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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Assessment of cognitive fatigue in persons with MS

Arthur Bukavyn
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Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

PROMOTOR :
Prof. dr. Peter FEYS

COPROMOTOR :
Mevrouw Fanny VAN GEEL

2016
2017

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Assessment of cognitive fatigue in persons with Multiple Sclerosis

OUTLINE

Research question: “How is cognitive fatigue measured objectively in persons with Multiple sclerosis (MS)?” The secondary question of this research was: “Does cognitive fatigue only appear in persons with MS or does it affect the healthy population as well?”

The key findings of this literature review (n=13) are the following:

- Cognitive fatigue can be measured objectively by the following measurement methods: Paced Auditory Serial Addition Test and Test Battery of Attentional Performance - Mobility version. These measures were based on a comparison of the first half of a prolonged task performance and the second half, or on a comparison of repeated task performances.
- Multiple sclerosis patients showed an abnormal change in objective performance during prolonged or repeated task performance compared to healthy controls.
- For further research it is necessary to assess cognitive fatigue with objective data. More objective measurement methods should be taken in consideration and tested for their ability to measure cognitive fatigue. On top of that, practice effects should be taken into account. These could lead to an underestimation of cognitive fatigue.

Students: Tom Venken, Arthur Bukavyn

Promotor: Prof. Dr. P. Feys

Co-promotor: Drs. F. Van Geel

CONTEXT OF THE MASTER THESIS

This thesis can be categorised in the research domain of neurologic rehabilitation. Persons with Multiple sclerosis often suffer from symptoms as cognitive impairments as well as an increase in fatigue. These symptoms have a disabling effect on many aspects of the patient's everyday life. Observation of the possible measurement methods that can objectively measure cognitive fatigue, therefore could be useful for healthcare providers.

In the first part, the primary research question of this literature review was "How is cognitive fatigue measured objectively in persons with MS?" The secondary question of this research was: "Does cognitive fatigue only appear in persons with MS or does it affect the healthy population as well?"
In the second part of this thesis, the focus will be set on the following research question: "What is the relationship between cognitive fatigue and motor performance in patients with MS?"

The central format was applied to this thesis.

This thesis was a duo Master's thesis. The entire review was written in a combined effort by Tom Venken and Arthur Bukavyn. Both researchers provided an equal contribution to the academic writing of the thesis.

Regarding the protocol of the observational study, the task for the students was to provide a detailed description of the research design and protocol. This protocol will be performed under the supervision of Prof. Dr. P. Feys and drs. F. Van Geel. The master students will assist in providing the baseline measurements as well as the following test measures. The students will also be responsible for the processing of the obtained results.

From November 2017 to March 2018 data will be gathered and examined from 60 participants, 30 MS patients and 30 healthy controls. The measurements will take place in the Rehabilitation and MS Hospital of Overpelt and at the UHasselt research centre REVAL of Diepenbeek. Final data-analysis is planned to be completed by April 2018.

We would like to express our gratitude towards Prof. Dr. Peter Feys and drs. Fanny Van Geel for their constructive feedback and guidance during the entire process of this thesis.

TABLE OF CONTENTS

PART 1: OVERVIEW OF THE LITERATURE

PART 2: RESEARCH PROTOCOL

PART 1: OVERVIEW OF THE LITERATURE

1. Abstract

Background: Multiple sclerosis (MS) is a neurodegenerative disease that is responsible for 2,3 million victims worldwide. Persons with MS often suffer from symptoms as cognitive impairments such as a decline in alertness, attention, working memory, learning, information processing speed, as well as an increase in fatigue. These symptoms have a disabling effect on many aspects of the patient's everyday life. Research has shown that cognitive fatigue, defined as: "prolonged continuous performance of a cognitively demanding task induces cognitive fatigue and is associated with a time-related deterioration of objective performance, the degree of which is referred to as cognitive fatigue", can be measured objectively, but only limited information about the possible measurement methods is examined.

Objective: The primary aim of this literature study is to give an overview of the objective measurement tools that are applied, hereby answering the question: "How is cognitive fatigue measured objectively in persons with MS?". The secondary aim of the study is to determine if cognitive fatigue only appears in persons with MS or if it affects the healthy population as well.

Methods: Two electronic databases (PubMed and Web of Science) were consulted using the following search strategies:

- PubMed: "Multiple Sclerosis (MeSH-term)" and "cognitive fatigue (Title/Abstract)"; This search resulted in 56 articles.
- Web Of Science: "TITLE: (multiple sclerosis) AND TOPIC: (cognitive fatigue) AND TOPIC: (performance) AND TOPIC: (impairment) AND TOPIC: (fatigue) NOT TOPIC: (review) and NOT TOPIC: (case report)"; This search resulted in 161 articles.

Results: After applying in- and exclusion criteria a total of 13 articles that measured cognitive fatigue in persons with MS were included. Five articles showed a clear decrease in performance in persons with MS when comparing the first half of the test to the second half of the Paced Auditory Serial Addition Test (PASAT). The Test Battery for Attention Performance - version Mobility (TAP-M) was able to effectively measure cognitive fatigue when combined with a supplemental load. The Computerized Assessment of Response Bias (CARB) was utilised to measure reaction time variability (RTV), which in turn correlated with cognitive fatigue in persons with MS. The n-back test suggested a decline in performance in the MS group compared to healthy controls, however a strong practice effect is proven towards the end of the task.

Discussion and conclusion: We consider the PASAT and TAP-M to be more useful compared to other measurement methods of cognitive fatigue. Multiple sclerosis patients showed an abnormal change in objective performance during prolonged or repeated task performance compared to healthy controls. Domains of cognition most commonly evaluated for cognitive fatigue were: alertness, attention, working memory, learning and information processing speed.

Most important keywords: Multiple sclerosis, cognitive fatigue, performance

2. Introduction

Multiple sclerosis (MS) is an autoimmune and -neurodegenerative disease that is responsible for 2,3 million victims worldwide. Symptoms of MS can be explained as the result of plaques of demyelination within the central nervous system (CNS) and a chronic inflammatory process[1]. The symptoms start to present themselves early in young individuals aged from 20 to 40-years, with a male to female ratio of 1:2[2]. Most common symptoms include visual disturbance, sensory loss, double vision, muscle weakness, cognitive impairments, fatigue, ataxia and impaired balance. Patients who suffer from MS experience disturbances in activities of daily life (ADL) and tend to have a lower quality of life (QoL) compared to the general population and those suffering from other chronic diseases[3, 4].

Cognitive decline can manifest in multiple cognitive domains: working memory, attention, processing speed, visuospatial abilities, and executive functions. Research has shown that cognitive impairments are progressive and become more widespread in long-term (4-10 years) follow-ups[5].

Symptoms of fatigue are often present and have a disabling effect on the functioning of persons with MS. Fatigue can be explained as “a sense of exhaustion, lack of energy, or tiredness[6].

In this research a differentiation between subjective and objective fatigue will be made.
The following two definitions will be used[7]:

1) Subjective fatigue (or perceived fatigue): subjective sensations
2) Objective fatigue (or performance fatigue): objective change in performance during continuous or repeated tasks

Both cognitive impairments and fatigue are highly prevalent (58,1%) in persons with MS, therefore a combination of these symptoms is possible. It is given that such patients experience an adverse relationship between the level of their fatigue and the actual cognitive performance[6, 8-10]. The following definition will be used in this research to explain cognitive fatigue: “prolonged continuous performance of a cognitively demanding task induces cognitive fatigue and is associated with a time-related deterioration of objective performance, the degree of which is referred to as cognitive fatigue”[11].

Until now it is not well understood what is the best measurement method to sensitively detect cognitive fatigue. Therefore, this literature review aims to provide a comprehensive summary of the methods used to assess objective measurement of cognitive fatigue in persons with MS. Furthermore it will be investigated whether cognitive fatigue is abnormal in persons with MS or if it affects the healthy population as well. This could also be relevant in physical rehabilitation, given that many motor tasks require a higher level of cognitive control.

3. Method

3.1 Research questions

The primary aim of this literature study was to give an overview of the most commonly used objective measurement tools, hereby answering the question: “How is cognitive fatigue measured objectively in persons with MS?”. The secondary aim of the study was to determine if cognitive fatigue only appears in persons with MS or if it affects the healthy population as well.

3.2 Literature search

PubMed and Web of Science were consulted for the literary sources. The search strategy for PubMed consisted of using the keywords “Multiple Sclerosis (MeSH-term)” and “cognitive fatigue (Title/Abstract)”. These keywords were combined using the Boolean operator “AND”. Executing this search strategy on 20/06/2017 resulted in 56 articles.

