the central nervous system. Thus, it is important to study the phenomenon with patients who do not suffer from depressive symptoms.

## **1.5 The neurophysiological markers of cognitive fatigue in MS**

The etiology of cognitive fatigue, when defined as deterioration in sustained cognitive performance or the inability to sustain cognitive effort, remains unclear in MS. Different etiologies of the phenomenon have been proposed and tested with studies using physiological tools such as magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI) or electroencephalogram (EEG) as well as cognitive tasks.

### 1.5.1 MRI and fMRI

MRI is based on the magnetic characteristics of the imaged tissue. In the procedure, the imaged tissue is magnetized. The various degrees of signal intensity detected after magnetization provide an image of a given tissue (Ajtai, Lindzen, & Masdeu, 2012). fMRI, in turn, is influenced by the blood oxygen level-dependent effect, which is due to local hyperoxygenation of the venous blood, resulting in a relative increase in signal intensity. The blood oxygen level-dependent effect is related to changes in regional cerebral blood flow as well as to neuronal activity. After time series are analyzed statistically, fMRI allows the researcher to form maps illustrating regions with a task-specific statistically significant difference in brain activation (Meyer, Rijntjes, & Weiller, 2012).

Previous research with MRI scans has revealed that MS patients with subjective cognitive fatigue assessed with the cognitive part of the fatigue Scale for Motor and Cognition had alterations in the thalamic regions of the brain. The subjectively fatigued patients could not be differentiated from the non-fatigued patients in cognitive tests (Wilting et al., 2015). Reduced integrity in the deep left frontal white matter has been associated with subjective fatigue scores measured with the Modified Fatigue Impact Scale (MFIS) in patients with clinically relevant fatigue (MFIS score  $\geq 38/84$ ). The authors did not find any significant association between subjective fatigue scores and cognitive scores of processing speed. The correlation between subjective fatigue scores and mean fractional anisotropy used to assess white matter pathology were also nonsignificant (Pardini, Bonzano, Mancardi, & Roccatagliata, 2010). Besides white matter lesions, subjective fatigue evaluated with MFIS has been associated with gray matter atrophy of the brain in the frontal regions, the left superior frontal gyrus and bilateral middle frontal gyri (Sepulcre et al., 2009). It has been suggested that the brain networks which are involved in cognitive and attentional processes are impaired and associated with fatigue (Sepulcre et al., 2009).

When compared to healthy controls, MS patients have shown a greater increase over time in cerebral activation, measured as processing speed and accuracy, during cognitive task performance. Behaviorally, the two study groups were equally accurate but processing speed in the MS patients was slower. This increased cerebral activation was associated with increased activation in the basal ganglia, frontal areas, parietal regions, thalamus and the occipital lobes (DeLuca, Genova, Hillary, & Wylie, 2008). Tartaglia et al. (2004) also found signs of an association between subjective fatigue and increased cerebral activity in MS. They suggested that widespread axonal dysfunction, and thus increased recruitment of cortical areas and pathways, in response to brain injury in MS may cause patients to feel that the effort required to perform actions is greater than usual.

MRI and fMRI studies have yielded information about brain atrophy and abnormal brain activation in MS patients. In some studies, these changes have

shown an association with both subjective fatigue and subjective cognitive fatigue but not necessarily with objective cognitive fatigue or poorer cognitive performance. This provides some indication that objective cognitive fatigue and subjective cognitive fatigue may be separate symptoms, not necessarily associated to one another.

### **1.5.2 Components of event-related potentials**

An objective way to evaluate aspects of cognitive irregularities in MS patients besides behavioral data is the recording of brain activity by electroencephalogram. EEG is a measure of the electrical activity generated by the central nervous system. Small fluctuations in the EEG related to the processing of external stimuli are known as event-related potentials (ERPs). ERPs indicate the activity of the human brain elicited by stimuli and/or reflect processes, such as decision making, example given, during preparation for an event or for one's own behavioral response.

#### **Contingent negative variation**

One component of interest in ERP studies is contingent negative variation (CNV), which was discovered by Walter et al. (Walter et al., 1964). It is a prolonged surface negative deflection measurable, like the more typical ERPs, from the scalp, but in this case often in specific locations, most dominantly in frontal areas. CNV usually depends on the association of two successful stimuli (Tecce, 1970) that begins approximately 400 ms after the onset of a stimulus (S1) and terminates after the onset of another stimulus (S2) demanding a response or decision by the subject (Rockstroh, Elbert, Birbaumer, & Lutzenberger, 1982). CNV is generated in a situation when an individual is directing her behavior toward a planned action such as inhibiting a motor response, holding a motor response in readiness, or preparing for a cognitive decision (Donchin, Ritter, & McCallum., 1978). CNV appears to be linked to effortful task preparation, as its amplitude increases along with the increase in effort following instruction (Falkenstein, Hohnsben, Hoormann, & Kleinsorge, 2003). As the attention of the subject increases, the amplitude of the CNV has also been noticed to increase (Tecce, 1972).

Little research exists on the possible connections of CNV with cognitive deficits or cognitive fatigue in MS. Differences in CNV amplitudes between MS patients and healthy controls observed during visual-spatial cueing have been interpreted as indicators of possible deficits in MS patients in the activation of orientation and preparation mechanisms and as increased attention at the beginning of the preparation stage or as greater task motivation (Gonzales-Rosa et al., 2011). The results of another study suggested impairment of the alerting and orienting mechanisms in MS patients (Vázquez-Marrufo et al., 2014). In yet another study, smaller (more positive) CNV amplitudes at the Pz of MS patients when compared to the corresponding values of healthy controls have been associated with worse performance on measures of speed of information



processing speed, verbal fluency, verbal learning and verbal recall (Uysal et al., 2014).

The relationship between cognitive impairment and CNV has been studied in a group of elderly people by Wild-Wall, Hohnsbein and Falkenstein (2007). They investigated whether a decline in executive functions with age affects cognitive task preparation, manifested as decreased CNV amplitude. They also sought to find out if the elderly people used compensatory means to maintain their level of performance. They expected that such compensation to be seen as increased effort in task preparation and reflected in a frontally pronounced CNV. It was also proposed that in elderly people fatigue (defined as time on task) may modulate the ability to efficiently prepare for a task, which could be compensated for by an increase in effort. The results of the study suggested that enhancement of effortful task preparation in the elderly manifested as increased (more negative) frontal CNV amplitude.

With young, healthy participants, it has been found that whereas subjective evaluations of mental fatigue (defined as change experienced in the psycho-physiological state during and following prolonged periods of demanding cognitive activity requiring sustained mental efficiency) increased with time on cognitive task, negative CNV amplitudes became significantly smaller. This change was interpreted to reflect a reduction in top-down modulation of cognitive functions with an increasing sense of mental fatigue (Lorist, 2008).

CNV is closely related to attention, and some results have been published on the association between subjective mental fatigue and declining CNV amplitudes in healthy people. As attention deficit is common in MS patients, CNV might be a good way to investigate cognitive fatigue. There are two possible ways that cognitive fatigue might manifest in CNV. First, CNV amplitudes may decline with time on task, as keeping up a stable level of attention becomes more difficult. Another possibility is that, to keep up a stable level of performance, MS patients increase their cerebral activation, manifested as increased CNV amplitudes.

### **P3**

Among the many event-related potentials that reflect cognitive and linguistic functions, P3 (also referred to as P3b in the literature) is probably the cerebral wave that has been most used in studies evaluating cerebral information processing during the course of various neurological diseases (Magnano, Aiello, & Piras, 2006). P3 is a positive peak in an ERP with a post-stimulus latency that usually varies between 250-350 milliseconds. The latency depends on the time the subject requires to recognize and evaluate the relevance of the stimulus (Donchin et al., 1978). P3 is related to the cognitive processes of volitional target detection and is generated over widespread cortical regions in healthy subjects (Juckel et al., 2012). It has also been considered to reflect context updating (Polich, 2007) and/or the categorization of task-relevant events (Kok, 2001). P3 amplitude increases in proportion to the amount of attentional resources

devoted to a given task. Any neurological disorder which affects cognitive processes may reduce P3 amplitude and increase latency (Polich & Herbst, 2000). The possible association between MS-related cognitive fatigue and irregularities in the P3 have not been widely studied.

Chinnadurai et al. (2016) assessed cognitive fatigue with tasks demanding attention, information processing speed and concentration, alongside ERP P3-evoked potentials. They measured cognitive fatigue by calculating the ratio of the first 60-second score (multiplied by three to equalize the lengths) and the 180-second score for each cognitive test. The latency and amplitude of P3 were measured as the average of 50 rare stimuli or 250 frequent stimuli. After delivery of 150 rare stimuli or 750 frequent stimuli, P3 average latency and amplitude were measured again. The ratio of the latter and the first average for latency and amplitude were considered to be physiological markers for cognitive fatigue, since latency increases while amplitude decreases as the sustaining attention becomes more difficult with fatigue. The results for MS patients were compared to those for healthy controls. The authors found that the electrophysiological markers of cognitive fatigue differed between the two study groups and that some of the cognitive markers of cognitive fatigue also differed between the MS patients and healthy controls. The results showed longer P3 latencies in the MS group than in the healthy controls, while the calculated electrophysiological markers revealed that the latency parameter for fatigue was larger and the amplitude marker smaller in the MS patients than healthy controls.

Sandroni, Walker and Starr (1992) assessed reaction times and ERPs accompanying the performance of auditory memory tasks in ten MS patients with subjective fatigue. The patients were assessed when they were rested and when they were fatigued. Fatigue was assessed as subjective feeling of fatigue rated on a scale from 0 ("no fatigue") to 10 ("the most severe state of exhaustion ever experienced"). All the patients showed a minimum difference score of four between the rested and fatigued state. When rested, the reaction times of the patients were significantly longer in the short-term memory but not in the target-detection tasks when compared to those of healthy controls. When fatigued, the reaction times of the patients increased significantly in all tasks compared to their performance when rested. No differences in the P3 amplitudes or latencies were observed between the rested and fatigued conditions. The authors interpreted the results to indicate that fatigue in patients with MS does not appear to significantly affect the systems subserving stimulus classification. They also suggested that fatigue in MS patients is accompanied by increased reaction times without changes in P3, which indicates that the neural processes intervening between stimulus evaluation and the initiation of motor events are affected. The study did not focus on the development of fatigue during assessment but on state fatigue.

In another study MS patients were assessed with the FSS and MFIS. Cognitive functions were assessed with the BRBNT and P3 amplitudes and latencies were assessed using an auditory oddball paradigm with target and

non-target tones. It was found that, compared to healthy controls, MS patients showed longer latency and a smaller P3 amplitude. P3 latency was associated with the MFIS scores (Pokryszko-Dragan et al., 2016). The development of fatigue was not assessed; instead fatigue was evaluated as a stable state rather than as a symptom developing during cognitive strain.

P3 amplitude and reaction time have been found to associate with cognitive performance in MS (Sundgren et al., 2014). Previous research has also found that in healthy participants delayed P3 latency and smaller P3 amplitude are related to increased reaction time in a sustained attention task demanding vigilance. P3 was furthermore found to be associated with visuomotor speed, but not with overall cognitive impairment (Portin et al., 2000). In healthy participants during a Go/No-Go task, the No-Go P3 amplitude was found to decrease significantly with time on task as reaction times, number of errors and mental fatigue scores also increased significantly with time on task (Kato, Endo, & Kizuka, 2009).

Like CNV, P3 is also closely associated with attention and speed of processing. In healthy participants, there are signs that P3 amplitude might be associated with declining cognitive performance over time alongside increasing subjective fatigue scores. There are also signs of P3 irregularities in MS patients when compared to healthy participants. It is possible that cognitive fatigue would manifest in P3 as increased latencies with time on task alongside increased reaction times. Another possible manifestation of cognitive fatigue may be changes in the P3 amplitude. As sustaining attention becomes harder for MS patients with time on task, this might show as a decrease in P3 amplitudes.

## 1.6 Aims and hypotheses

The first aim of this study was to investigate if signs of objective cognitive fatigue are present in neuropsychological tests using different scoring methods.

Objective cognitive fatigue was defined either as a decline in performance during a test demanding sustained attention and working memory or as greater difficulty in sustaining a stable level of vigilance. Decline in performance was defined as either increased reaction times or as an increase in the number of mistakes made within a test. Difficulty in sustaining a stable level of vigilance was defined as higher variability/inconsistency in reaction times or, in performance during a test, as higher response time variability, as a higher coefficient of variance or as lower dyad scores or percent dyad scores.

Based on the previous research, it was hypothesized that although the patients participating in this study had a mild form of the disease they may nevertheless manifest deficits in processing speed. It was also hypothesized that their performance will show more variability manifested as a higher response time variability and higher CoV, as a decline in performance towards the end of

the neuropsychological tests, or as lower dyad and percent dyad scores when compared to the findings for healthy controls.

The second aim was to determine whether MS patients give higher self-ratings of subjective cognitive fatigue than healthy controls and whether subjective recovery from cognitive strain differs between the two groups. The MS patients were expected to give higher self-ratings of subjective cognitive fatigue than the healthy controls. The MS patients were also expected not to recover from cognitive strain as well as the healthy controls.

The third aim was to investigate whether signs of cognitive fatigue are present in ERP measurements, with a focus on CNV and Go/No-Go P3. On the ERPs it was hypothesized that the MS patients would exhibit smaller (less negative) CNV and P3 amplitudes and increased P3 latencies than the healthy controls. It was also hypothesized that because sustaining the same cognitive performance level becomes more difficult with time on task due to cognitive fatigue, P3 latencies would increase and the amplitudes of both P3 and CNV decrease.

The fourth aim was to investigate if the possible manifestations of objective cognitive fatigue during neuropsychological test performance and in ERPs are associated with possible subjective cognitive fatigue.