The search strategy for Web of Science was the following: “TITLE: (multiple sclerosis) AND TOPIC: (cognitive fatigue) AND TOPIC: (performance) AND TOPIC: (impairment) AND TOPIC: (fatigue) NOT TOPIC: (review) and NOT TOPIC: (case report)”. This combination of search terms on 20/06/2017 produced a total of 161 articles.
An overview of all search strategies is provided in the appendix (table 1).

Following this search the resulting articles were deemed either relevant or irrelevant by screening the abstract and applying the inclusion and exclusion criteria. In case of uncertainty regarding the relevance of an article, a consensus was reached through discussion and deliberation of the two authors of this review or by asking additional advice of the (co-)promotors.

3.3 Selection criteria

<u>Inclusion criteria:</u>

- adults (≥ 18 years) diagnosed with definite MS
- cognitive fatigue was measured by using an objective clinical measurement instrument and is defined in accordance to the selected definition in this study
- the studies were described in the English or Dutch language

<u>Exclusion criteria:</u>

Exclusion criteria were: a) no objective measure of cognitive fatigue; b) reviews; c) other neurological conditions; d) case reports (n<15 participants)

3.4 Quality assessment

To assess the quality of the articles found using the aforementioned search strategy the STROBE statement checklist was used. Questions 6b, 12c, 13b, 13c, 14b,14c, 16a, 16b and 16c do not apply to observational studies and are therefore removed from the original scale prior to assessment.

3.5 Data extraction

The following data was extracted from the included articles: descriptive data, research design and outcome measures of cognitive fatigue. When viewed together these data should give an accurate summary of the methods most commonly used to measure cognitive fatigue in persons with MS and whether results are abnormal compared to healthy subjects.

An overview of the included articles is provided in the appendix (table 2).

4. Results

4.1 Results study selection

All articles that were found on PubMed (56) and Web of Science (161) were filtered using the selection criteria as a guideline. This process was based primarily on the article's abstract, but was extended by use of the full texts if needed, due to a lack of information in the abstract itself. Afterwards all remaining articles were thoroughly screened for quality, potential biases and level of evidence using the full text. The results of this screening process are shown in figure 1 in the appendix.

Inclusion criteria

a) Having been diagnosed with MS was a requirement for being included in this literature review, seeing as the primary goal was to provide an overview of the different methods used to examine cognitive fatigue in persons with MS.

b) One of the most recurring reasons for exclusion was the lack of an objective measurement of cognitive fatigue as is defined this literature study. The definition for cognitive fatigue that was utilised in this review is a decrease in objective performance and subjective perception of effort induced by the performance of a continuous task[11]. Guided by this definition many articles (n= 180) that did not measure cognitive fatigue, but rather dual task cost or cognitive motor interference, were excluded. Other studies did not provide an objective quantitative measure of cognitive fatigue.

c) The search strategy was limited to articles that were either written in English or in Dutch. These are the only languages in which assessment was fully possible. Six articles in the German (n=2), Portuguese, Spanish and French (n=2) language were excluded for this reason.

Exclusion criteria

In order to gather as many valid and reliable studies as possible, case reports (n=2) were excluded due to their limited level of evidence.

In total 193 articles were excluded.

An overview of all excluded articles is provided in table 3 in the appendix .

4.2 Results quality assessment

We eliminated questions of checklist that did not apply to the included literature search. A score of 25 would therefore correspond with a maximum quality. After conversion of the scores to a percentage a mean score of 71% was observed. The percentage scores ranged from 68% to 80%, hence there was no need to exclude articles based on their quality. Overall, we conclude that the studies have a sufficient quality based on the STROBE checklist.

A summary of quality assessment is provided for every included article in table 4 in the appendix.

All articles discussed the scientific background and rationale for their investigation in the introduction. They also stated their specific objectives -including some prespecified theories- and presented key elements of the study design early on in their paper. All research settings, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection were defined in the included articles. All cross-sectional studies included in this literature review described the eligibility criteria, and the sources and methods of selection of participants used to execute their research. All outcomes, exposures, predictors, potential confounders, and effect modifiers were clearly defined. For each variable of interest, sources of data and details of methods of assessment (measurement) were given.

Only three studies[12-14] mentioned any efforts to address potential sources of bias. Even though this gives the impression that the articles must therefore contain several biases, a thorough screening of the included articles ensured that any biases that were present in the studies are defined. No study mentioned or explained the choice of their sample size. A total of nine articles[12-20] described a sensitivity analysis.

All articles reported numbers of individuals at each stage of study enrolment including numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. All but one article[19] gave characteristics of study participants (eg demographic, clinical, social). All articles reported numbers of outcome measures. Only two included articles[12, 21] did not report other analyses done such as analyses of subgroups and interactions, and sensitivity analyses.

4.3 Results data extraction

The sample size of the studies was small. There is a range of between 31[22] and 230[17] subjects in the studies. The mean age of the healthy controls ranged from 33.6 years[20] to 60.18 years[22] and the mean age of the MS patients ranged from 33.6 years [20] to 58.29 years[22]. All studies include more women than men. The MS characteristics were mostly defined with the Expanded Disability Status Scale (EDSS) and with the Ambulation Index (AI) which is used in one article[23]. Both the EDSS and the AI measure the progression of MS and other neurological impairments. Twelve articles measured the EDSS at baseline, one article did not measure the EDSS at any point. The mean EDSS varied from 1.8[23] to 7.68[22]. The mean disease duration varied from 4.35 years[14] to 59 years[22].

All articles were observational studies with a cross-sectional design. The population always consisted of a MS group and a healthy control group. An overview of the descriptives of all articles is provided in table 5 in the appendix.

Most articles paired a measurement of objective fatigue (performance fatigue) with a measurement of subjective fatigue (or perceived fatigue). This with the aim of examining if there was any relation between perceiving oneself as fatigued and objectively delivering a reduced performance in these moments. These subjective measurements comprised of several questionnaires such as the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS) that investigated whether or not the examined persons perceived themselves as being more fatigued than normal. An overview of all included objective measurement methods and the mean EDSS per article is provided in table 1.

The primary aim of this study was to measure cognitive fatigue objectively. Although it was not the primary purpose in all the included articles, measurement methods and data-analyses were described in every article. **The secondary aim** was investigated in all articles (n=13) by determining if cognitive fatigue only appears in persons with MS or if it affects the healthy population as well.

A description of the objective measurement methods below is provided in the appendix (Table 2).

Paced Auditory Serial Attention Test (PASAT): information processing speed

Five out of 13 articles mentioned using the PASAT to objectively measure cognitive fatigue in persons with MS. In the article written by Schwid et al (2003) the MS patients showed a 5.3% decline in the amount of correct answers in the second half of the PASAT compared to the first half of the PASAT. This was in contrast with the control group who did not show any decline. Cognitive fatigue showed no relation to age, gender, or depressive symptoms.

Same results were shown by Morrow et al (2015). An average of two to three fewer correct responses were given in the last third of the PASAT than in the first third in the MS group, while contrary results were seen in the healthy control group. The controls managed to give on average two more correct responses in the last third of the PASAT than in the first third. Rosti et al (2006) indicated a fade in performance that was seen in the second half of the PASAT in the MS group in comparison with the healthy controls. Bryant, Chiaravalloti & DeLuca (2004) showed a similar decrease in task efficiency when task duration increased but only when using the dyad scoring method.

Walker, Berard, Berrigan, Rees & Freedman (2012) administered the PASAT three times, each time with both the 3″ and 2″ inter-stimulus intervals (ISI) by both groups. Irrespectively of which ISI was used, overall task performance did not differ between both groups. Multiple sclerosis patients showed a significant decrease in performance in the second half of the PASAT versus first half when using the dyad scoring method. This effect was not be observed when simply comparing correct responses between the first half of the test versus the second half of the test. Subjects showed parallel performances in the first half of the task compared to the second half the task.