Further aims were to investigate whether the results support the existence of a phenomenon that can be called cognitive fatigue and, if so, whether possible markers of cognitive fatigue are associated with health-related quality of life and whether cognitive fatigue affects not only MS patients but also healthy people.

## 2 METHODS

### 2.1 Participants

A total of 25 patients (21 female, 4 male) with clinically definite relapsing-remitting multiple sclerosis (MS) according to the criteria proposed by McDonald (McDonald et al., 2001; Polman et al., 2005) were originally recruited for the study. Of these patients, 21 were treated at the Department of Neurology, Jyväskylä Central Hospital and four at Jokilaakso Hospital in Jämsä. The control group comprised 20 participants (16 female, 4 male) who were employees of Jyväskylä Central Hospital or their friends or acquaintances. Patients and controls meeting any of the following criteria were excluded: additional neurological or psychiatric disorders (controls with any neurological disorder), alcohol or drug abuse, experiencing an acute relapse, an additional disorder affecting the autonomous nervous system, an Expanded Disability Status Scale (EDSS; Kurtzke, 1983) value over 4.0, or age over 50 years. To avoid depressive symptoms influencing the results, the subjects filled in Beck Depression Inventory II, Finnish version (BDI-II; Beck et al., 2006), self-evaluating their mood. Any participant scoring 14 or more points was excluded from the study. After the baseline screening, the four patients scoring 14 points or more in the BDI-II, indicating depressive symptoms, and one patient who did not complete the study procedure (finished the baseline screening but could not participate in the second phase of the study due to work commitments) were excluded. Thus, a total of 20 subjects with relapsing-remitting MS participated (16 female, 4 male). All participants received written and oral information about the study procedure and signed a written consent form before participating in the study. The study protocol was approved by the Ethics Committee of Jyväskylä Central Hospital.

## 2.2 Evaluation of cognitive status

At the beginning, the cognitive baseline performance of the participants was screened with the Brief Repeatable Battery of Neuropsychological Tests (BRBNT). The battery consists of five subtests, comprising measures of sustained attention and processing speed (Paced Auditory Serial Addition Test, Symbol Digit Modalities Test), verbal learning and delayed recall (Buschke Selective Reminding), visuospatial learning and delayed recall (10/36 Spatial Recall), and semantic retrieval (Word List Generation) (Rao, 1990). Version B was used with all the participants. In previous research, the test battery has been found to be sensitive to the cognitive deficits accompanying multiple sclerosis (Sepulcre et al., 2006; Solari et al., 2002).

## 2.3 Evaluation of cognitive performance profile

### The Rapid Visual Perception (RVP) test

The RVP is part of the computerized CANTAB test developed at the University of Cambridge (CANTAB Eclipse 3.0. Cambridge Cognition, 2006). It measures processing speed and sustained attention. Previous research has suggested that processing speed may be associated to objective cognitive fatigue (Neumann et al., 2014; Nepal et al., 2013) which makes RVP a plausible task detecting objective cognitive fatigue. In RVP test, single digits are presented in a random order in the middle of a white box on a computer screen. Examinees are asked to detect a series of digits included among the presented digits (for example 2-4-6, 3-5-7, 4-6-8) and press a button on a press pad as quickly as possible after detecting each series. The test proper is preceded by a training period. To find out whether task performance changes towards the end of the test, each performance was analyzed in three blocks. This made it possible to analyze whether an individual's performance changes with time on task, as in the studies by Kujala et al. (1995), Schwid et al. (2003), Rosti et al. (2006) and Rosti-Otajärvi et al. (2015). Response time variability was calculated as the standard deviation of the response times taken to identify the correct series of digits during the test.

### The Paced Auditory Serial Addition Task (PASAT)

The PASAT (Gronwall & Wrightson, 1974; Gronwall, 1977) primarily measures attention and processing speed. In this test, subjects are instructed to listen to 61 digits presented first at three-second (3'') intervals and then at two-second (2'') intervals. The subject is instructed to add every consecutive two digits in a row and to give the answer orally to the examiner. Before the final test, a practice round of ten digits is presented to ensure that the subject has understood the

addition procedure. If necessary, a demonstration with written numbers is provided until the examinee understands how to perform the task. Both subtests were re-coded into three blocks of 20 calculations and the scores for correct calculations in each block served as the variables used to analyze whether task performance changed towards the end of the test. To find out if the patients were able to sustain their level of attention and performance, the dyad score and percent dyad score were also calculated according to Snyder et al. (2001). Previous research has shown PASAT to be sensitive in detecting cognitive decline with time on task (eg. Schwid et al., 2003; Rosti et al., 2006; Rosti-Otajärvi et al., 2015)

### **The Continuous Performance Task (CPT)**

The CPT is a computer-based Go/No-Go task that measures a person's processing speed and accuracy, and response inhibition and impulsiveness. Previous research has suggested that processing speed may be associated to objective cognitive fatigue (Neumann et al., 2014; Nepal et al., 2013) which makes CPT a plausible task detecting objective cognitive fatigue. The 30-minute test serves as a measure of sustained attention. It is a modification of the original CPT presented by Rosvold et al. (1956). It is based on the S1-S2 anticipating paradigm with the difference that the trial length is varied. Stimulus 1 is a plus sign presented in the middle of the computer screen for either a fixed duration of 6500 ms (every second trial) or a variable duration of 5500, 6500, 7500 or 8500 ms in pseudo-randomized order. Stimulus 2 is either an asterisk (\*, probability 0.75) or a circle (o, probability 0.25) and is of a constant duration of 500 ms. Subjects are instructed to press a button on a press pad with their dominant hand as quickly as possible when the plus sign changes into an asterisk (Go) and to do nothing if the plus sign changes into a circle (No-Go). During the task, reaction times, omissions and commissions were recorded. The task was divided into three blocks. The mean of the reaction times in each block of the task served as the variables used to analyze whether task performance changed towards the end of the test. Response time variability was calculated as the standard deviation of the correct response times during the task.

## **2.4 Evaluation of subjective cognitive fatigue**

The Visual Analogue Scale for Fatigue (VAS-F; Lee, Hicks, & Nino-Murcia, 1991) is a 50- or 100-cm line along which patients are asked to evaluate their level of fatigue on a scale of 0 (no fatigue at all) to 100 (fatigue as bad as can be) by marking their degree of fatigue on the line. The initial screening populations were sleep-disordered and healthy people but it has also been used in patients with MS (Rammohan et al., 2002; Weinschenker et al., 1992). The VAS-F has been established as a valid and reliable instrument for the evaluation of self-reported fatigue (Benito-León et al., 2007; Lee et al., 1991). In the present study,

a modified version (10 cm line) of the VAS-F scale was used. Each participant evaluated their degree of subjective cognitive fatigue at the beginning of the testing session, after each neuropsychological test and once more after a delay of 30 minutes. The self-ratings of cognitive fatigue were the variables analyzed.

## 2.5 The 15-D generic questionnaire of quality of life

The 15-D is a generic, comprehensive, standardized, self-administered measure of health-related quality of life (Sintonen, 2001). It has 15 different dimensions: breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression. For each dimension, the person is asked to evaluate the level of difficulty they experience from 1 (no difficulty) to 5 (highest level of difficulty), by which more or less of the attribute is distinguished. The 15-D questionnaire takes approximately 5-10 minutes to fill in. It has been widely used to measure health-related quality of daily life with different patient groups including neurological diseases and, for example, cancer patients (e.g., Karttunen et al., 2011; Martinez-Martin et al., 2011; Torvinen et al., 2013). The overall score served as the analyzed variable but comparisons of each individual modality between the two study groups were also made.

## 2.6 Collection and evaluation of neurophysiological data

E-prime (version 1.0) was used to control the timing and presentation of the stimuli. The electroencephalogram (EEG) and behavioral data were recorded with Brain Vision Recorder (version 1.1). The EEG data were analyzed with Brain Vision Analyzer (version 2.0). The EEG was recorded according to the international 10-20 system (Jasper, 1958) by using an EEG cap (ECI) in an electrically attenuated room. Nine sites were used. Three frontal sites (F3, Fz, F4), three central sites (C3, Cz, C4) and three parietal sites (P3, Pz, P4). The distribution of the used measurement sites can be seen in Figure 1. The impedance level was always below 10 k $\Omega$  and mostly under 5k $\Omega$ . The electro-oculograph (EOG) was recorded with disposable electrodes (Ambu Neuroline 725) positioned above the canthus of the right eye and below of the canthus of the left eye approximately 2 cm below the pupil. Linked mastoids were used as a reference for both the EEG and EOG recordings and one electrode located on the forehead was used as a ground electrode. Trials contaminated by EOG shifts or movement artifacts exceeding  $\pm 100 \mu\text{V}$  were excluded from the analysis.



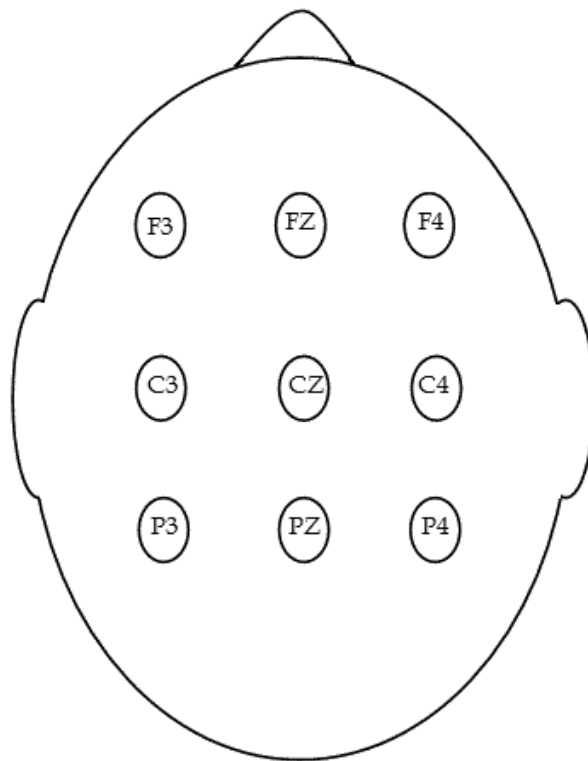


FIGURE 1 Distribution of the ERP sites. F3, Fz and F4 = frontal sites. C3, Cz and C4 = central sites. P3, Pz and P4 = parietal sites, ERP = event-related potentials

For contingent negative variation (CNV), the baseline was set at 1000-1100ms after stimulus onset and CNV was measured at 1100 - 6000ms post stimulus. For P3, the baseline was set at 52ms before the stimulus to the beginning of the stimulus and P3 defined as a highest positive peak during the 200-700ms post stimulus. The Go and No-Go trials were analyzed separately. To study the possible development of fatigue during the test, the EEG sequence in each block was segmented into three sections of 60 Go stimuli.

## 2.7 Procedure

All participants were initially screened with the BRBNT, 15D and BDI-II. They were also clinically interviewed and the patients were assessed with the EDSS by an experienced neurologist. They were then tested three to four weeks after the BRBNT screening at their own convenience. Half of the participants were tested at 8 a.m. and half at 12 noon to avoid the possible effect of time of day on the results. After the neuropsychological tests, the participants rested for 30 minutes on a bed in a quiet room before the last VAS-F evaluation. The test

order was the same for each participant: First VAS-F rating, RVP; second VAS-F rating, PASAT 3" and 2" intervals (version A); third VAS-F rating, CPT and ERP measurements; fourth VAS-F rating, 30-minute rest period; fifth VAS-F rating. The duration of each session was approximately 90 minutes. The procedure can be seen in Figure 2.



FIGURE 2 Procedure of the study protocol. VAS-F = visual analogue scale, RVP = Rapid Visual Perception Test, PASAT = Paced Auditory Serial Addition Task, CPT = Continuous Performance Task.

## 2.8 Statistical analyses

Data were analyzed using IBM SPSS Statistics 19 for Windows. The differences between the study groups in age, education, mood, BRBNT tests, total performance in the RVP, PASAT and CPT and overall measures of CNV and P3 were analyzed with independent samples t-test or the Mann-Whitney U-test depending on whether the data collected for a variable showed a normal distribution according to Shapiro-Wilk's test of normality. Repeated measures analysis of variance (ANOVA) was used to evaluate the effects of group (MS vs. healthy controls), time on the cognitive performance test (beginning, middle, and end of the test) and subjective feeling of cognitive fatigue (VAS-F1-VAS-F5), and the interaction between these factors. If the interaction between group and time on test was significant, tests of within-subject contrasts were carried out to determine whether the change in performance time from the beginning to the end of the test was different between the subjects in the study groups. The sphericity of the models was checked and non-sphericity was corrected by Greenhouse-Geisser adjustment. Adjusted degrees of freedom and significances are reported. In the PASAT, the analyses were separately performed for the 3" and 2" versions.

Response time variability (RTV), coefficient of variation (CoV), dyad scores and percent dyad scores of the control and patient groups were analyzed using parametric or non-parametric statistics (independent samples t-test, Mann-Whitney U-test) depending on whether the variable was normally distributed or not according to Shapiro-Wilk's test of normality.

Averaged event-related potentials (ERPs) were used in the statistical analyses of the electrocortical responses. In the statistical analyses, CNV amplitude was measured by calculating the averaged activity in the period of 1100–6000ms after stimulus onset and relating it to baseline activity. Repeated measures analysis of variance was used to evaluate the effects of group (MS vs.

healthy controls) and time on test (beginning, middle, end) on the CNV and P3 measurements. If the interaction between group and time on test was significant, tests of within-subject contrasts were carried out to determine whether the change in amplitude or latency from the beginning to the end of the test was different between the study groups. The sphericity of the models was checked, and non-sphericity was corrected by Greenhouse-Geisser adjustment. Adjusted degrees of freedom and significances are reported.

The association between ERP measures and the behavioral data, namely RTV and overall performance (reaction time, correct answers) in the CPT were analyzed with Pearson's correlation coefficient. In the statistical analyses of P3 the time window was 200–700ms following the onset of S2. The Go and No-Go conditions of P3 were analyzed separately.