Table 1: Overview of all the included objective measurement methods and the mean EDSS

	PASAT	TAP-M	SDMT	CARB	N-Back	Other	EDSS (mean)
Claros-Salinas et al., 2013		**P*°, C*°**					**3.6**
Neumann et al., 2014		**C*°**					**3.8**
Bruce et al., 2010				**X *°**			**4.5**
Claros-Salinas et al., 2010		**C*°**					**NA**
Schwid et al., 2003	**X (3”)*°**					**X**	**3.8**
Morrow et al., 2015	**X (3”)*°**						**2.0**
Krupp et al., 2000						**C*°**	**3.8**
Bryant et al., 2004	**Z*°**						**1.8**
Chinnadurai et al., 2016			**X**			**X*°**	**4.6**
Holtzer et al., 2013			**X*°**				**2.45**
Bailey et al., 2007					**X*°**		**7.68**
Rosti et al., 2006	**X (3”)*°**						**2.9**
Walker et al., 2012	**X (3” and 2”)*°**						**1.83**

Legend:

* = Significant measurement of cognitive fatigue

°= Significant difference between MS patients versus healthy controls

P=Physical load

C= Cognitive load

3”= PASAT 3 second version

2”= PASAT 2 second version

NA= not available

Z= 4 PASAT trials were executed. Digit presentation rate was 2.4, 2.0, 1.6, and 1.2 s for trials 1, 2, 3, and 4, respectively.

Test Battery for Attention Performance - version Mobility (TAP-M): alertness, selective attention and divided attention

In Claros-Salinas et al (2013) a measurement method named TAP-M was used. The purpose of this battery is to test alertness, selective attention and divided attention. Multiple sclerosis patients showed a significant increase in reaction time (RT) induced by cognitive and physical load. Healthy controls did not show this relation. No significant change in RT was measured in the condition without cognitive or physical load. MS patients showed no significant increase in RT after cognitive and physical load when performing the Go/NoGo test. In rest conditions a significant reduction of RT was observed. Cognitive and physical load did not induce a significant increase of RT in the Divided attention task. The reduction of the RT for the visual task was significant. Compared to the rest conditions patients reported a significantly higher cognitive fatigue than during load.

Another article written by Claros-Salinas et al (2010) also included the TAP-M. In this article the TAP-M was combined with a cognitive task, resembling the subject's occupation in between test moments, in order to measure cognitive fatigue. Three test moments repeated on two consecutive days were used to complete the measures. Objective performance was poorer in the MS group. Reaction time increased significantly in the afternoon compared to the morning session for alertness and selective attention.

A comparable research method was used by Neumann et al (2014). The short version of the TAP-M was combined with a cognitive load. The outcome showed that mean RT was longer in MS patients than in controls at baseline (t1). Reaction time increased significantly in patients after exerting cognitive load (t2), but not in controls. Reaction time decreased back to baseline levels at t3 in patients, controls showed an even larger decrease. Based on all studies, the increase in RT resulting from a cognitive or physical load is most noticeable in the alertness subscale, suggesting that cognitive fatigue can be measured objectively with the TAP-M combined with a cognitive load

Symbol Digit Modalities Test (SDMT): attention, information processing speed and working memory

A modified version of the SDMT (mSDMT) was used by Chinnadurai et al (2016). No significant results were found using this method. Using the SDMT Rao's adaptation, Holtzer et al (2013) showed a significant decrease in the amount of correct responses given in the third administration of the SDMT (Rao's adaptation) compared to the first. This decline in performance could only be observed in the MS group. Thus patients with MS showed cognitive fatigue.

Computerized Assessment of Response Bias (CARB): alertness

Bruce et al (2010) used a measuring tool named CARB. A significantly higher RTV was found in MS patients compared to healthy controls using the CARB. A strong relation between total RTV and cognitive fatigue was found in the MS group.

N-back test: alertness

Bailey et al. (2007) utilized the n-back test to assess cognitive fatigue over time by comparing the performance across the first, second and third pairs of blocks in the test. For one of the tasks (0-back), the MS, but not the control participants, showed deterioration in accuracy over blocks during the two presentations of the task. For the 1-back task, the MS, but not the control participants, were less accurate on the second than the first presentation. Although the MS group was slower than the control group in both the 0-back and 1-back tasks, the RT data did not suggest cognitive fatigue effects, since responding became faster rather than slower over time for both groups. The 0-back task showed a deterioration in accuracy over blocks during the two presentation for the MS group. The 1-back test showed less accurate results on the second compared to the first presentation for the MS group. Both groups showed a faster responding over time, suggesting no significant cognitive fatigue was shown.

Other measurement methods

Beside the Stroop test, the SDMT Cum Addition Test (SDMCAT), the Serial Addition Test (SAT) and the the 3 Digit Serial Addition Test (3DSAT) were also used in Chinnadurai et al (2016). A clear pattern was seen when comparing the 60 seconds version of the tests to the 180 seconds version. No significant differences were observed between the groups in the 60 second versions, this in contrast with the 180 second versions, which did show a significant decrease in performance in the MS group. This did not apply to the SAT. When viewing the ratio of correct responses scored in three executions of the 60 second version versus those in the 180 second versions of the SDMCAT, the 3DSAT and the STROOP test, a significant difference was seen between MS patients and healthy controls. This implied that the MS group showed more cognitive fatigue.

In the article written by Krupp et al (2000) patients first completed the neuropsychological test battery. Patients then performed the Alpha-Arithmetic test which served as a continuous cognitive effort task. Afterwards the patients completed the neuropsychological test battery once more. Different neurological tests were used: Selective Reminding Test (SRT) to assesses learning and memory, 10/36 spatial recall test for visuospatial memory, Tower of Hanoi test (TOH) for conceptual planning and procedural learning, Digit span test for auditory attention and Controlled Oral Word Association (COWA) for verbal fluency. Multiple sclerosis patients showed a decline in performance on the SRT, 10/36, TOH following the A-A test, where controls showed an improvement. There were no significant group differences in the pattern of change following the A-A Test for Digit Span or COWA. Multiple sclerosis and control participants reported an increased FSS across the testing sessions compared to their baseline values.

In the article written by Schwid et al (2003) no significant declines in performance were observed in both groups during administration of the Digit Ordering Test (DOT).

Table 2 below provides an overview of the measurement methods, experimental conditions and conclusions.

Table 2: Overview of measurement methods, experimental conditions and conclusions (n=13)

Article	Measurement method	Experimental Conditions	Conclusion
Claros-Salinas et al., 2013	Test Battery for Attention Performance(version mobility)(TAP-M)	The patients perform the attention tests on three different days under three different circumstances: - before and after a period of rest. - before and after cognitive load - before and after a physical load. The order in which subjects perform these test conditions is randomised.	Significant: - increased mRT (alertness) due to cognitive and physical load in MS patients
Neumann et al., 2014	TAP-M: alertness subtest	Alertness was measured before undergoing cognitive load (t1), directly after completion (t2), and after a 1 hour recovery period (t3).	Significant: - longer mean RT in MS patients (t1) - increase in RT in MS patients (t2) - decrease of RT to baseline in MS patients (t3)
Bruce et al., 2010	Computerized Assessment of Response Bias (CARB) Symbol Digit Modalities Test (SDMT)	CARB: - 3 blocks of 37 events each - progressively longer distraction period after each successive block	Significant: - higher RTV in MS patients (CARB) - lower performance in MS patients (SDMT)
Claros-Salinas 2010	TAP-M	3 test moments: - morning - noon - afternoon VAS: after each test moment Test are done on 2 consecutive days Subjects performed a cognitive task resembling their occupation in between test moments.	Significant : - poorer objective performance in MS patients - decline in cognitive performance between test days in MS patients
Schwid et al., 2003	Paced Auditory Serial Addition Test (PASAT)(3”) Digit Ordering Test (DOT)	Two identical test sessions separated by 4 - 10 days, within a month after 2 practice sessions. Subjects listen to music during a 10 minute break between the PASAT and DOT.	Significant: - Decline in performance in MS patients from start to end of PASAT
Morrow et al., 2015	PASAT (3”)	PASAT was performed together with other test in a single session of 90 minutes.	Significant: - increase in amount of incorrect responses in the last third of the PASAT than in the first third in MS patients