### **3 RESULTS**

#### **3.1 Results on cognitive status, mood and demographic variables**

The two matched study groups did not differ statistically from one another in age, education, mood or any measures of the Brief Repeatable Battery of Neuropsychological Tests (BRBNT), as can be seen in Table 1.

There was a tendency for the multiple sclerosis (MS) group to score higher on the Beck Depression Inventory II (BDI-II), but when the answers were analyzed in detail it was found that patients gave higher tiredness ratings than the controls and did not manifest signs of depressive symptoms. After the baseline assessment with the BRBNT and clinical interview, participants showing signs of depressive symptoms according to the BDI-II were excluded from the study assessment.

TABLE 1 Demographic, clinical and cognitive characteristics of the MS and control groups. All patients had a relapsing – remitting form of the disease.

Descriptive values	MS	Control	p
Age in years	38.0 (5.1) [31–45]	37.9 (4.5) [30–47]	0.935
Female/Male	16/4	16/4	1.0
Education in years	16.2 (2.0) [13–20]	17.7 (3.0) [13–25]	0.074
EDSS	1.9 (1.3) [0–4]	-	-
Number of years since MS diagnosis	7.9 (4.7) [2–18]	-	-
Disease-modifying medication	15/20		
BDI-II	5.2 (3.9) [0–13]	3.1 (3.0) [0–9]	0.058
Selective Reminding Test, total score	59.1 (5.8) [52–70]	57.6 (5.9) [49–71]	0.423
10/36 Spatial Recall Test, total score	24 (4.9) [12–30]	24.6 (3.9) [17–29]	0.913
PASAT 3", correct calculations	49.6 (8.6) [30–59]	49.2 (8.2) [26–59]	0.734
PASAT 2", correct calculations	35.2 (14.9) [3–56]	39.3 (10.1) [15–59]	0.254
SDMT, total score	57.3 (10.9) [40–82]	61.6 (12.5) [42–91]	0.119
Selective Reminding Test , delayed recall	10.7 (1.4) [8–12]	9.9 (1.9) [6–12]	0.195
10/36 Spatial Recall Test, delayed recall	8.9 (1.8) [4–10]	9.0 (1.3) [6–10]	0.825
Word List Generation (animals)	30.4 (6.2) [20–44]	32.1 (8.6) [22–50]	0.860

Mean (standard deviation) [range], except in gender and medication. EDSS = Expanded Disability Status Scale, BDI-II = Beck Depression Inventory II, PASAT = Paced Auditory Serial Addition Task, SDMT = Symbol Digits Modalities Test

## 3.2 Cognitive performance profiles

### 3.2.1 Rapid visual perception

In the rapid visual perception (RVP) test, repeated measures analysis of variance (ANOVA) showed no significant interaction between time and group in either accuracy or reaction times. The results indicate that the performance of the MS group did not differ from the performance of the control group as the test proceeded. The main effect of group was also insignificant, revealing no significant difference between the performance of the patients and the controls. However, a significant main effect of time ( $F(2, 76) = 4.55, p = 0.014$ ) in reaction time was observed, indicating that the performance of the participants differed from one measurement point in the test to another. The tests of within-subjects contrasts showed that performance in the last third of the test differed from that in the first third ( $F(1, 38) = 8.52, p = 0.006$ ), as the reaction times of the participants were slower during the last part of the test. No statistical differences in reaction times were observed between the second and third parts of the test. The results can be seen in Table 2.

TABLE 2 Cognitive performance in RVP, PASAT 2", 3" and CPT.

	Beginning		Middle		End		Time x group	Time	Group
RVP Rt(MS)	395.2 (90.7) [251-611]	448.8 (94.2) [295-628]	458.9 (125.8) [284-747]						
RVP Rt(HC)	406.5 (65.4) [264-552]	399.4 (88.3) [275-653]	446.1 (87.4) [337-637]				0.484	0.014	0.355
RVP mistakes (MS)	3.6 (2.5) [0-9]	3.6 (2.6) [0-8]	4.4 (3.4) [0-10]						
RVP mistakes (HC)	3.2 (2.0) [0-8]	4.0 (2.4) [0-9]	3.6 (2.2) [0-8]				0.209	0.230	0.424
PASAT 3" (MS), correct calculations	17.8 (2.5) [11-20]	17.7 (3.3) [9-20]	16.4 (3.8) [9-20]						
PASAT 3" (HC), correct calculations	18.9 (1.2) [16-20]	17.9 (2.0) [13-20]	17.1 (2.1) [13-20]				0.244	<0.001	0.168
PASAT 2" (MS), correct calculations	15.6 (3.8) [7-19]	13.3 (4.8) [1-20]	13.8 (4.4) [5-19]						
PASAT 2" (HC), correct calculations	16.2 (4.0) [5-20]	13.8 (4.9) [4-20]	13.8 (3.9) [5-20]				0.476	<0.001	0.758
CPT Rt (MS)	475.6 (85.1) [369-751]	486 (118.3) [368-906]	492.3 (97.0) [385-809]						
CPT Rt (HC)	424 (43.8) [353-527]	417.2 (43.8) [337-521]	424.6 (38.5) [362-487]				0.409	0.358	0.018
CPT mistakes (MS)	1.3 (1.3) [0-4]	2.0 (5.5) [0-24]	1.7 (2.9) [0-12]						
CPT mistakes (HC)	1.1 (0.8) [0-3]	0.7 (0.7) [0-2]	0.8 (0.8) [0-2]				0.697	0.994	0.221

Mean (standard deviation) [range]. Rt (reaction time) values in milliseconds p values are shown for time x group interaction, and time and group main effects. HC = healthy controls, RVP = Rapid Visual Perception, PASAT = Paced Auditory Serial Addition Task, CPT = Continuous Performance Task.

### 3.2.2 Paced auditorial serial addition task 2'' and 3''

In the Paced auditorial serial addition task (PASAT) 3'', the interaction of time by group and the main effect of group were non-significant. No signs of a steeper deterioration in performance towards the end of the test was observed among the MS patients when compared to controls and the performance of the MS group was no worse than that of the controls. The number of correct calculations decreased from the beginning to the end of the test in both study groups, and was revealed as a main effect of time in the repeated measures analysis of variance (ANOVA) ( $F(2, 76) = 12.19, p < 0.001$ ). Further analysis of the within-subjects contrasts showed that in the last third of the test individuals' performance was worse than in the first third ( $F(1, 38) = 19.20, p < 0.001$ ) and or second part of the test ( $F(1, 38) = 13.45, p = 0.001$ ), indicating that the participants' performance deteriorated steadily from the beginning to the end of the test.

In the PASAT 2'', while the interaction of time by group and the main effect of group were non-significant, the number of correct calculations decreased from the beginning to the end of the test equally in both study groups, manifested as a significant main effect of time ( $F(2, 76) = 21.20, p < 0.001$ ). Further analysis of within-subjects contrasts revealed that during the second part of the test the participants' performance was already worse than in the first part of the test ( $F(1, 38) = 35.24, p < 0.001$ ) but did not significantly deteriorate further in the third part of the test. The results are shown in Table 2.

### 3.2.3 Continuous Performance Task

In the Continuous Performance Task (CPT), the time-by-group interaction and the main effect of time were non-significant for performance accuracy and reaction times. This indicates that the performance of the two study groups did not deteriorate towards the end of the task and that the performance profiles of the two study groups were similar. There was a significant main effect of group ( $F(1, 38) = 6.16, p = 0.018$ ), revealing significantly longer reaction times in the patient group than healthy controls. The results are shown in Table 2.

### 3.2.4 Ability to sustain attention by response time variability, coefficient of variation, dyad scores and percent dyad scores

Response time variability (RTV) was evaluated in the RVP test and in the CPT, but the differences between the two study groups were not statistically significant in either test. This indicates that the two study groups did not differ from one another in their ability to sustain attention during the two tasks.

Coefficient of variation (CoV) was evaluated in the RVP test and in the CPT. In the RVP test the CoV was significantly higher in the control group than MS group ( $t = 2.769, p = 0.009$ ). In the CPT, the CoV did not differ significantly between the two study groups. This indicates that during the RVP test, it was harder for the control group to sustain their attention during the test.

Dyad scores and percent dyad scores were evaluated from the PASAT 3" and 2" tests, but neither showed statistically significant differences between the two study groups. This also indicates no differences in the ability to sustain attention during the tests between the two groups. The values of all the tests are shown in more detail in Table 3.

TABLE 3 Ability to sustain attention in RVP, PASAT 3", PASAT 2" and CPT.

Test	MS	Control	p
RTV (RVP)	124.33 (73.16) [42–298]	160.83 (59.27) [64–279]	0.122
RTV (CPT)	94.06 (42.71) [65–255]	78.89 (10.65) [58–103]	0.113
CoV (RVP)	0.27 (0.12) [0.12–0.52]	0.38 (0.11) [0.16–0.057]	0.009
CoV (CPT)	0.19 (0.04) [0.15–0.32]	0.19 (0.02) [0.13–0.23]	0.586
Dyad Score (PASAT 3")	44.83 (13) [12–59]	48.00 (8.19) [26–59]	0.183
Dyad Score (PASAT 2")	33.56 (16.15) [2–54]	32.06 (16.65) [0–57]	0.969
Percent Dyad Score (PASAT 3")	84.27 (14.95) [40–98.33]	88.32 (8.82) [61.9–98.33]	0.154
Percent Dyad Score (PASAT 2")	71.99 (22.33) [12.5–94.74]	67.34 (26.49) [0–96.61]	0.746

Mean (standard deviation) [range]. RTV = response time variability, CoV = coefficient of variation, RVP = Rapid Visual Perception, CPT = Continuous Performance Task, PASAT = Paced Auditory Serial Addition Task

### 3.3 Results for subjective cognitive fatigue

In the visual analogue scale for fatigue (VAS-F), a significant time-by-group interaction ( $F(3, 99) = 3.14, p = 0.035$ ) and a significant main effect of time ( $F(3, 99) = 24.26, p < 0.001$ ) were observed. There was a tendency for the MS group compared to healthy controls to evaluate themselves as more cognitively fatigued after the PASAT tests ( $F(1, 38) = 4.02, p = 0.052$ ) and the CPT ( $F(1, 38) = 3.28, p = 0.078$ ), but the values did not reach statistical significance. Subjective feelings of fatigue in both study groups increased from the beginning to the end of the neuropsychological testing procedure (VAS-F1 vs. VAS-F4) ( $F(1, 38) = 44.91, p < 0.001$ ). Within-subject contrasts showed that the subjective feeling of cognitive fatigue of the MS patients differed from that of the HCs at the end of the rest interval (VAS-F5) ( $F(1, 38) = 9.14, p = 0.004$ ), the MS patients evaluating themselves as significantly more fatigued after resting than at the beginning of the testing procedure. Furthermore, the MS patients reported a higher level of cognitive fatigue after resting than after the RVP test (VAS-F2) ( $F(1, 38) = 5.34, p = 0.026$ ). In turn, the controls reported recovery from cognitive strain during the rest interval. Details on the evaluations of subjective cognitive fatigue are given in Figure 3.



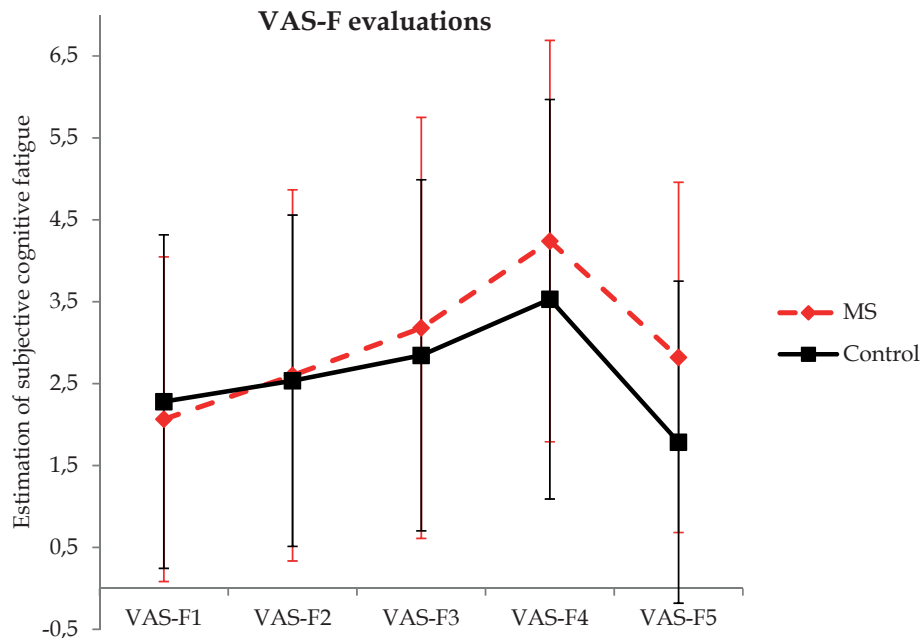


FIGURE 3 Visual analogue scale for fatigue (VAS-F) evaluations. Mean  $\pm$  standard deviation. VAS-F1 = beginning of the study procedure, VAS-F2 = after rapid visual perception test (RVP), VAS-F3 = after Paced Auditory Serial Addition task (PASAT), VAS F4 = after Continuous Performance Task (CPT), VAS-F5 = after rest

### 3.4 Results for ratings of quality of life

The two study groups differed in their ratings of their overall health-related quality of daily life. The MS group compared to healthy controls reported experiencing more difficulties ( $t = -3.50$ ,  $p = 0.002$ ), and thus lower overall health-related quality of life. The ratings for each dimension of the quality of daily life are shown in Figure 4. When the individual dimensions of the 15-D were analyzed, the MS patients gave higher ratings for difficulties in mobility ( $t = -3.11$ ,  $p = 0.005$ ), elimination ( $t = -3.80$ ,  $p = 0.001$ ) and usual activities ( $t = -3.11$ ,  $p = 0.005$ ). More specifically, these results indicate that the MS patients experienced more difficulties than the healthy controls in walking and moving about, with their bladder and/or bowel function and in performing daily activities such as working, studying, housework and leisure activities.

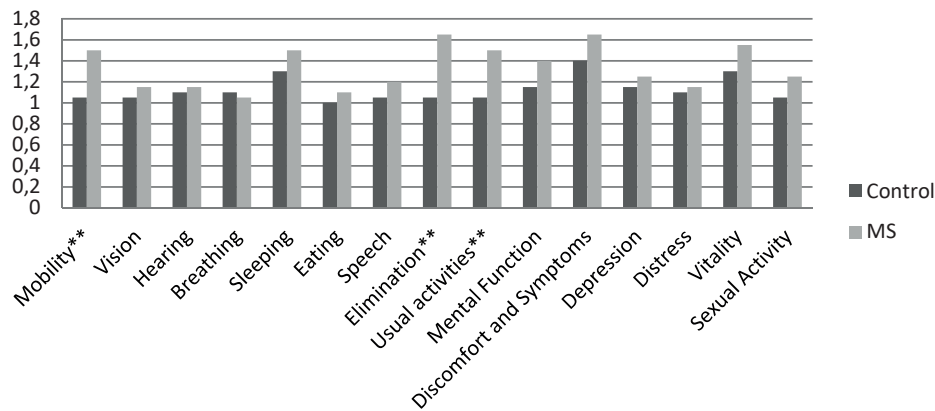


FIGURE 4 Health-related quality of life. \*\*  $p < 0.01$

### 3.5 Results of the ERPs

#### Contingent negative variation

In the first part of the test, the healthy controls displayed contingent negative variation (CNV) in six sites, viz. F3, Fz, F4, Cz, C4 and Pz, whereas no CNV was detected among the MS patients. In the second part of the test, the controls displayed CNV in all nine sites measured. At the same time, the MS patients displayed CNV in two parietal sites: Pz and P4. In the third part of the test, the controls displayed CNV in all the frontal sites and in C4. They also displayed some indication of CNV in C3, Cz, Pz and P4, but the amplitudes were small. In the third part of the test, no CNV was observed among the MS patients.

To assess whether these deflections differed from random, they were evaluated with repeated measures ANOVA. No significant time-by-group interaction or main effect of time were observed in any of the electrode sites measured. This indicates that as the CPT proceeded, the amplitude of the CNV did not change differently between the test and control groups. It also indicates that the participants' CNV amplitude did not change towards the end of the test. On the level of brain activity, the two groups maintained a stable level of performance with no signs of deterioration towards the end of the test. There was, however a significant main effect of group in the frontal electrode sites (F3;  $F(1, 38) = 5.684, p = 0.022$ , Fz;  $F(1, 38) = 5.743, p = 0.022$ , F4;  $F(1, 38) = 7.743, p = 0.008$ ) revealing a smaller CNV amplitude in the MS group than controls throughout the test; this in turn indicated that the preparation for the upcoming stimulus was not as powerful in the MS patients as it was among the healthy controls. The CNV amplitudes obtained at the different measurement sites are

shown in more detail in Table 4, while the comparisons of the averaged slow-wave responses across the two study groups are given in Figures 5-13.

TABLE 4 CNV values during CPT.

Site	<u>Beginning</u>	<u>Middle</u>	<u>End</u>	p
	MS/Control	MS/Control	MS/control	
F3	.21 (4.52) / -2.7 (11.9)	.43 (3.61) / -4.97 (13.67)	.94 (2.55) / -3.60 (6.60)	0.022
Fz	1.07 (3.92) / -2.08 (10.69)	1.02 (3.39) / -4.0 (13.67)	1.65 (2.50) / -2.72 (6.47)	0.022
F4	.01 (3.8) / -3.06 (11.05)	.031 (2.65) / -5.54 (13.03)	.64 (2.20) / -4.23 (7.00)	0.008
C3	1.30 (1.28) / .53 (10.83)	1.62 (1.37) / -1.05 (13.2)	1.99 (1.59) / -.25 (5.17)	0.210
Cz	1.10 (1.47) / -.21 (10.96)	.90 (1.46) / -1.26 (13.01)	1.26 (1.87) / -.61 (5.13)	0.263
C4	.35 (1.19) / -1.14 (11.34)	.27 (1.12) / -2.07 (13.03)	.76 (1.71) / -1.56 (5.39)	0.188
P3	.92 (1.61) / 1.08 (12.42)	.59 (1.86) / -.71 (13.86)	.49 (2.2) / .14 (4.85)	0.768
Pz	.44 (1.75) / -.33 (11.58)	-.24 (1.86) / -1.63 (13.09)	-.27 (2.29) / -.95 (4.37)	0.616
P4	-.03 (1.95) / .33 (12.12)	-.48 (1.87) / -1.58 (13.68)	-.42 (1.98) / -.94 (4.98)	0.799

Mean (standard deviation), values in microvolts. p values refer to the main effect of group in the repeated measures ANOVA, CNV = contingent negative variation, CPT = Continuous Performance Task, F3, Fz, F4 = frontal sites; C3, Cz, C4 = central sites; P3, Pz, P4 = parietal sites

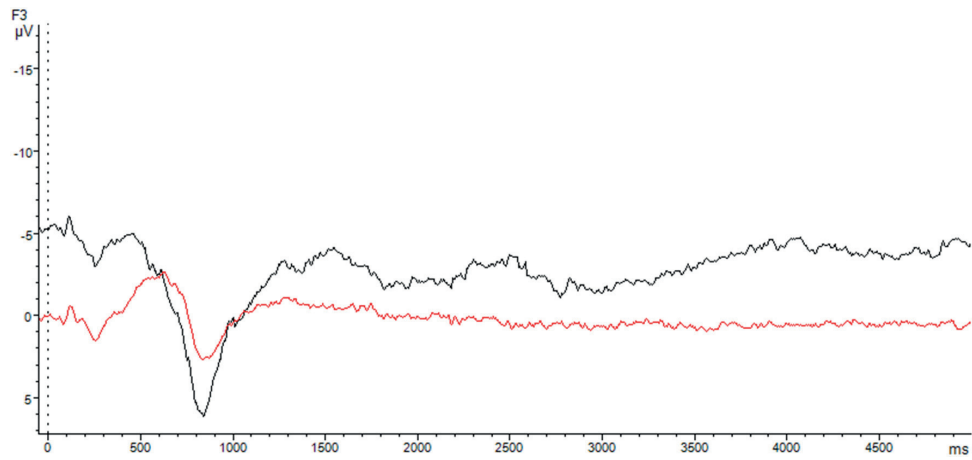


FIGURE 5 CNV at F3, first part of the CPT. CNV = Contingent negative variation. CPT = Continuous Performance Task. — MS, — Control,  $\mu V$  = microvolt, ms = millisecond

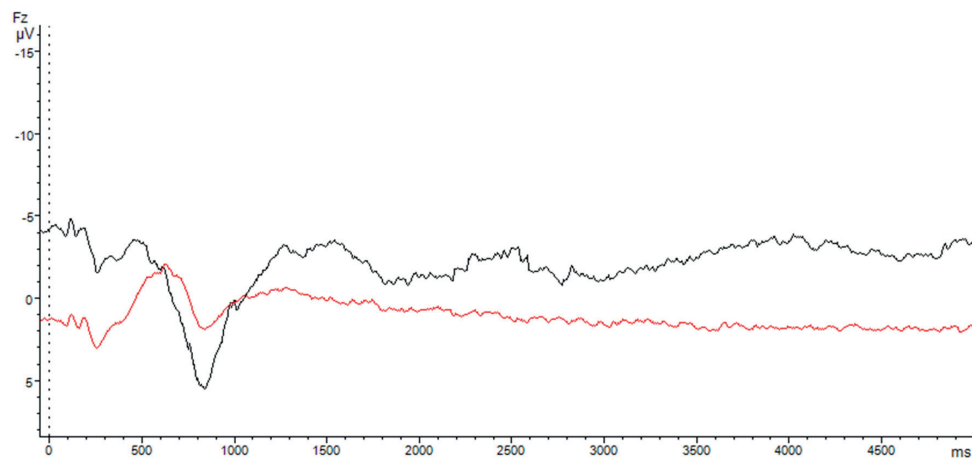


FIGURE 6 CNV at Fz, first part of the CPT. CNV = Contingent negative variation, CPT = Continuous Performance Task. — MS, — Control,  $\mu V$  = microvolt, ms = millisecond

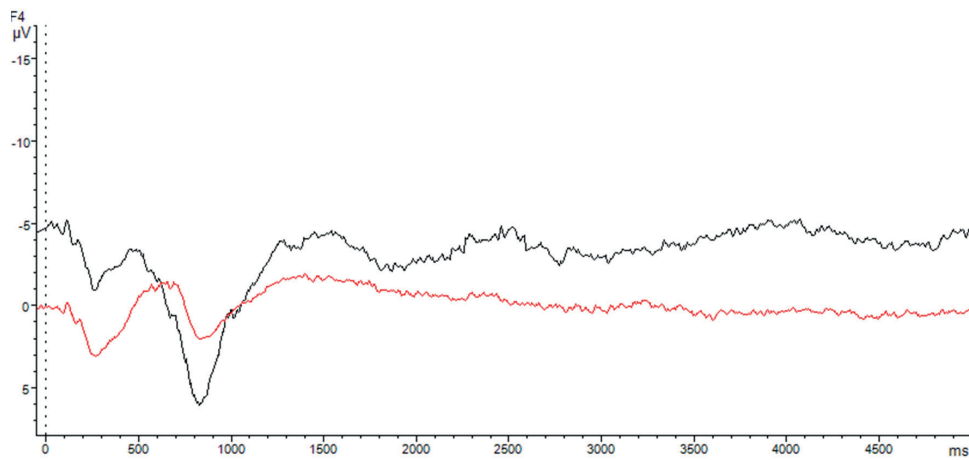


FIGURE 7 CNV at F4, first part of the CPT. CNV = Contingent negative variation, CPT = Continuous Performance Task. — MS, — Control,  $\mu\text{V}$  = microvolt, ms = millisecond

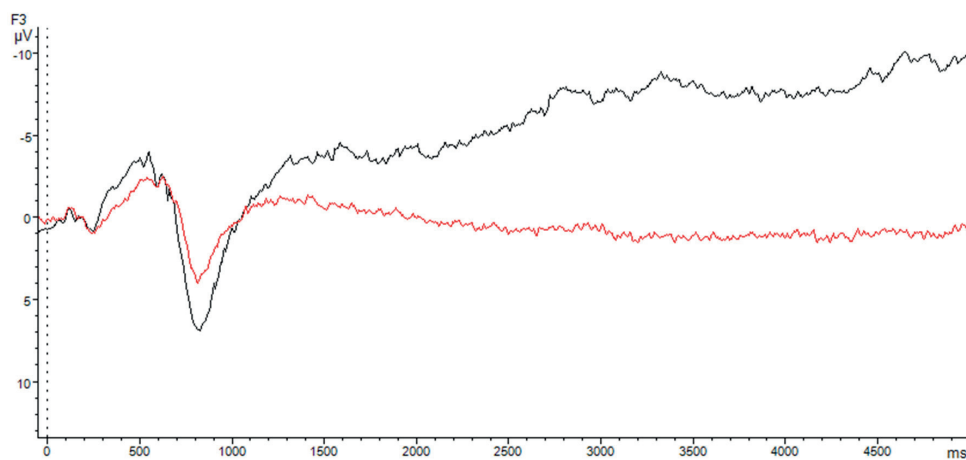


FIGURE 8 CNV at F3, second part of the CPT. CNV = Contingent negative variation, CPT = Continuous Performance Task. — MS, — Control,  $\mu\text{V}$  = microvolt, ms = millisecond

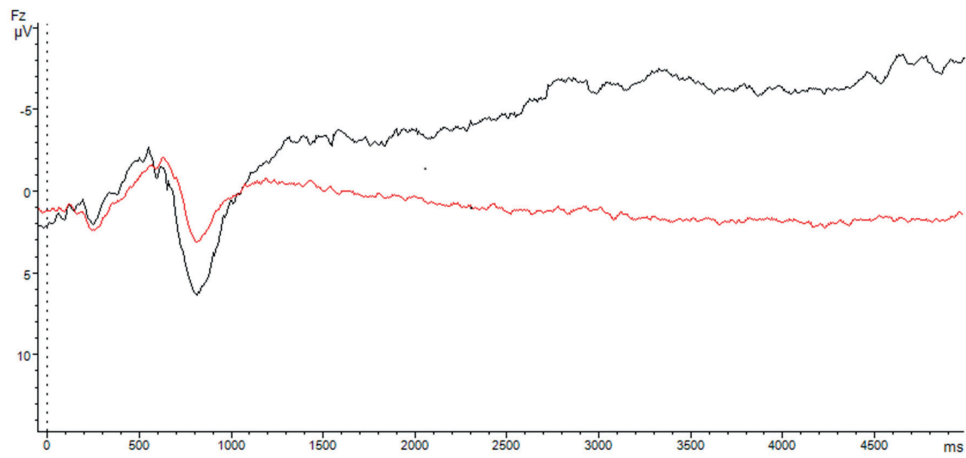


FIGURE 9 CNV at Fz, second part of the CPT. CNV = Contingent negative variation, CPT = Continuous Performance Task. — MS, — Control,  $\mu V$  = microvolt, ms = millisecond