Krupp et al., 2000	<u>Neuropsychological tests:</u> Selective Reminding Test (SRT) 10/36 spatial recall test Tower of Hanoi test (TOH) Digit span test Controlled Oral Word Association (COWA)	Neuropsychological test taken before and after cognitive load.	Significant: - decline in performance on the SRT, 10/36, TOH for MS patients
Bryant et al., 2004	PASAT	4 PASAT trials were executed. digit presentation rate was 2.4, 2.0, 1.6, and 1.2 s for Trials 1, 2, 3, and 4, respectively.	Significant: - increased cognitive fatigue in MS patients in second halves of trials - decrease in task efficiency when task duration increases
Chinna durai et al., 2016	The Stroop test SDMT Cum Addition Test (SDMCAT) modified SDMT (mSDMT) Serial Addition Test (SAT) 3 Digit Serial Addition Test (3DSAT)	Either 3x60 seconds or 180 seconds was given to execute the test. A 20 minute break time between tests was obligatory.	Significant: - decrease in performance in the MS group in the 180 seconds versions (excluding SAT) - difference between MS patients and healthy controls in ratio of correct responses scored in three executions of the 60 second version versus those in the 180 second versions of the SDMCAT, the 3DSAT and the stroop test - decrease in task efficiency in the MS group with increased task duration
Holtzer et al., 2013	SDMT: Rao's adaptation, oral version	SDMT was performed 3 times per session, at 3 different days for a total of 9 administrations. Each test administration was separated by a 5 minute interval.	Significant: - decline in performance in MS patients for increasing SDMT duration
Bailey et al., 2007	N-back test - 0-Back test - 1-Back test	Performance across the first, second and third pairs of blocks in the test were compared.	Significant: - deterioration in accuracy over blocks during the two presentations of the 0-back task in MS patients - decrease in accuracy in second versus first presentation of the 1-back test in MS patients
Rosti et al., 2006	PASAT(3")	The amount of errors and omission made in the first third of the test is compared	Significant: - decline in amount of correct answers in the last third of the

		to the amount made at the end of the series.	PASAT compared to the first third in MS patients
Walker et al., 2012	PASAT Computerized Test of Information Processing (CTIP)	Scores are compared between first and second half of the trial in both healthy controls and MS patients. PASAT is completed three times, each time with both the 3″ and 2″ inter-stimulus intervals (ISI). Test administrations are interspersed with other other tests in the neuropsychological battery.	Significant: - significant decrease in performance in the second half of the PASAT versus first half when using the dyad scoring method in MS patients

5. Discussion

5.1 Reflection on the quality of the included studies

All included articles (n=13) gave a detailed view of the reasoning behind their investigation early on in their paper. This ensured a full understanding of what was done in the paper. Nearly all studies (n=12) were comprehensive in their description of study participants regarding demographics, clinical and social characteristics. The sample size went from small (n=31) to fairly large (n=230). This large range of sample size can be explained by a lack of strict inclusion criteria used for the population characteristics in this research. Most articles (n=12) reported a more detailed analysis of potential between-group interactions. After conversion of the scores to a percentage a mean score of 71% was observed, hence there was no need to exclude articles based on their quality. Overall we can conclude that based on the STROBE checklist.

5.2 Reflection on the findings in function of the research questions

This literature study showed that multiple measurement methods exist to measure cognitive fatigue objectively. Comparing results of these methods led to five relevant measurement methods. An overview of domains of cognition tested and administration time per test is provided in table 7 in the appendix.

PASAT

Some methods, like the PASAT, are capable of measuring cognitive fatigue on their own due to the nature of their design. The PASAT is considered to be sensitive to limitations of information processing speed and cognitive flexibility. Furthermore it is based on a continuous task with repeated measures that can measure change in objective performance. Thus, perfectly tuned for the aim of our primary research question. Results show a clear pattern when comparing performance in the first half of the test to performance in the second half.

TAP-M

Other tests, like the TAP-M, have to be combined with a supplemental load in order to effectively measure cognitive fatigue. This load can be administered in the form of a physically exerting task or a cognitively demanding task. By measuring objective performance both before and after external loading, cognitive fatigue can be detected. Significant results were found only in the alertness and selective attention subscales of the test.

SDMT

The third test we consider to be relevant to the primary aim of our literature search is the SDMT. Different versions of the SDMT were used in the studies. Holtzer et al (2013) was able to measure cognitive fatigue with the SDMT (Rao's adaptation). However one article[20] could not objectively measure cognitive fatigue by using the mSDMT.

CARB

The CARB was utilised to measure RTV, which in turn correlated with cognitive fatigue in persons with MS. A considerable advantage of this test can be found in its method. By combining a forced-choice paradigm with a distraction task, this test avoids the possibility of a practice effect. Due to limited data on this test method, statements about its value cannot be made with absolute certainty.

N-back test

Lastly the n-back test was found in this literature search. Even though this test suggested a decline in performance in the MS group compared to healthy controls, a strong practice effect was proven towards the end of the task[22]. This raises questions towards the suitability of this test for measuring changes in objective performance. The reason behind the problem could be explained by its difficulty. The purpose of the test is to react as fast as possible to the appearance of a target stimuli. This is less difficult than the PASAT, where participants are asked to make calculations as fast as possible. Thus, it is more likely to achieve a practice effect when a task is less demanding.

Multiple sclerosis patients versus healthy controls

Multiple sclerosis patients showed an abnormal change in objective performance during prolonged or repeated task performance compared to healthy controls. The fact that this result was found in all articles answers the secondary research question formed in the beginning of this literature review.

5.3 Reflection on the strengths and limitations of the literature study

An overview of the strengths and limitations of the included studies is shown in table 6 in the appendix.

<u>The most important strengths are the following:</u>

- Multiple measurement methods are used with different types of external load. This wide approach challenges different categories of cognition that could be actors of cognitive fatigue
- Nearly all articles (n=11) provide detailed descriptions of measurement methods
- The inclusion and exclusion criteria for participation are clearly defined in all articles
- All studies compare performance between MS and healthy controls. This comparison gives the opportunity to examine the difference of cognitive fatigue behaviour in persons with MS compared to a healthy population.
- The quality was assessed by two independent researchers.
- Two databases (PubMed and Web of Science) were used for this research
- All articles contain a decent sample size ranging from 31 to 60 participants, with the exception of one study containing 230 participants[17]

<u>The most important limitations are the following:</u>

- Some articles are difficult to generalize due a respectively high or a respectively low mean EDSS score. It is not possible to apply the results of severely ill patients to patients with mild disease severity.
- Some articles describe assessment methods that are very time consuming which could lead to a lack of motivation in subjects. This can introduce a bias of the results because of an underestimation of their performance capacities. These results may lead to a misinterpretation when comparing the results to those of different studies that use less extensive test batteries.

- Most measurement methods (PASAT, SDMT, TAP-M, n-back) that were used showed a practice effect. Practice effects lead to an underestimation of the severity of cognitive fatigue present in test subjects. One test (CARB) shows no practice effects and does not need a preceding trial in order to obtain a stabilised test performance.
- This literature review contains a low number of included articles (n=13) which could be a result of the limited research done by other researchers on this topic.

5.4. Recommendations for further research

- Practice effects should be avoided by exposing subjects to one or more preceding trials in order to minimize underestimation of cognitive fatigue. The results of these practice sessions should not be included in the final statistical analysis.
- The measurement of cognitive fatigue can and should be based on objective data. More objective measurement methods should be taken in consideration and tested for their ability to measure cognitive fatigue.
- Test batteries combined with a standardized cognitive load allow for a more comprehensive manner of identifying cognitive fatigue in persons with MS.
- The relationship between fatigue and other measures of current mood or motivation should be taken into account.

6. Conclusion

According to the literature search cognitive fatigue can be measured objectively. We consider the PASAT and TAP-M to be superior compared to other measurement methods of cognitive fatigue. Furthermore MS patients showed an abnormal change in objective performance during prolonged or repeated task performance compared to healthy controls, showing that cognitive fatigue in MS patients is to be expected.