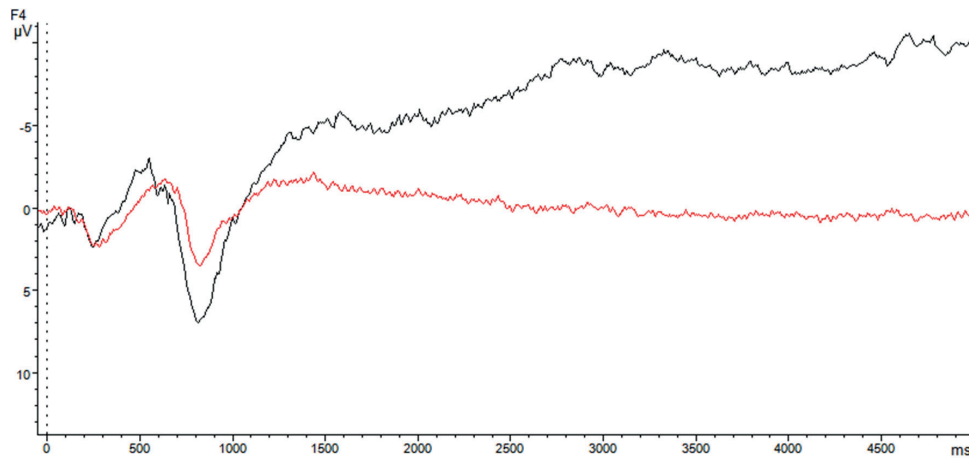


FIGURE 10 CNV at F4, second part of the CPT. CNV = Contingent negative variation, CPT = Continuous Performance Task. — MS, — Control,  $\mu V$  = microvolt, ms = millisecond

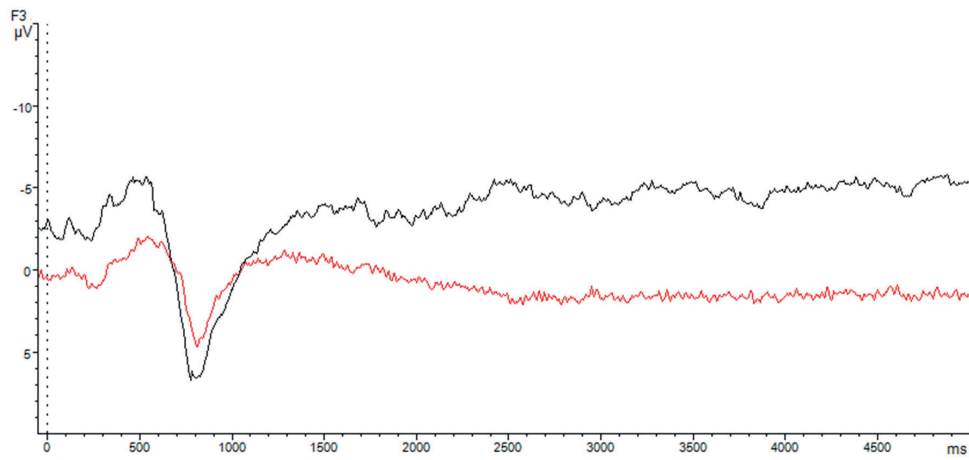


FIGURE 11 CNV at F3, third part of the CPT. CNV = Contingent negative variation, CPT = Continuous Performance Task. — MS, — Control,  $\mu\text{V}$  = microvolt, ms = millisecond



FIGURE 12 CNV at Fz, third part of the CPT. CNV = Contingent negative variation, CPT = Continuous Performance Task. — MS, — Control,  $\mu\text{V}$  = microvolt, ms = millisecond

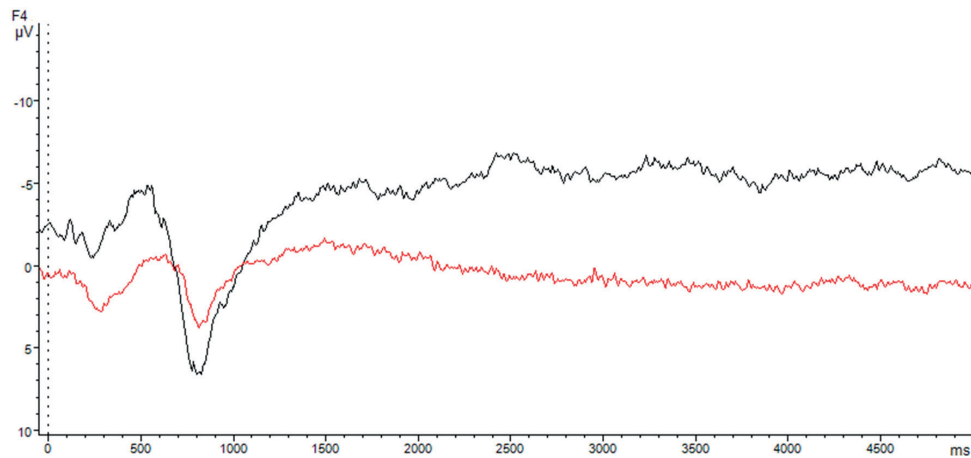


FIGURE 13 CNV at F4, third part of the CPT. CNV = Contingent negative variation, CPT = Continuous Performance Task. — MS, — Control,  $\mu\text{V}$  = microvolt, ms = millisecond

### P3

The P3 amplitudes of two control participants could not be used due to the presence of too many artifacts in one case in the Go condition measurements and in the other in the No-Go condition measurements. The P3 amplitudes of one MS patient could not be used due to too many artifacts in the No-Go condition measurements. The repeated measures ANOVA revealed that the Go P3 latencies showed no significant time-by-group interaction or main effect of time at any of the measured electrode sites, indicating that either the response of the two study groups to the CPT stimuli did not differ from one another during the task, or that the latencies did not become longer as the task proceeded. A main effect of group was found at the Cz electrode site, where the latencies of Go P3 were shorter in the MS group than in the controls (Cz:  $F(1, 36) = 11.89, p = 0.001$ ). At the P3 electrode site, a non-significant tendency towards prolonged latency was observed among the MS patients

The repeated measures ANOVA showed no significant differences in the Go P3 amplitudes between the two study groups for time by group, main effect of time or main effect of group at any of the measured electrode sites. This indicates that the amplitude of the Go P3 response to the stimulus in CPT was equally large in both study groups and that the amplitude of the Go P3 response did not deteriorate during the CPT. The latencies and amplitudes of measured Go P3 values at the different electrode sites are shown in more detail in Table 5 (latencies) and Table 6 (amplitudes).



TABLE 5 P3 latencies during CPT, Go condition.

Site	<u>Beginning</u> MS/Control	<u>Middle</u> MS/Control	<u>End</u> MS/control	p
F3	282.53 (111.59) / 320.00 (174.79)	319.16 (137.55) / 316.84 (155.79)	345.89 (168.60) / 286.95 (138.11)	0.838
Fz	280.84 (50.22) / 311.16 (137.12)	262.53 (40.82) / 349.26 (168.59)	294.32 (75.09) / 341.68 (163.63)	0.111
F4	314.53 (104.63) / 276.42 (62.07)	276.42 (41.57) / 291.16 (110.61)	323.79 (121.83) / 303.16 (131.31)	0.544
C3	456.00 (204.56) / 453.47 (149.82)	444.42 (192.66) / 457.05 (155.70)	480.00 (182.54) / 396.00 (157.25)	0.508
Cz	340.84 (191.09) / 451.58 (179.45)	274.53 (125.79) / 470.74 (160.77)	338.32 (155.15) / 467.58 (166.54)	0.001
C4	439.37 (132.13) / 404.00 (162.23)	402.32 (139.15) / 412.84 (151.66)	428.00 (128.63) / 408.84 (145.02)	0.676
P3	485.68 (113.34) / 473.89 (103.35)	507.16 (120.71) / 467.79 (103.67)	489.47 (116.79) / 474.53 (97.35)	0.435
Pz	408.84 (153.20) / 380.21 (117.25)	424.84 (107.05) / 366.53 (86.46)	438.32 (88.81) / 383.58 (82.04)	0.053
P4	464.63 (139.05) / 471.58 (129.25)	488.84 (101.80) / 481.05 (123.52)	478.74 (113.60) / 434.11 (120.78)	0.591

Mean (standard deviation), values in milliseconds, p values refer to the main effect of group in the repeated measures ANOVA. CPT = Continuous Performance Task. F3, Fz, F4 = frontal sites; C3, Cz, C4 = central sites; P3, Pz, P4 = parietal sites

TABLE 6 P3 amplitudes during CPT, Go condition.

Site	Beginning MS/Control	Middle MS/Control	End MS/control	p
F3	2.78 (1.39) / 3.46 (1.68)	2.93 (1.55) / 3.19 (1.51)	2.81 (1.48) / 2.97 (1.72)	0.419
Fz	3.08 (1.58) / 3.27 (1.67)	3.09 (1.32) / 2.98 (1.81)	3.22 (1.15) / 2.81 (1.44)	0.771
F4	3.59 (1.83) / 3.65 (1.84)	3.45 (1.03) / 3.48 (1.98)	3.44 (1.22) / 3.31 (1.48)	0.978
C3	1.51 (1.40) / 2.09 (1.56)	1.09 (2.64) / 2.07 (1.72)	1.55 (1.01) / 2.04 (1.45)	0.146
Cz	1.97 (.91) / 3.04 (2.23)	2.12 (.67) / 3.08 (2.62)	2.04 (.81) / 2.91 (2.03)	0.074
C4	2.09 (.91) / 2.94 (2.18)	2.36 (.77) / 3.10 (2.62)	2.30 (.67) / 2.84 (1.99)	0.180
P3	2.49 (.94) / 3.15 (1.57)	2.61 (1.02) / 3.43 (2.00)	2.85 (1.37) / 3.22 (1.91)	0.180
Pz	3.04 (1.16) / 3.71 (1.95)	3.31 (1.19) / 3.88 (2.31)	3.35 (1.30) / 3.90 (2.16)	0.257
P4	2.99 (1.16) / 3.51 (1.74)	3.10 (1.52) / 3.71 (1.85)	3.45 (1.71) / 3.60 (2.02)	0.394

Mean (standard deviation), values in microvolts, p values refer to the main effect of group in the repeated measures ANOVA, CPT = Continuous Performance Task. F3, Fz, F4 = frontal sites; C3, Cz, C4 = central sites; P3, Pz, P4 = parietal sites

The latencies in the No-Go condition showed no differences between the two study groups for time by group or main effect of time or group, indicating that the reaction to the stimulus was similar in the two study groups and did not change with time on task.

The No-Go P3 amplitude showed a main effect of group at the Cz electrode site ( $F(1, 36) = 4.36, p = 0.044$ ), where the measured amplitude was smaller in the MS group than in the healthy controls. Otherwise no time-by-group interaction or main effect of time was observed; instead, as the CPT proceeded, the No-Go P3 amplitudes did not differ between the groups and showed no overall change. The latencies and amplitudes of the No-Go P3 values at the different electrode sites are shown in more detail in Table 7 (latencies) and Table 8 (amplitudes). Figures 14-16 show the ERP No-Go P3 component at the Cz site in the first, second and third part of the CPT across the study groups.

TABLE 7 P3 latencies during CPT, No-Go condition.

	<b>Beginning</b> MS/Control	<b>Middle</b> MS/Control	<b>End</b> MS/control	<b>p</b>
F3	370.74 (137.62) / 349.68 (129.67)	381.05 (128.82) / 334.32 (124.94)	373.47 (145.58) / 359.37 (131.31)	0.409
Fz	372.42 (135.77) / 415.58 (119.02)	373.26 (144.95) / 405.26 (146.87)	378.32 (134.16) / 369.05 (122.72)	0.528
F4	339.37 (126.58) / 340.63 (118.92)	337.05 (117.95) / 321.89 (111.92)	384.42 (152.71) / 384.21 (167.26)	0.889
C3	472.63 (146.77) / 448.21 (130.58)	407.37 (147.07) / 443.58 (128.34)	464.00 (167.40) / 419.79 (147.85)	0.751
Cz	434.32 (175.11) / 442.95 (140.08)	440.42 (198.99) / 412.63 (143.30)	480.63 (188.44) / 470.95 (141.64)	0.824
C4	405.47 (148.47) / 422.74 (156.59)	446.95 (176.59) / 436.00 (170.45)	478.11 (155.09) / 422.74 (179.79)	0.709
P3	462.11 (169.27) / 467.37 (155.31)	447.79 (167.69) / 464.63 (131.79)	404.84 (139.63) / 470.11 (155.33)	0.429
Pz	410.74 (166.91) / 463.79 (147.68)	399.16 (175.95) / 388.00 (133.53)	356.21 (150.63) / 441.47 (152.62)	0.284
P4	447.16 (169.57) / 485.68 (170.09)	452.42 (146.91) / 508.63 (156.50)	485.47 (162.85) / 493.68 (159.00)	0.439

Mean (standard deviation), values in milliseconds, p values refer to the main effect of group in the repeated measures ANOVA, CPT = Continuous Performance Task. F3, Fz, F4 = frontal sites; C3, Cz, C4 = central sites; P3, Pz, P4 = parietal sites

TABLE 8 P3 amplitudes during CPT, No-Go condition.

Site	Beginning MS/Control	Middle MS/Control	End MS/control	p
F3	4.02 (1.78) / 4.91 (3.33)	4.51 (2.10) / 4.44 (2.45)	4.06 (2.23) / 3.89 (2.35)	0.763
Fz	4.19 (1.62) / 4.72 (3.62)	4.01 (1.36) / 4.28 (3.04)	3.99 (2.21) / 3.71 (2.16)	0.805
F4	4.28 (1.64) / 5.09 (3.82)	4.41 (2.29) / 4.84 (2.12)	4.15 (2.02) / 4.33 (2.96)	0.510
C3	1.75 (1.34) / 3.14 (3.23)	2.38 (1.63) / 2.91 (2.15)	1.66 (1.33) / 2.54 (1.64)	0.117
Cz	2.53 (1.02) / 3.55 (3.30)	2.53 (1.25) / 3.73 (1.96)	2.29 (1.14) / 3.59 (1.92)	0.044
C4	3.13 (1.00) / 3.93 (3.10)	3.02 (1.41) / 3.98 (2.68)	3.21 (2.16) / 3.79 (1.98)	0.221
P3	3.09 (1.31) / 3.88 (2.32)	3.33 (1.91) / 3.87 (1.65)	3.66 (2.44) / 3.86 (1.76)	0.378
Pz	3.99 (1.31) / 3.94 (2.45)	4.13 (1.58) / 4.20 (1.91)	4.05 (1.50) / 4.39 (2.27)	0.821
P4	4.16 (1.56) / 4.79 (2.21)	4.31 (2.07) / 4.98 (2.74)	4.71 (2.29) / 4.96 (1.98)	0.400

Mean (standard deviation), values in microvolts, p values refer to the main effect of group in the repeated measures ANOVA, CPT = Continuous Performance Task. F3, Fz, F4 = frontal sites; C3, Cz, C4 = central sites; P3, Pz, P4 = parietal sites

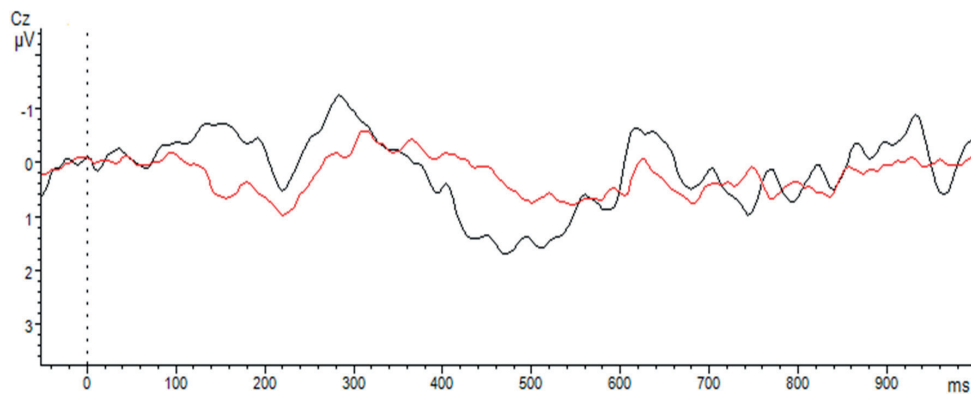


FIGURE 14 P3 ERP component at Cz site during CPT, No-Go condition; first part of the task. ERP = event-related potential, CPT = Continuous Performance Task. — MS, — Control,  $\mu\text{V}$  = microvolt, ms = millisecond

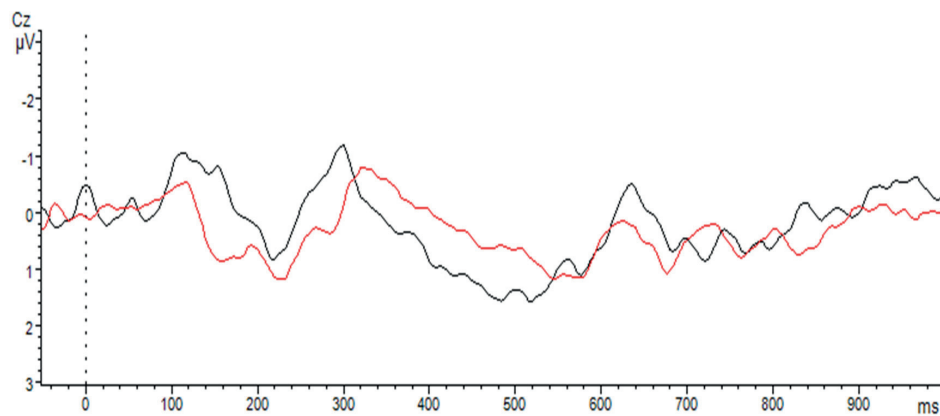


FIGURE 15 P3 ERP component at Cz site during CPT in No-Go condition; second part of the task. ERP = event-related potential, CPT = Continuous Performance Task. — MS, — Control,  $\mu\text{V}$  = microvolt, ms = millisecond

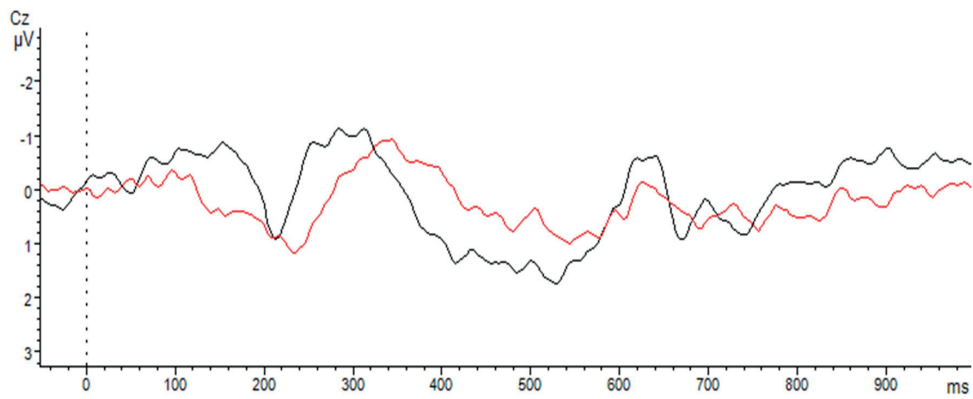


FIGURE 16 P3 ERP component at Cz site during CPT in No-Go condition; third part of the task. ERP = event-related potential, CPT = Continuous Performance Task. — MS, — Control,  $\mu\text{V}$  = microvolt, ms = millisecond

### **3.6 Associations between the neuropsychological data, subjective evaluations and neurophysiological data**

The significant differences between the study groups found in the neuropsychological and electrophysiological data were compared with the subjective evaluations of cognitive fatigue to see whether there were significant correlations between these measures. The results indicated that the increased reaction times of the MS patients during the CPT were not significantly correlated with the ratings of for subjective cognitive fatigue. The smaller CNV amplitudes, shorter P3 Go latencies or smaller P3 No-Go amplitude at the Cz site of the MS patients measured during the CPT did not correlate significantly with the increased reaction times measured during the task or with the subjective ratings of cognitive fatigue. The ratings of subjective cognitive fatigue throughout the testing procedure had a significant positive correlation with the lower ratings of the quality of daily life in the MS group but not in the healthy controls (15D - VAS-F1,  $r = .627$ ,  $p = .003$ ; 15D - VAS-F2,  $r = .656$ ,  $p = .002$ ; 15D - VAS-F3,  $r = .67$ ,  $p = .001$ ; 15D - VAS-F4,  $r = .589$ ,  $p = .006$ ; 15D - VASF-5,  $r = .519$ ,  $p = .019$ ).

## 4 DISCUSSION

The purpose of this study was to evaluate different aspects of fatigue in multiple sclerosis (MS) by focusing on cognitive fatigue. This was done by assessing objective neuropsychological performance, collecting subjective ratings of cognitive fatigue and registering electroencephalogram (EEG) measurements contingent negative variable (CNV) and P3 during cognitive strain. Another feature of interest was the possible association of objective cognitive fatigue with subjective cognitive fatigue, neurophysiological measures and health-related quality of life.

Objective cognitive fatigue was defined as a decline in cognitive performance during a cognitive test or as greater inconsistency in cognitive performance. This manifested either as prolonged reaction times towards the end of the test, increased inaccuracy towards the end of the test or as the inability to sustain attention during a cognitive test. Subjective cognitive fatigue was evaluated throughout the testing procedure, including recovery from subjective cognitive fatigue. It was hypothesized that MS patients have smaller (less negative) CNV and P3 amplitudes and longer P3 latencies than healthy controls. It was also hypothesized that the CNV and P3 amplitudes would decrease and P3 latencies increase in MS patients the longer the time spent on the task.

### 4.1 Neuropsychological variables measuring objective cognitive fatigue

The results for objective cognitive performance revealed that, in the Rapid Visual Perception (RVP) test, the reaction times of the participants in both groups were slower towards the end of the test and that this decline was similar across the two groups. In other words, the MS patients did not manifest greater objective cognitive fatigue than the healthy controls. Performance accuracy and processing speed were also similar between the MS patients and healthy



controls. The same phenomenon was seen in the Paced Auditory Serial Addition Task (PASAT), both in the easy (3") and hard (2") condition. Namely, on both occasions both groups showed similar signs of deterioration in their performance towards the end of the tests.

In this study, objective cognitive fatigue was seen in healthy people as well as in MS patients. The objective cognitive fatigue observed in healthy controls in this study is in line with previous findings on healthy participants. When exposed to multiple physical stressors, the level of cognitive performance of healthy people has been found to decline when compared to the level of pre-exposition, especially in the domains of sustained attention and processing speed (Lieberman et al., 2006). In less extreme conditions, and during a single test, reaction times in tasks demanding long-term sustained attention have shown similar deterioration towards the end of the test (e.g., Lorist et al., 2000; Möckel, Beste & Wascher, 2015).

In the Continuous Performance Task (CPT), the performance of the two groups differed in processing speed, which was slower in the MS group than healthy control group throughout the task. During the task, no sign of deterioration in performance or signs of accuracy deficits that would have differentiated the MS patients from the controls were found. The results of the processing speed deficits are in line with previous findings (DeLuca et al., 2004; Denney, Sworowski, & Lynch., 2005; DeLuca et al., 2008; Hankomäki et al., 2014; Neumann et al., 2014). It has been hypothesized that MS patients have a fundamental difficulty in processing speed that leads to difficulties in other cognitive processes (DeLuca et al., 2004). This view is supported by Hankomäki et al. (2014), who found that processing speed among MS patients was already worse than that of healthy controls shortly after diagnosis of the disease.

In this study, despite the difference in level of performance found between the MS patients and healthy controls in the CPT, no such differences between the two groups were observed in the RVP and PASAT tests. There are two possible explanations for this. First, the type of processing demanded in the performance of the tests was different. Previous research has made a distinction between automatic and controlled processing, and motor programming when investigating deficits in information processing speed in MS (e.g., Kujala, Portin, Revonsuo, & Ruutinen, 1994). In an automatic visual processing task, the recognition of stimuli is relatively effortless and fast. Controlled processing, on the other hand, demands conscious decision-making in the working memory (Kujala et al., 1994). In this study, the RVP test and both conditions of the PASAT test demanded much more controlled and conscious processing as well as a better working memory than the CPT. In the RVP, three different number sequences, each comprising three digits, have to be identified in a string of single digits. The PASAT, in turn, requires arithmetic calculations to be performed quickly and efficiently. The CPT requires recognition of only two types of stimuli. In MS, controlled processing has been found to be impaired while automatic processing has remained intact (e.g., Paul et al., 1998). A more general slowing of information processing has also been reported in MS (e.g.

Denney et al., 2005). Thus some discrepancies exist between the previous findings and those of the present study.

Another possible explanation for the differences in performance observed during the study procedure is objective cognitive fatigue. The two groups showed no signs of differences in deterioration in cognitive performance from the beginning to the end of the separate cognitive tests. The CPT was the only test in which the performance of the MS patients and healthy controls differed from one another. During the task, the reaction times of the MS patients were longer than those of the healthy controls. However, the CPT was also the last test in the series during the study procedure. It is thus possible that objective cognitive fatigue did not manifest during the separate tests but emerged towards the end of the whole testing session, as also seen in the study by Krupp and Elkins (2000).

Andreasen, Spliid, Anderson and Jakobsen (2010) studied the connection between fatigue and processing speed. They suggested that not only is the information processing speed of MS patients impaired in general, but that fatigue is also related to deficits in processing speed. They found that when the processing speed of non-fatigued patients (Fatigue Severity Scale [FSS] scores  $\leq 3.5$ ) was compared to that of a group of primary fatigued (fatigued patients without fatigue-related symptoms or events, FSS score  $\geq 5.0$ ) and secondary fatigued subjects (FSS score  $\geq 5.0$  as well as any of the following symptoms: poor sleep, poor well-being, depression, pain, infection, spasticity and tiredness), the processing speed of both the primary and secondary fatigued patients was slower than that of the non-fatigued patients. Neumann et al. (2014) have found that reaction time performance is a good marker of fatigue as it is sensitive to cognitive load, and can thus be used as an objective index of fatigability. It is thus possible that the increased reaction times of the MS patients in the present study indicated objective cognitive fatigue.

There was no evidence of higher response time variability during the RVP or CPT among the MS patients in the present study. This finding conflicts with the findings of Bruce et al. (2010). In their study, MS patients demonstrated significantly higher response time variability than healthy controls on a forced-choice task measuring reaction time and working memory. Some possible explanations can be offered for the discrepancy between the results of Bruce et al. (2010) and those of the present study. First, the state of progression of the disease differed between the patients in the two studies. In the present study, the mean Expanded Disability Severity Scale (EDSS) value of the patients was 1.9, indicating a mild form of the disease. The patients in Bruce et al. (2010) were in a more advanced stage of the disease, with a mean EDSS value of 4.5. In the present study, the EDSS value was assessed by an experienced neurologist, whereas in Bruce et al. (2010) the patients evaluated the EDSS themselves, a procedural choice which may have affected the evaluations. Second, disease duration was also shorter in the present study (7.9) than in Bruce et al. (2010) (10.86). Third, there were differences between the patient groups. While in the present study all the patients had a relapsing-remitting form of MS, Bruce et al.

(2010) also included patients with a secondary progressive form of the disease. Previous research has indicated that slowing of information processing speed is more prominent in the secondary progressive form than relapsing remitting form of MS (DeLuca et al., 2004; Denney et al., 2005). Response time variability was calculated from each participant's standard deviations across the task trials. Some researchers have argued that a correlation exists between the standard deviation of a reaction time and the mean reaction time, meaning that the increased variability of the MS patients reported by Bruce et al. (2010) could have been a byproduct of their longer mean reaction times (Bodling et al., 2012). This in turn means that the inclusion of patients with a secondary progressive form of MS in the study by Bruce et al. (2010) increases the observed variability in reaction times when compared to that in the present study.