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8. Appendices part 1- overview of the literature

- Table 1: An overview of all search strategies
- Table 2: An overview of the included articles
- Table 3: Overview of excluded articles with reason for exclusion
- Table 4: Quality assessment – STROBE Statement
- Table 5: An overview of the descriptives
- Table 6: An overview of the strengths and limitations of included articles
- Table 7: Domains of cognition tested and administration time per test
- Figure 1: Flowchart of the in- and excluded studies
- Table 8: List of abbreviations

Table 1: An overview of all search strategies

MeSh/Keywords	Items found in PubMed
Multiple Sclerosis AND cognitive fatigue	56

Keywords	Items found in WoS
Multiple Sclerosis AND cognitive fatigue AND performance AND impairment AND fatigue	175
NOT review NOT case report	161

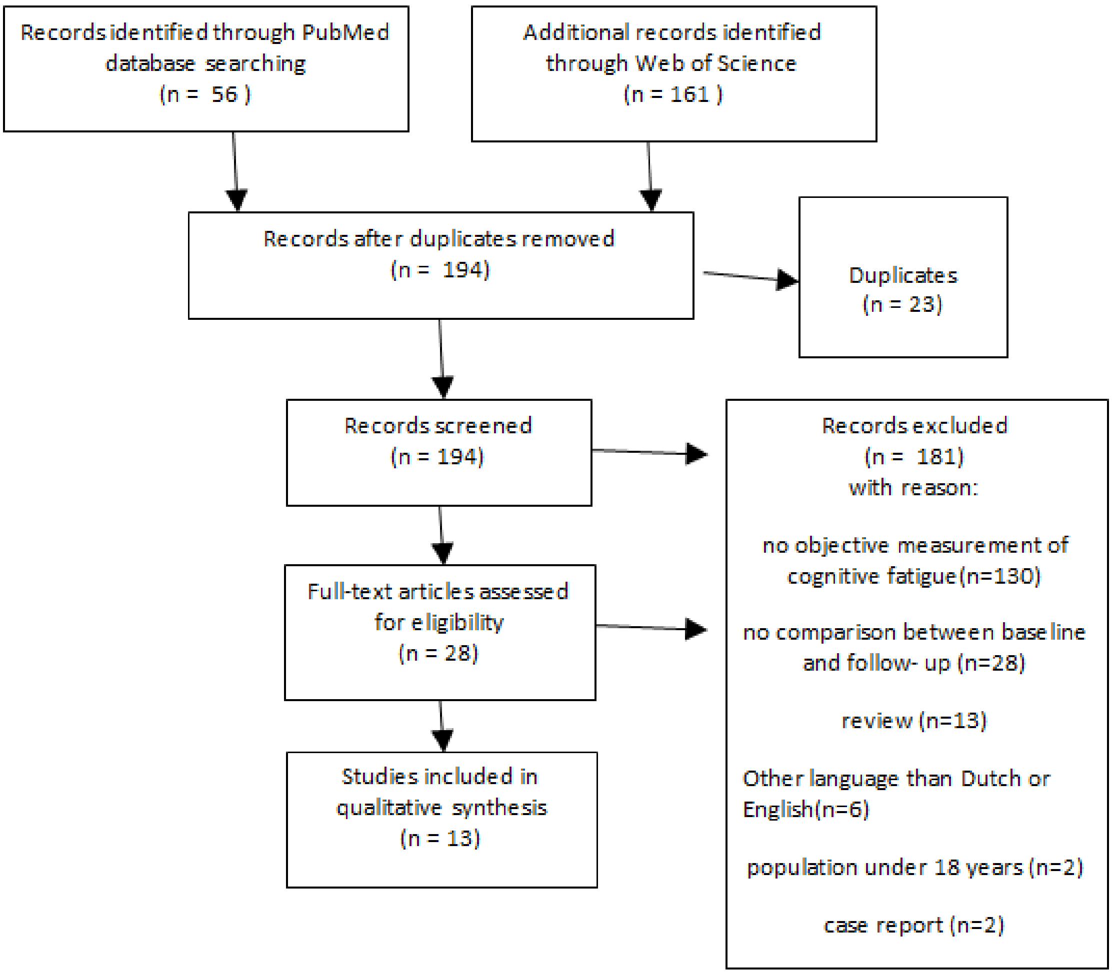

Figure 1: Flowchart of the in- and excluded studies

Table 2: An overview of the included articles

Article	Measurement method	Conclusion
Claros-Salinas et al., 2013	Subjective cognitive fatigue: - Self-reported rating scale ranging from 0 (no cognitive fatigue) to 9 (extreme cognitive exhaustion) Test Battery for Attention Performance(version mobility)(TAP-M) - Alertness: 3 minutes lasting reaction task measures median reaction time (mRT). Subject are asked to press an external response key with their right index finger as quickly as possible after a stimulus is presented. - Selective attention: Go/NoGo task lasting 3 minutes with two visual stimuli (X or +). Response key pressed with right index finger as quickly as possible. Measures provided are median RT's and errors. - Divided attention: Dual-task paradigm lasting 4 minutes, containing both a visual and an auditive discrimination task. o Visual task: Subjects are asked to press the response key when the target configuration is presented. o Auditive task: Subjects are asked to press the response key when a repetition of tone frequency is detected. Cognitive load: A test battery consisting of frequently used paper-and-pencil tests covering the domains of attention, word recognition, verbal fluency, memory, and calculation, as well as visuo-spatial and reasoning abilities is used. Task duration is 2.5 hours including a 15-minute break. Physical load: treadmill walking until exhaustion The patients perform the attention tests on three different days under three different circumstances: - before and after a period of rest. - before and after cognitive load - before and after a physical load. The order in which subjects perform these test conditions is randomised.	MS patients show a significant increase in mRT induced by cognitive and physical load. Healthy controls did not show this relation. No significant change in mRT is measured in the condition without cognitive or physical load. MS patients show no significant increase in mRT after cognitive and physical load when performing the Go/NoGo test. In rest conditions a significant reduction of mRT is observed. Cognitive and physical load do not induce a significant increase of mRT in the Divided attention task. The reduction of the mRT for the visual task is significant. During loading patients report a significantly higher cognitive fatigue than compared to the rest conditions. The subjective cognitive fatigue reported during the cognitive load is significantly higher compared to the perceived subjective fatigue during the physical load condition. Physical and cognitive load can induce a decline of cognitive function. This difference in function can be measured objectively by using repeated attention measurements.
Neumann et al.,	TAP-M: reaction time (RT) is measured in 2 test conditions. In one condition subjects are asked	Mean RT is longer in MS patients than in controls at baseline (t1).

2014	to respond with their right index finger as quickly as possible when a white X appears on the screen. In the second condition an acoustic warning signal precedes the appearance of the white X. Cognitive load: A test battery consisting of frequently used paper-and-pencil tests covering the domains of attention, word recognition, verbal fluency, memory, and calculation, as well as visuo-spatial and reasoning abilities is used. Task duration is 2.5 hours including a 15-minute break. Alertness was measured before undergoing the test battery (t1), directly after completion (t2), and after a 1 hour recovery period (t3).	RT increases significantly in patients after exerting cognitive load (t2), but not in controls. RT decreases back to baseline levels at (t3) in patients. Controls show an even larger decrease.
Bruce et al., 2010	Computerized Assessment of Response Bias (CARB) - To assess response time variability - Digit remembering task with distraction task - 3 blocks of 37 events each - RTV (response time variability) is calculated as a standard deviation of the correct response times (i.e. the increase in time needed to answer correctly, results in an increase of the standard deviation) Symbol Digit Modalities Test (SDMT)	A significantly higher RTV is found in MS patients compared to healthy controls using the CARB. A strong relation between total RTV and cognitive fatigue is found in the MS group. MS patients perform worse on the SDMT than controls.
Claros-Salinas 2010	3 test moments: - morning - noon - afternoon Visual Analogue Scale (VAS) for subjective cognitive fatigue after each test moments. Test are done on 2 consecutive days. Subjects work on cognitive task resembling their work in between test moments. Tests: TAP-M - Reaction time task (alertness) - Go/NoGo (test for selective attention) - Dual-task paradigm (divided attention)	Objective performance is poorer in MS group. The patient group shows a decline in cognitive performance between test days, controls do not. Subjective reports of cognitive fatigue are correlated with cognitive performance.
Schwid et al., 2003	Paced Auditory Serial Addition Test (PASAT)(3") - It is considered to be specifically sensitive to limitations of information processing speed. In this test, single digits are presented every 3 seconds using an audio-device to ensure a standardised rate of stimulus presentation. The patient is asked to add each new digit to the one preceding it. Scoring the test is done by assessing	MS patients show a significant 5.3% decline in performance from start to end of the PASAT. Controls do not show any decline in performance in the PASAT. Cognitive fatigue has no relation to age, gender, or depressive symptoms. No significant declines in performance are observed