Possible difficulty in sustaining a stable level of performance was also investigated in the present study in the way proposed by Bodling et al. (2012). They assessed individual variability in performance by calculating the coefficient of variation, and found that individual variability in the speed of information processing was greater in the MS patients than healthy controls. The present results differed from those of Bodling et al. (2012). During the RVP, the coefficient of variation was greater among the healthy controls than MS patients, whereas no such difference was found in the CPT. These contradictory results may be explained by motivational factors or by the fact that Bodling et al. (2012) also included MS patients with a secondary progressive form of the disease in their study.

In the PASAT, individual variability in performance was assessed by using scoring methods found to be sensitive to objective cognitive fatigue and cognitive impairment (Rosti et al., 2006; Walker et al., 2012;), namely dyad scores and percent dyad scores. In the present study, these measures did not differentiate the two study groups. These results conflict with the results of Rosti et al. (2006). Their study procedure also included an extensive neuropsychological examination. If the neuropsychological examination had been completed before the PASAT, the cognitive load preceding the PASAT would have been much higher than it was in the present study, where PASAT was only preceded by RVP. This could also explain the present findings of no differences between the MS patients and healthy controls in any of the PASAT measures.

The results obtained from this study did not give a clear answer to the question of whether focusing on declining performance over time or time on task is a better way to detect cognitive fatigue in MS patients than focusing on the ability to sustain a stable level of attention. As some signs were detected of declining performance with time on task, it may be that focusing on declining performance is a more effective way to detect cognitive fatigue.

## 4.2 Subjective cognitive fatigue

Both study groups reported subjective cognitive fatigue during the testing procedure. This contrasts with the previous results of Bailey et al. (2007), Sandry et al. (2014) and Genova et al. (2013). Bailey et al (2007) examined cognitive performance and ratings of subjective fatigue. The participants were advanced MS patients (EDSS 7.68) with a chronic progressive form of the disease. The participants were tested in two separate sessions each consisting of repeated evaluations of subjective fatigue and a working memory test measuring the ability to hold, updated, and manipulate information in a temporary memory store. This test was also repeated during each testing session. The patient group reported a greater increase in the level of subjective fatigue than the control group. Sandry et al. (2014) found more prominent growth in subjective feelings of cognitive fatigue over time in patients with MS than in healthy controls. They found that the subjective cognitive fatigue increased as the length of the task increased. The cognitive tasks used in the study demanded processing speed and working memory. Genova et al. (2013) studied the development of fatigue during a task-switching paradigm, where the participants had to switch randomly between two sets of tasks – a color judgment task and a speed judgment task – based on a cue before each trial. The participants worked through six blocks of 32 trials each. Mental fatigue was assessed with the Visual Analogue Scale for Fatigue (VAS-F) seven consecutive times during the procedure. The results indicated that the MS patients reported more fatigue relative to the healthy controls but the severity of fatigue did not increase differently over time in the MS patients than in the healthy controls. The patients in the study by Bailey et al. (2007) had a more severe form of MS than the present patients, which may explain the conflicting results. Sandry et al. (2014) assessed patients with mild to moderate progression of MS, as evaluated by the Ambulatory Index, but their patients were clearly older than those in the present study (48.23 vs. 38.0 years), as was also the case in the study by Genova et al. (2013).

Subjective feeling of cognitive fatigue was evaluated five times in the present study. The evaluations were made before the testing procedure, after each cognitive test and after a rest interval of half an hour. After resting, the MS group reported feeling more cognitively fatigued than at the beginning of the testing procedure whereas no such difference was reported by the controls. Conversely, the controls gave lower ratings of subjective cognitive fatigue after resting than at the beginning of the testing procedure. The MS patients also showed a trend towards a higher, although not statistically significant, level of subjectively evaluated cognitive fatigue earlier during the testing procedure. It seems that cognitive strain causes subjective cognitive fatigue in healthy controls as well as in MS patients. However, healthy controls seem to recover quickly and effectively whereas MS patients need more time to subjectively recover from mental effort. There are findings of a slower recovery from

cognitive strain also in actual cognitive performance. Hämäläinen et al. (2012), who studied the effect of heat stress on cognition in MS patients found that exposure to heat partially worsened the patients' level of cognitive performance. One hour after exposure the MS patients' performance had almost returned to the baseline level. In the present study, recovery time was half an hour.

This subjective difficulty in recovering from cognitive strain may cause MS patients to experience difficulties in initiating new tasks after resting, if recovery from previous strain is insufficient and the recovery time not long enough. To the present author's knowledge, the prevalence of continuing subjective cognitive fatigue after a period of rest following cognitive strain has not previously been investigated. To determine how long it takes for MS patients to feel recovered, it would be important in future research to evaluate recovery from subjective cognitive fatigue with repeated evaluations of subjective cognitive fatigue during longer periods of rest.

### 4.3 Neurophysiological measures

In the EEG measurements, the CNV was pronounced at the frontal electrode sites (F3, Fz, F4) in both groups, with significantly larger amplitudes in the controls than MS in all three parts of the CPT. Effortful task preparation thus seems to be compromised in MS patients when compared to healthy controls. Previous research has also reported a lower CNV amplitude in MS patients than healthy controls, but at the parietal site (Pz) during a S1-S2 paradigm, where S1 was a sound and S2 a blinking light (Uysal et al., 2014). The present procedure demanded more complex processing of the stimuli, as the participants had to decide whether to respond to the stimuli by pressing a button or to inhibit that response. The results of the present study were partially consistent with the results of Vázquez-Marrufo et al. (2014), who found smaller CNV amplitudes in the central and frontal electrodes in MS patients than in healthy controls during an attention test using central and spatial cueing. These results were interpreted as indicating impairment in the central cueing mechanism and a worse orienting response.

In a healthy sample, CNV amplitude was higher in the older participants than younger participants, suggesting cognitive and effortful preparation. The authors also suggested that the larger amplitude they observed during a more demanding cognitive task towards the end of the test may be linked to increased effort to maintain performance over time (Wild-Wall et al., 2007). A previous study with functional magnetic resonance image (fMRI) and magnetic resonance image (MRI) found signs of increased cortical activity over time in MS patients performing a cognitive task but such difference in healthy controls (DeLuca et al., 2008). It may be that to maintain their performance level MS patients need to activate larger areas of their brain. In the present study, there were no signs of increased cortical activity in terms of CNV amplitude. MS

appears to affect the way patients are able to prepare themselves for cognitive tasks demanding sustained attention. It is nevertheless possible that had the study procedure been longer, signs of increased cortical activity would have been observed. The present study also found no signs of declining CNV amplitudes with time on task, as reported by Lorist (2008) for healthy participants. It is possible that the patients participating in this study had such a mild form of the disease that the study procedure was of insufficient duration to detect the symptom. In the study by Lorist (2008), the CNV amplitudes remained stable for 1.5 hours before diminishing. In the present study, the CPT took only half an hour to complete, which is much shorter.

The event-related potential (ERP) measures of the P3 component in the Go condition revealed that while the Go P3 latencies at the Cz electrode site were shorter in the MS group than controls, the latencies did not increase with time on task. There were no statistical differences between the two study groups in the Go P3 amplitudes at the measured electrode sites. This indicates that the MS patients reacted quicker than the healthy controls to the target stimulus in the CPT, although no differences in the amplitudes were observed between the two study groups. These results conflict with those of Pokryszko-Dragan et al. (2016), who found longer P3 latencies in MS patients than in healthy controls. The fact that Pokryszko-Dragan et al. (2016) used auditory P3 whereas in this study a visual paradigm was used could explain the discrepancy; moreover, they did not assess the development of fatigue with time on task. It is possible that motivational factors also explain the faster Go P3 latencies of the MS group. Chinnadurai et al. (2016) found that P3 latencies and amplitudes could be useful markers of cognitive fatigue in MS. They formed a ratio of an average of a longer period of cognitive strain to an average of a shorter period of strain and compared this ratio in MS to that in healthy controls. They found that while MS patients had longer P3 latencies than healthy controls in both the shorter and longer periods of assessment, there were no differences in P3 amplitudes between the two study groups. Chinnadurai et al. (2016) studied a patient group with an EDSS value of 4.6, and thus a more severe form of MS than the patients in the present study, whose mean value was 1.9.

The No-Go P3 amplitude at the Cz electrode site was smaller in the MS group than in the healthy controls throughout the task, but did not decrease in time on task. Frontocentral No-Go P3 from a cued Go/No-Go task is evoked when a No-Go imperative stimulus unexpectedly follows a go cue (Aasen & Brunner, 2016). Previously, the No-Go P3 has been associated with inhibitory (Smith, Johnstone, & Barry, 2006; Wessel & Aron, 2014) and evaluative processes (Sehlmayer et al., 2010; Schmajuk, Liotti, Busse, & Woldorf, 2006), the latter hypothesis gaining more support in a No-Go P3 review (Huster et al., 2013). It was suggested in the review that the No-Go P3 could reflect either evaluation of the outcome of inhibition, or an evaluation of the inhibitory process itself. Kato et al. (2009) proposed that lower No-Go P3 amplitudes are related to difficulty in allocating resources for No-Go stimulus detection. They also found decreasing No-Go P3 amplitudes with increasing time on task when

assessing healthy subjects. Their study procedure took 60 minutes to complete, which could explain the discrepancy between their results and those of the present study where No-Go P3 amplitudes were not observed to decrease with time on task in the shorter, approximately 30-minute CPT. The present results indicate that MS patients may have difficulties in evaluating inhibitory processes or investing resources in No-Go stimulus detection, even when the detection of a Go stimulus remains intact.

#### **4.4 Correlation between neuropsychological variables, subjective cognitive fatigue estimations and neurophysiological measures**

The results indicated that the longer reaction times detected during the CPT did not correlate with the subjective estimations of cognitive fatigue. The fact that the neuropsychological measures did not correlate with the subjective evaluations of cognitive fatigue are in line with many previous research results (e.g. Bailey et al., 2007; Beatty et al., 2003; Genova et al., 2013; Parmenter et al., 2003). Genova et al. (2013) suggested that behavioral neuropsychological performance is not the best objective measure of fatigue and that objective cognitive fatigue and subjective cognitive fatigue may be separate symptoms from each other.

Thus far, apart from this study, only Sandry et al. (2014) have studied the association between objective and subjective cognitive fatigue. They found that subjective and objective cognitive fatigue seem to be independent symptoms and that cognitive fatigue does not depend on cognitive load. Subjective cognitive fatigue increased with time in all participants but the increase was more prominent in the MS group than healthy controls. The research team suggested that cognitive fatigue in patients with multiple sclerosis is a function of time, as the longer the study participants were engaged in a cognitive task, the more likely they were to report increasing levels of cognitive fatigue (Sandry et al., 2014). The results of the present study were partially in line with those findings.

The smaller CNV amplitudes of the MS patients in the frontal ERP sites during the CPT did not correlate either with longer reaction times or with subjective estimations of cognitive fatigue. To the present author's best knowledge, no previous research exists on the possible association between cognitive fatigue and CNV. In healthy participants, larger CNV has been associated with shorter reaction time, and this association was enhanced in a situation designed to be motivational for the participants (Vuiller, Whitebread, & Szucs, 2015). It is possible that the CNV deficits observed in the present study were the result of cognitive deficits caused by MS and that these deficits do not have a direct association with objective cognitive fatigue. It is also possible that as the length of the task was not long enough to detect a decline in CNV over

time, it was also not possible to detect a connection between CNV and subjective cognitive fatigue.

At the Cz site, the shorter Go P3 latencies or smaller No-Go P3 amplitudes found in the MS patients did not have a significant association with their subjective estimations of cognitive fatigue. This is partly in line with the Pokryszko-Dragan et al. (2016), who found a significant correlation of P3 latency with Modified Fatigue Impact Scale (MFIS) and MFISmod total scores. But when they examined the correlation with the subscores of the MFISmod, they found that P3 latency was correlated with the physical dimension of fatigue, but not with the cognitive fatigue subscale score. They suggested that ERP parameters cannot be treated as direct indicators of the level of fatigue but more as an electrophysiological marker of cognitive deficits, which in turn they saw as significantly related to fatigue. In this study, the participants were specifically asked to evaluate their feeling of cognitive fatigue, not physical fatigue.

The shorter Go P3 latencies at the Cz site were not significantly associated with the increased reaction times of the MS patients. At other EPR measuring sites, no differences in P3 latencies were found between the two study groups. This indicates that the reaction to the stimulus on the brain activity level was as fast or even faster in the MS patients than in the healthy controls, although the motor reaction to the stimulus was slower in the MS patients as it took them more time to press the button after detecting the stimulus. This supports Sandroni et al. (1992), who found that when MS patients were subjectively fatigued compared to not fatigued, their performance showed increased reaction times but not changes in P3 latencies or amplitudes. This was interpreted to indicate that neural processes intervening between stimulus evaluation and the initiation of motor events are affected.

The MS patients' subjective ratings of cognitive fatigue were positively correlated with their lower ratings of their health-related quality of life. Similar results were reported by Pittion-Vouyovitch et al. (2006), who found that the cognitive dimension of fatigue was associated with lower ratings of quality of life. In the present study, depression was one of the exclusion criteria. This criterion was set to diminish the influence of possible secondary causes of fatigue. In Pittion-Vouyovitch et al. (2006), 74.8% of the MS patients participating in the study were depressed. Other studies have also reported an association between fatigue and depression (e.g., Morrow et al., 2009; Niino et al., 2014). However, the present results seem to indicate that MS patients can suffer from subjective cognitive fatigue without signs of depression. The present patients reported significantly more difficulties in their daily lives in the dimensions of mobility, elimination and usual activities than the healthy controls. It is possible that as coping with certain aspects of life demand increasing effort, this also increases the feeling of strain in other dimensions of life, such as cognition.



## 4.5 Strengths and weaknesses of the present study

Few previous studies have focused on cognitive fatigue in patients with a mild form of MS. In this study, the patient group had such a mild form of the disease that the baseline cognitive assessment, using the Brief Repeatable Battery of Neuropsychological Tests (BRBNT), did not differentiate the two study groups. Cognitive fatigue was approached broadly, using multiple methods and approaches, with the aim of gaining a versatile picture of the phenomenon. In this study, the participants were asked to evaluate their feeling of cognitive fatigue and the changes in it, whereas previous studies have mostly operationalized fatigue as a more general feeling of tiredness. Moreover, recovery from the subjective cognitive fatigue was also taken into account in this study. To the author's best knowledge, this is the first time recovery from subjective cognitive fatigue has been studied with MS patients.

Another strength of this study was that the associations of the ERP components Go/No-Go P3, and especially CNV, with cognitive fatigue in MS have not been widely studied. Again, to the author's best knowledge, this is the first time the association between cognitive fatigue and abnormalities in CNV have been studied with MS patients.

This research also has its weaknesses. The sizes of the two study groups were relatively small. The effect of small group size was, however, controlled for by matching the two study groups in age, gender, education, baseline cognitive performance, mood and health (excluding MS). The tests performed during the testing procedure were selected from those known to be sensitive to MS-related cognitive impairment, namely sustained attention, working memory and information processing speed. The selected tests were also such that included multiple trials, thus diminishing the possibility of random errors or chance/temporary slowness. Useful information might have been yielded if some of the tests had been performed twice during the study procedure; as both a first and last cognitive task. This would have enabled the development of cognitive fatigue to be evaluated over time, as was done in the study by Krupp and Elkins (2000).

It is possible that the study procedure was not long enough to detect cognitive fatigue. The procedure took about 90 minutes to complete, including the rest interval after cognitive strain, whereas in some studies the procedure has lasted over two hours (Möckel et al., 2015; Neumann et al., 2014). Although the previously mentioned studies assessed healthy participants, it may be that because the patients in the present study had such a mild form of the disease, a longer assessment procedure would have been more effective in detecting objective cognitive fatigue in both the neuropsychological tests and ERP measurements.

Another weakness in this study was that the possible effect of motivation on cognitive performance was not taken into account. In healthy participants, Möckel and her team (2015) observed that deteriorating processing speed was

not be completely explained by mental fatigue: motivational effects in the course of the task also affected performance. They observed that when the participants performed a lengthy cognitive task demanding sustained attention and processing speed, their mental fatigue significantly increased and their motivation to continue the test significantly decreased as the test proceeded. It is possible that in the present study the motivation of the controls was not as high as that of the MS patients; if so, this difference could have influenced the results.

## 4.6 Conclusions

The aim of this study was to evaluate cognitive fatigue in patients with a mild form of MS. Three different approaches to study the symptom was used: objective cognitive, subjective cognitive and neurophysiological. Objective cognitive measures consisted of tasks that demand sustained attention, processing speed and working memory. Previous studies have found these cognitive domains to be sensitive to cognitive fatigue. The tasks used in the study were Rapid Visual Perception (RVP), Paced Auditory Serial Addition Task (PASAT) with 3" and 2" stimulus intervals and Continuous Performance Task (CPT). Subjective cognitive fatigue was assessed with self-reported values. The participants evaluated their subjective feeling of cognitive fatigue five consecutive times; before the study protocol, after each cognitive task and after 30 minutes rest. In this way the development of subjective cognitive fatigue as well as recovery from it could be evaluated. Neurophysiological assessment included measurements of event-related potentials, more specifically CNV and P3, during CPT. Alongside these measurements the participants evaluated their quality of life. 20 patients with MS and 20 healthy controls participated the study. Before the actual study procedure they were clinically interviewed and tested with the BRBNT, which has been found to be sensitive to cognitive deficits related to MS. In order to avoid the effect of possible depressive symptoms to the results, the participants were evaluated with the BDI-II. The two study groups did not differ from one another in any measured demographic, clinical or cognitive characteristics.

According to the results of this study, patients with a mild form of MS had some cognitive deficits in the area of processing speed when they were more extensively assessed, although in a short screening this group was not differentiated in cognitive performance from matched healthy controls. The patients also showed possible signs of MS-related objective cognitive fatigue, as their reaction times in the last task of the study procedure were slower than those of the healthy controls. The various scoring methods used in the PASAT test did not differentiate the MS patients from the healthy controls. Similarly, neither the coefficient of variation (CoV) or response time variability (RTV) were sensitive to possible cognitive deficits or a higher level of objective cognitive fatigue in the MS patients. In fact, in one of the cognitive measures

(RVP), the CoV was higher in the controls. No differences in performance were observed between the two study groups in any of the other cognitive measures during the study procedure, although both study groups showed some signs of deteriorating performance during the tests. In future research, it would be important to ensure that the study procedure is long enough in duration to effectively capture the phenomenon of cognitive fatigue in MS patients.

The MS patients appeared to display a deficit in the mechanism of preparing to focus attention in the frontal area of the brain. This deficit was not associated with slowness in reaction, indicating that this problem might be linked to motor programming problems. It may be that MS patients need more time to prepare a motor program for executing the muscle movements required by the task – in this case, pressing a button. The patients also reported more difficulty in mobility than the healthy controls. The patients also exhibited signs of deficits in the ability to devote attentional resources to irrelevant stimuli (No-Go). It would be important in future work to study the association between ERPs and cognitive fatigue in MS patients in more detail, through, for example, closer analysis of the individual ERP components. Go P3 latency was faster in the MS patients than healthy controls in the Cz electrode site; this may be due to higher motivation. The measured ERP values did not change with time on task, and thus revealed no evidence of objective cognitive fatigue.

During cognitive strain, while subjective cognitive fatigue increased in both patients and healthy controls, the slower reaction times of the patients were not associated with the subjectively evaluated level of cognitive fatigue. Similarly, the frontal CNV atypicalities or smaller P3 No-Go amplitudes were not associated with subjective feelings of cognitive fatigue. The MS patients did not report as high a level of recovery from cognitive strain as the healthy controls. It seems that, when the conditions are right, objective and subjective cognitive fatigue are separate symptoms that affect healthy people as well as MS patients. The ratings of health-related quality of life of MS patients were lower than those of the healthy controls. In the MS patients, subjective cognitive fatigue was associated with lower ratings of subjective health-related quality of life. These two factors may have a significant effect on the MS patients' ability to stay in employment and should therefore be further studied to find ways of helping MS patients to remain employed as long as possible.

## YHTEENVETO

### **Kolme lähestymistapaa kognitiiviseen uupumukseen lievää MS-tautia sairastavilla potilailla: objektiivinen kognitiivinen, subjektiivinen kognitiivinen ja neurofysiologinen**

Tämän tutkimuksen tarkoituksena oli arvioida kognitiivista uupumusta lievää MS-taudin muotoa sairastavilla potilailla. Ilmiön tutkimiseen käytettiin kolmea eri lähestymistapaa: objektiivista kognitiivista, subjektiivista kognitiivista ja neurofysiologista. Objektiivista kognitiivista uupumusta arvioitiin tehtävillä, jotka mittaavat tarkkaavuuden ylläpitoa, prosessointinopeutta sekä työmuistia. Aiemmissa tutkimuksissa on havaittu, että näillä kognition osa-alueilla kognitiivinen uupumus tulee herkästi esille. Tutkimuksessa käytetyt objektiiviset kognitiiviset tehtävät olivat Rapid Visual Perception (RVP), Paced Auditory Serial Addition Task (PASAT) (3 ja 2 sekunnin ärsykkeen esittämisenopeus) sekä Continuous Performance Task (CPT). Subjektiivista kognitiivista uupumusta mitattiin itsearviolla. Osallistujat arvioivat kokemaansa kognitiivisen uupumuksen astetta viisi peräkkäistä kertaa; ennen tutkimuksen alkua, jokaisen kognitiivisen tehtävän jälkeen ja levättyään puoli tuntia kognitiivisten tehtävien jälkeen. Näin pystyttiin arvioimaan kognitiivisen uupumuksen kehitystä kognitiivisen rasituksen myötä, mutta myös toipumista siitä. Neurofysiologiset mitaukset käsittivät aivojen sähköisiin herätevasteisiin perustuvia havaintoja CPT tehtävän aikana. Mittareina olivat kontingentti negatiivinen variaatio (CNV) ja P3. Edellä mainittujen mittausten ohella tutkittavat arvioivat myös elämänlaatuun. Tutkimukseen osallistui 20 MS tautia sairastavaa ja 20 tervettä kontrollihenkilöä. Ennen varsinaista tutkimusajankohtaa osallistujat haastateltiin kliinisesti ja testattiin BRBNT -testistöllä, joka on havaittu herkäksi havaitsemaan MS tautiin liittyviä kognitiivisia häiriöitä. Tutkittavat arvioitiin myös BDI-II -kyselyllä, jotta mahdolliset depressiiviset oireet eivät vaikuttaisi tutkimuksen tuloksiin. Kaksi tutkimusryhmää eivät eronneet toisistaan demografisten, kliinisten tai kognitiivisten piirteiden osalta.

Tutkimuksen perusteella lievää MS-tautia sairastavilla potilailla oli havaittavissa muutoksia prosessointinopeudessa, kun heidät tutkittiin perusteellisemmin, vaikka suppeammassa kognitiivisten toimintojen arvioinnissa heitä ei voinut erotella kognitiivisen suoriutumisen perusteella verrallistetuista terveistä kontrollihenkilöistä. Tutkimuksen perusteella havaittiin myös mahdollisia merkkejä MS-tautiin liittyvästä objektiivisesta kognitiivisesta uupumuksesta, kun tutkimusprosessin viimeisessä tehtävässä MS potilaiden reaktioajat olivat terveitä verrokkeja hitaammat. Eri PASAT-tehtävän pisteytysmenetelmät eivät erotelleet kahta tutkimusryhmää toisistaan. Myöskään variaatiokerroin (CoV) tai reaktioaikavaihtelu (RTV) ei ollut tarpeeksi herkkä havaitsemaan MS-potilaiden mahdollisia kognitiivisia häiriöitä tai objektiivista kognitiivista uupumusta. Itse asiassa variaatiokerroin oli suurempi kontrollihenkilöillä yhdessä käytetyistä kognitiivisista tehtävistä (RVP). Muissa käytetyissä kognitiivisissa

tehtävissä tutkimusryhmien suoriutuminen ei eronnut toisistaan. Sen sijaan havaittavissa oli suoritustason heikentymistä osassa tehtäviä tehtävän kuluessa molemmassa tutkimusryhmissä. Tulevaisuudessa on tärkeää varmistaa, että tutkimusprosessi kestää tarpeeksi kauan, jotta MS-tautiin liittyvä objektiivinen kognitiivinen uupumus-ilmiö voidaan tavoittaa paremmin.

MS tautia sairastavilla potilailla näytti olevan häiriöitä aivojen etuosissa prosessissa, jossa valmistaudutaan kohdentamaan tarkkaavuus, mutta tämä häiriö ei ollut yhteydessä reaktioiden hitauteen. Tämä viittaa siihen, että ongelma voi liittyä motorisen ohjelmoinnin ongelmiin. On mahdollista, että MS-potilaat tarvitsevat enemmän aikaa motorisen ohjelman valmistamiseen voidakseen toteuttaa lihasliikkeet, joita tehtävän suorittamiseen tarvitaan – tässä tapauksessa napin painamiseen. Potilaat raportoivat myös enemmän liikkumiseen liittyvistä vaikeuksista kuin terveet verrokkihenkilöt. Tutkimuksessa oli lisäksi havaittavissa häiriöitä tarkkaavuuden suuntaamisessa ei-reagoitaviin ärsykeisiin. Tulevaisuudessa on tärkeää tutkia yksityiskohtaisemmin aivojen sähköisten herätevasteiden ja MS-tautiin liittyvän kognitiivisen uupumuksen välistä yhteyttä esimerkiksi analysoimalla tarkemmin yksittäisiä aivojen sähköisiä herätevasteita. Ärsykeisiin reagointi oli MS-potilailla jopa terveitä nopeampaa Cz-kanavassa, mikä saattaa selittyä potilaiden paremmalla motivaatiolla tehtävään. Mitatuissa ERP-arvoissa ei havaittu ajan kuluessa tapahtuvia muutoksia eikä siten merkkejä objektiivisesta kognitiivisesta uupumuksesta.

Kognitiivisen kuormituksen aikana subjektiivinen kognitiivinen uupumus lisääntyi sekä potilailla että terveillä kontrollihenkilöillä, mutta potilaiden hitaammat reaktioajat eivät olleet yhteydessä koettuun kognitiivisen uupumuksen tasoon. Myöskään poikkeavuudet frontaalikanavien CNV:ssä, Cz-kanavan reaktiota vaativan P3:n latenssissa tai inhibitiota vaativan P3:n amplitudissa eivät olleet yhteydessä subjektiiviseen kognitiiviseen uupumukseen. Toipuminen subjektiivisesta kognitiivisesta uupumuksesta ei ollut MS-potilailla yhtä tehokasta kuin terveillä kontrollihenkilöillä. Tutkimuksen perusteella näyttää siltä, että objektiivinen kognitiivinen ja subjektiivinen kognitiivinen uupumus ovat toisistaan riippumattomia oireita. MS-potilaat arvioivat elämänlaatunsa matalammaksi kuin tutkimuksen kontrollihenkilöt. MS-potilaiden subjektiivinen kognitiivinen uupumus oli yhteydessä matalampaan elämänlaatuun. Näillä kahdella asialla voi olla merkittävä vaikutus potilaiden kykyyn pysyä työelämässä ja ne pitäisi ottaa huomioon, jotta MS-potilaat voisivat pysyä työssä mahdollisimman pitkään.

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