	the amount of correct answers out of a total of 60. The PASAT is also a component of the Multiple sclerosis Functional Composite (MSFC) together with the Timed 25 foot Walk Test and the 9-Hole Peg Test (9HPT). Digit Ordering Test (DOT): - In the DOT the subject is asked to memorize up to seven digits and to recall in them in ascending order. Fatigue Severity Scale (FSS): - The FSS is a scale containing nine items that measure the severity with which fatigue experienced by the test subject influences one's activities and lifestyle. Modified Fatigue Impact Scale (MFIS): - The MFIS assesses the degree to which one suffers from fatigue in terms of physical, cognitive, and psychosocial functioning. Twenty-one items are questioned in the full version. Rochester Fatigue Diary (RFD) - The RFD is a self-report measure of lassitude or tiredness Two identical test sessions separated by 4 - 10 days, within a month after 2 practice sessions. Subjects listen to music during a 10 minute break between the PASAT and DOT.	in both groups during administration of the DOT. There is no significant association between cognitive fatigue and self-reported fatigue in the MFIS or the RFD. There is a significant association between cognitive fatigue and self-reported fatigue in the FSS.
Morrow et al., 2015	PASAT (3”)	Controls score on average 2 more correct responses in the last third of the PASAT than in the first third. The patients with MS score on average 2 to 3 fewer correct responses in the last third than the first third. This study shows that comparing responses between the first and last thirds of the PASAT is a reliable method to measure cognitive fatigue in patients with MS.
Krupp et al., 2000	Patients first complete baseline descriptive self-report measures, followed by the neuropsychological test battery. Patients then complete the Alpha-Arithmetic test which serves as a continuous cognitive effort task. Afterwards the patients complete the neuropsychological test battery once more. Self-report measures of fatigue and affect are completed before each step of the testing session. <u>Neuropsychological tests:</u> Selective Reminding Test (SRT): - Assesses learning and memory	MS patients show a decline in performance on the SRT, 10/36, TOH following the A-A test, where controls show an improvement. There are no significant group differences in the pattern of change following the A-A Test for Digit Span or COWA. MS and control participants report an increased FSS across the testing sessions compared to their baseline values.

	10/36 spatial recall test: - Visuospatial memory Tower of Hanoi test (TOH): - Conceptual planning and procedural learning Digit span test: - Auditory attention Controlled Oral Word Association (COWA) - Verbal fluency <u>Self-reported measures:</u> Fatigue Severity Scale (FSS) <u>Cognitive load:</u> The Alpha-arithmetic test (A-A) - Subject is asked to assess the correctness of 160 equations consisting of a letter and a number (e.g. A+1=B is correct)	
Bryant et al., 2004	PASAT	All subjects show a greater margin of error in the second half than in the first half of each PASAT trial. When however examining PASAT performance as the extent to which responses are generated within the working memory demand of the test, an increased cognitive fatigue effect in subjects with MS compared to healthy controls is revealed. It is therefore concluded that fatigue can influence performance even in the absence of cognitive impairment. Persons with MS are becoming cognitively overtaxed earlier (or at a lower central executive load) than the healthy controls on the PASAT. Fatigue can influence performance even in the absence of cognitive impairment. If the time spent on a task is increased, the efficiency becomes lesser, in MS group compared to healthy controls.
Chinnadurai et al., 2016	The Stroop test: sustained attention and information processing speed - subjects are given a sheet of paper containing 250 words (with font colours incoherent to their semantic meaning) and are instructed to name the colour of the font of the words in the list successively as quickly as possible. SDMT Cum Addition Test (SDMCAT): - Cognitively more demanding than SDMT - Subjects do not present the correct number associated with a symbol but instead calculate the total value of these numbers. modified SDMT (mSDMT): - Subjects are required to decode a string of 150 symbols. Each of these symbols correspond to a single digit number ranging from 1 to 9. This is done by	The P300-scores do correlate with the other clinical measures and hence may be used as a relatively quick test to identify MS patients who may be suffering from cognitive fatigue. A clear pattern is seen when comparing the 60 seconds version of the tests to the 180 seconds version. No significant differences are observed between the groups in the 60 second versions, this in contrast with the 180 second versions, which do show a significant decrease in performance in the MS group. This does not apply to the SAT. When viewing the ratio of correct responses scored in three executions of the 60 second version versus those in the 180 second versions of the SDMCAT, the 3DSAT and the stroop test, a significant difference can be seen between MS patients and healthy controls. This implies that the MS group shows more cognitive fatigue. This difference can not however be observed in the SAT and mSDMT tests.

	using a code sheet.
	
	Serial Addition Test (SAT):
	- for assessing attention calculation, and information processing speed
	- The test measures the time required by a patient to calculate the sum of 250 paired single digits
	
	3 Digit Serial Addition Test (3DSAT): assesses the influence of increasing cognitive load on fatigue.
	- Subjects calculate the sum of three consecutive digits
	
	Either 60 seconds or 180 seconds was given to execute the test.
	P300 latency:
	- electrophysiological measures designed specifically to reveal cognitive fatigue
	- subjects were checked for two measures:
	  - the P300 peak latency (P300L)
	  - the peak amplitude (P300A)
	
	A 20 minute break time between tests was obligatory.
		Increased task duration correlates with a greater decrease in efficiency in the MS group compared to healthy controls.
		
		MS patients may not be as capable of carrying out a task with increasing cognitive demand as their healthy counterparts.

Holtzer et al., 2013	SDMT: Rao's adaptation, the oral version - 3 times, separated by 5 minute interval - A total of 9 administrations - In the Rao adaptation of the task, patients are asked to respond orally with the number that corresponds with each symbol as rapidly as possible. The dependent variable is the total number correct in 90 s.	A decline in performance when performing a sustained effort shows cognitive fatigue during the SDMT.
Bailey et al., 2007	N-back test: used to assess cognitive fatigue over time by comparing the performance across the first, second and third pairs of blocks in the test.	For one of the tasks (0-back), the MS, but not the control participants, show deterioration in accuracy over blocks during the two presentations of the task. For the 1-back task, the MS, but not the control participants, are less accurate on the second than the first presentation. Although the MS group is slower than the control group in both the 0-back and 1-back tasks, the RT data does not suggest cognitive fatigue effects since responding becomes faster rather than slower over time for both groups. The 0-back task shows a deterioration in accuracy over blocks during the two presentations for the MS group. The 1-back test shows less accurate results on the second compared to the first presentation for the MS group. Both groups show a faster responding over time, suggesting no significant cognitive fatigue is shown.

Rosti et al., 2006	PASAT(3”) - the amount of errors and omission made in the first third of the test is compared to the amount made at the end of the series.	A decline in amount of correct answers in the last third of the PASAT compared to the first third is seen in MS patients but not in healthy controls.

Walker et al., 2012	PASAT scores are compared between first and second half of the trial in both healthy controls and MS patients. Each participant completes the PASAT three times, each time with both the 3″ and 2″ inter-stimulus intervals (ISI). These administrations are interspersed with other other tests in the neuropsychological battery.
	
	Computerized Test of Information Processing (CTIP):
	- 3 tasks, contain 3 blocks of 10 trials each
	  - Simple RT (SRT): press for X
	  - Choice RT (CRT): press left key for one word, right key for another word
	  - Semantic Search RT (SSRT): press left key if a word is not in a particular semantic category, press right key if a word is in a particular semantic category
	
	PASAT and CTIP were administered twice, but only the second administration was analysed. This in order to avoid a practice effect.
		Irrespectively of which ISI is used, overall task performance does not differ between both groups.
		
		CTIP shows no significant difference in reaction times for either groups when comparing the SRT, CRT and SSRT.
		
		MS patients show a significant decrease in performance in the second half of the PASAT versus first half when using the dyad scoring method. This effect cannot be observed when simply comparing correct responses between the first half of the test versus the second half of the test.
		
		All subjects show equal performances for the duration of the task.

Table 3: Overview of excluded articles with reason for exclusion

Source	Title	Reason of exclusion
Marrie et al., 2017	Upper limb impairment is associated with use of assistive devices and unemployment in multiple sclerosis.	No objective measurement of cognitive fatigue
Ribbons et al., 2017	Anxiety Levels Are Independently Associated With Cognitive Performance in an Australian Multiple Sclerosis Patient Cohort.	No comparison between baseline and follow-up
Randolph et al., 2017	Association Between Cognitive Complaints and Vulnerability to Environmental Distraction in Multiple Sclerosis.	No comparison between baseline and follow-up
Benesova et al., 2017	Cognition and fatigue in patients with relapsing multiple sclerosis treated by subcutaneous interferon beta-1a: an observational study SKORE.	No objective measurement of cognitive fatigue

Weygandt et al., 2016	Stress-induced brain activity, brain atrophy, and clinical disability in multiple sclerosis	No objective measurement of cognitive fatigue
Sundgren et al., 2015	Event related potential and response time give evidence for a physiological reserve in cognitive functioning in relapsing-remitting multiple sclerosis	No comparison between baseline and follow-up
Pravata et al., 2016	Hyperconnectivity of the dorsolateral prefrontal cortex following mental effort in multiple sclerosis patients with cognitive fatigue	No objective measurement of cognitive fatigue
Hayter et al., 2016	The impact of health anxiety in patients with relapsing remitting multiple sclerosis: Misperception, misattribution and quality of life	No comparison between baseline and follow-up
Novo et al., 2016	Apathy in multiple sclerosis: gender matters	No comparison between baseline and follow-up
Kluckow, Steffens et al., 2016	What you get from what you see: Parametric assessment of visual processing capacity in multiple sclerosis and its relation to cognitive fatigue	No comparison between baseline and follow-up
Rocca et al., 2016	Functional MRI in investigating cognitive impairment in multiple sclerosis.	Review
Pokryszko-Dragan et al., 2016	Event-related potentials and cognitive performance in multiple sclerosis patients with fatigue	No comparison between baseline and follow-up
Braley et al., 2016	Sleep and Cognitive Function in Multiple Sclerosis.	No objective measurement of cognitive fatigue
Mercan et al., 2016	Effects of motor-motor and motor-cognitive tasks on balance in patients with multiple sclerosis	No objective measurement of cognitive fatigue
Wolkorte et al., 2016	Reduced Voluntary Activation During Brief and Sustained Contractions of a Hand Muscle in Secondary-Progressive Multiple Sclerosis Patients	No objective measurement of cognitive fatigue
Ayache et al., 2016	Prefrontal tDCS Decreases Pain in Patients with Multiple Sclerosis	No objective measurement of cognitive fatigue

Triche et al., 2016	Changes in Cognitive Processing Speed, Mood, and Fatigue in an Observational Study of Persons With Multiple Sclerosis Treated With Dalfampridine-ER	No objective measurement of cognitive fatigue
Yaldizli et al., 2016	The association between olfactory bulb volume, cognitive dysfunction, physical disability and depression in multiple sclerosis	No comparison between baseline and follow-up
Ford-Johnson et al., 2016	Cognitive Effects of Modafinil in Patients With Multiple Sclerosis: A Clinical Trial	No objective measurement of cognitive fatigue
Wilting et al., 2016	Structural correlates for fatigue in early relapsing remitting multiple sclerosis	No comparison between baseline and follow-up
Bhargav et al., 2016	Immediate effect of two yoga-based relaxation techniques on cognitive functions in patients suffering from relapsing remitting multiple sclerosis: A comparative study	No objective measurement of cognitive fatigue
Palm et al., 2016	Effects of transcranial random noise stimulation (tRNS) on affect, pain and attention in multiple sclerosis	No objective measurement of cognitive fatigue
Surya et al., 2015	Rehabilitation of multiple sclerosis patients in India	Review
Pottgen et al., 2015	Perceived and Objective Attentional Deficits in Multiple Sclerosis	No comparison between baseline and follow-up
Gravesande et al., 2015	Characteristics of multiple sclerosis in children and adolescents	Other language than Dutch or English
Goverover et al., 2015	Factors That Moderate Activity Limitation and Participation Restriction in People With Multiple Sclerosis	No comparison between baseline and follow-up
Prosperini et al., 2015	Investigating the phenomenon of "cognitive-motor interference" in multiple sclerosis by means of dual-task posturography	No objective measurement of cognitive fatigue
Roberg et al.,2015	Articulation Time Does Not Affect Speededmultiple Cognitive Performance in Multiple Sclerosis	No objective measurement of cognitive fatigue

Sharbanian et al., 2015	Contribution of symptom clusters to sclerosis consequences	No comparison between baseline and follow-up
Fiorini et al., 2015	A Machine Learning pipeline for Multiple Sclerosis course detection from Clinical Scales and Patient Reported Outcomes	No objective measurement of cognitive fatigue
Magnin et al., 2015	Verbal Fluencies and Fampridine Treatment in Multiple Sclerosis	No objective measurement of cognitive fatigue
Nunnari et al., 2015	Impact of Depression, Fatigue, and Global Measure of Cortical Volume on Cognitive Impairment in Multiple Sclerosis	No comparison between baseline and follow-up
Cecchetto et al., 2015	Facial and Bodily Emotion Recognition in Multiple Sclerosis: The Role of Alexithymia and Other Characteristics of the Disease	No objective measurement of cognitive fatigue
Rosti-Otajarvi et al., 2014	Relationship between subjective and objective cognitive performance in multiple sclerosis	No comparison between baseline and follow-up
Miller et al., 2014	Pain is associated with prospective memory dysfunction in multiple sclerosis	No objective measurement of cognitive fatigue
Pardini et al., 2014	Isolated cognitive relapses in multiple sclerosis	No objective measurement of cognitive fatigue
Burschka et al., 2014	Mindfulness-based interventions in multiple sclerosis: beneficial effects of Tai Chi on balance, coordination, fatigue and depression	No objective measurement of cognitive fatigue
Ukueberuwa et al., 2014	Evaluating the Role of Coping Style as a Moderator of Fatigue and Risk for Future Cognitive Impairment in Multiple Sclerosis	No comparison between baseline and follow-up
Barr et al., 2014	Walking for six minutes increases both simple reaction time and stepping reaction time in moderately disabled people with Multiple Sclerosis	No objective measurement of cognitive fatigue
Berneiser et al., 2014	Impaired recognition of emotional facial expressions in patients with multiple sclerosis	No objective measurement of cognitive fatigue

Wajda et al., 2014	Correlates of dual task cost of standing balance in individuals with multiple sclerosis	No objective measurement of cognitive fatigue
Hulst et al., 2014	Indicators for cognitive performance and subjective cognitive complaints in multiple sclerosis: a role for advanced MRI?	No comparison between baseline and follow-up
Caceres et al., 2014	Cognitive and neuropsychiatric disorders among multiple sclerosis patients from Latin America: Results of the RELACCEM study	No comparison between baseline and follow-up
Saadat et al., 2014	Prevalence and predictors of depression in Iranian patients with multiple sclerosis: a population-based study	No comparison between baseline and follow-up
Thelen et al., 2014	Polypharmacy in multiple sclerosis: Relationship with fatigue, perceived cognition, and objective cognitive performance	No comparison between baseline and follow-up
Hildebrandt et al., 2014	A longitudinal study on fatigue, depression, and their relation to neurocognition in multiple sclerosis	No objective measurement of cognitive fatigue
Pokryszko et al., 2014	Magnetic resonance spectroscopy findings as related to fatigue and cognitive performance in multiple sclerosis patients with mild disability	No comparison between baseline and follow-up
Goretti et al., 2014	Anxiety state affects information processing speed in patients with multiple sclerosis	No objective measurement of cognitive fatigue
Akinwuntan et al., 2014	Improvement of Driving Skills in Persons With Relapsing-Remitting Multiple Sclerosis: A Pilot Study	No objective measurement of cognitive fatigue
Yaldizli et al., 2014	The relationship between total and regional corpus callosum atrophy, cognitive impairment and fatigue in multiple sclerosis patients	No comparison between baseline and follow-up
Hofstetter et al., 2014	Progression in disability and regional grey matter atrophy in relapsing-remitting multiple sclerosis	No objective measurement of cognitive fatigue
Weier et al., 2014	Cerebellar Abnormalities Contribute to Disability Including Cognitive Impairment in Multiple Sclerosis	No comparison between baseline and follow-up

Holland et al., 2014	Fatigue, emotional functioning, and executive dysfunction in pediatric multiple sclerosis	Population under 18 years
Pusswald et al., 2014	A neuropsychological rehabilitation program for patients with Multiple Sclerosis based on the model of the ICF	No objective measurement of cognitive fatigue
Wojtowicz et al., 2014	Stability of intraindividual variability as a marker of neurologic dysfunction in relapsing remitting multiple sclerosis	No objective measurement of cognitive fatigue
Faiss et al., 2014	Reduced magnetisation transfer ratio in cognitively impaired patients at the very early stage of multiple sclerosis: a prospective, multicenter, cross-sectional study	No objective measurement of cognitive fatigue
Iaffaldano et al., 2014	The improvement of cognitive functions is associated with a decrease of plasma Osteopontin levels in Natalizumab treated relapsing multiple sclerosis	No objective measurement of cognitive fatigue
Amato et al., 2014	Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial	No objective measurement of cognitive fatigue
Rosti-Otajarvi et al., 2013	Patient-related factors may affect the outcome of neuropsychological rehabilitation in multiple sclerosis	No objective measurement of cognitive fatigue
Wieder et al., 2013	Low contrast visual acuity testing is associated with cognitive performance in multiple sclerosis: a cross-sectional pilot study	No objective measurement of cognitive fatigue
Gierer et al., 2013	Fatigue and cognitive impairment in multiple sclerosis patients lead to impaired performance in computer-assisted test for driving fitness	No objective measurement of cognitive fatigue
Schwartz et al., 2013	Cognitive reserve and patient-reported outcomes in multiple sclerosis	No measurement of cognitive fatigue
Papadopoulou et al., 2013	Contribution of cortical and white matter lesions to cognitive impairment in multiple sclerosis	No comparison between baseline and follow-up
Bester et al., 2013	Tract-specific white matter correlates of fatigue and cognitive impairment in benign multiple sclerosis	No comparison between baseline and follow-up

Vanotti et al,. 2013	Cognitive performance of neuromyelitis optica patients: comparison with multiple sclerosis	No objective measurement of cognitive fatigue
Preston et al., 2013	The executive dysfunctions most commonly associated with multiple sclerosis and their impact on occupational performance	No objective measurement of cognitive fatigue
Wojtowicz et al., 2013	Indices of Cognitive Dysfunction in Relapsing-Remitting Multiple Sclerosis: Intra-individual Variability, Processing Speed, and Attention Network Efficiency	No objective measurement of cognitive fatigue
Sundgren et al., 2013	Cognitive Impairment Has a Strong Relation to Non somatic Symptoms of Depression in Relapsing Remitting Multiple Sclerosis	No comparison between baseline and follow-up
Scarpazza et al., 2013	Education protects against cognitive changes associated with multiple sclerosis	No objective measurement of cognitive fatigue
Devos et al., 2013	Driving performance in persons with mild to moderate symptoms of multiple sclerosis	No objective measurement of cognitive fatigue
Brissart et al., 2012	Verbal episodic memory in 426 multiple sclerosis patients: impairment in encoding, retrieval or both?	No objective measurement of cognitive fatigue
Patti et al., 2012	Longitudinal changes in social functioning in mildly disabled patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: results from the COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study (II)	No objective measurement of cognitive fatigue
Bruce et al., 2012	Impact of Armodafinil on Cognition in Multiple Sclerosis: A Randomized, Double-blind Crossover Pilot Study	No objective measurement of cognitive fatigue
Heremans et al., 2012	The relation between cognitive and motor dysfunction and motor imagery ability in patients with multiple sclerosis	No objective measurement of cognitive fatigue
Jacobs et al., 2012	Effects of dual tasking on the postural performance of people with and without multiple sclerosis: a pilot study	No objective measurement of cognitive fatigue
Strober et al., 2012	Unemployment in multiple sclerosis: the contribution of personality and disease	No comparison between baseline and follow-up

Iaffaldano et al., 2012	Impact of Natalizumab on Cognitive Performances and Fatigue in Relapsing Multiple Sclerosis: A Prospective, Open-Label, Two Years Observational Study	No objective measurement of cognitive fatigue
Boes et al., 2012	Postural control in multiple sclerosis: Effects of disability status and dual task	No objective measurement of cognitive fatigue
Jongen et al., 2012	Cognitive impairment in multiple sclerosis	No objective measurement of cognitive fatigue
Hamalainen et al., 2012	The effects of heat stress on cognition in persons with multiple sclerosis	No objective measurement of cognitive fatigue
Goretti et al., 2012	Fatigue and its relationships with cognitive functioning and depression in paediatric multiple sclerosis	Population under 18 years
Roberg et al., 2012	How Patients With Multiple Sclerosis Perceive Cognitive Slowing	No objective measurement of cognitive fatigue
Ryan et al., 2012	Wechsler Adult Intelligence Scale-Fourth Edition performance in relapsing-remitting multiple sclerosis	No objective measurement of cognitive fatigue
Denney et al., 2011	Deficits in Processing Speed in Patients with Multiple Sclerosis: Evidence from Explicit and Covert Measures	No objective measurement of cognitive fatigue
Baumstarck-Barrau et al., 2011	Cognitive function and quality of life in multiple sclerosis patients: a cross-sectional study	No objective measurement of cognitive fatigue
Ferreira et al., 2011	Processing Speed, Depressive Symptoms and Working Memory: A Comparison between Aging Individuals and Multiple Sclerosis Patients	Other language than Dutch or English
Zinger et al., 2011	Return to Flight with Multiple Sclerosis: Aeromedical Considerations	Case report
Velikonja et al., 2010	Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis	No objective measurement of cognitive fatigue

Weinger-Evers et al., 2010	Correlation of self-assessed fatigue and alertness in multiple sclerosis	No objective measurement of cognitive fatigue
Kinsinger et al., 2010	Relationship Between Depression, Fatigue, Subjective Cognitive Impairment, and Objective Neuropsychological Functioning in Patients With Multiple Sclerosis	No objective measurement of cognitive fatigue
Korkmaz et al., 2010	The cognitive dysfunctions of multiple sclerosis: do we face from the early terms?	No objective measurement of cognitive fatigue
Lovera et al., 2010	Memantine for cognitive impairment in multiple sclerosis: a randomized placebo-controlled trial	No objective measurement of cognitive fatigue
Stoquart-ElSankari et al., 2010	Motor and cognitive slowing in multiple sclerosis: An attentional deficit?	No objective measurement of cognitive fatigue
Glanz et al., 2010	The association between cognitive impairment and quality of life in patients with early multiple sclerosis	No objective measurement of cognitive fatigue
Rosenblum et al., 2010	Evaluating functional decline in patients with Multiple Sclerosis	No objective measurement of cognitive fatigue
Drake et al., 2010	Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the Symbol Digit Modalities Test	No objective measurement of cognitive fatigue
Arnett et al., 2010	Cognitive and Affective Neuroscience Theories of Cognition and Depression in Multiple Sclerosis and Guillain-Barre Syndrome	No objective measurement of cognitive fatigue
Sweet et al., 2010	Subvocal articulatory rehearsal during verbal working memory in multiple sclerosis	No objective measurement of cognitive fatigue
Portaccio et al., 2009	APOE-epsilon 4 is not associated with cognitive impairment in relapsing-remitting multiple sclerosis	No objective measurement of cognitive fatigue
Morrow et al., 2009	Subjective fatigue is not associated with cognitive impairment in multiple sclerosis: cross-sectional and longitudinal analysis	No objective measurement of cognitive fatigue

Garcia et al., 2009	Executive function and memory in patients with relapsing-remitting multiple sclerosis	No objective measurement of cognitive fatigue
Denney et al., 2009	The impact of multiple sclerosis on patients' performance on the Stroop Test: Processing speed versus interference	No objective measurement of cognitive fatigue
Julian et al., 2009	Relationships among Anxiety, Depression, and Executive Functioning in Multiple Sclerosis	No objective measurement of cognitive fatigue
Christodoulou et al., 2009	Negative affect predicts subsequent cognitive change in multiple sclerosis	No objective measurement of cognitive fatigue
Vogt et al.,2009	Working memory training in patients with multiple sclerosis - comparison of two different training schedules	No objective measurement of cognitive fatigue
Nociti et al., 2008	Somatosensory evoked potentials reflect the upper limb motor performance in multiple sclerosis	No objective measurement of cognitive fatigue
Julian et al., 2008	Employment in multiple sclerosis Exiting and re-entering the workforce	No comparison between baseline and follow-up
Leocani et al., 2008	Physiopathology of fatigue in multiple sclerosis	Review
O'brien et al., 2007	Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes	No objective measurement of cognitive fatigue
Marrie et al., 2007	Validity of performance scales for disability assessment in multiple sclerosis	No objective measurement of cognitive fatigue
Rogers et al., 2007	Cognitive impairment in multiple sclerosis: Evidence-based analysis and recommendations	Review
Balsimelli et al., 2007	Attention impairment associated with relapsing-remitting multiple sclerosis patients with mild incapacity	No objective measurement of cognitive fatigue

Winkelmann et al., 2007	Cognitive impairment in multiple sclerosis	No objective measurement of cognitive fatigue
Parmenter et al., 2007	Information processing deficits in multiple sclerosis: A matter of complexity	No objective measurement of cognitive fatigue
Arango-Lasprilla et al., 2007	Neuropsychological profile of multiple sclerosis.	Other language than Dutch or English
Rouaud et al., 2006	Contribution of ecological evaluation of executive disorders in multiple sclerosis.	Other language than Dutch or English
Middleton et al., 2006	The relationship between perceived and objective cognitive functioning in multiple sclerosis	No objective measurement of cognitive fatigue
Amato et al., 2006	Benign multiple sclerosis - Cognitive, psychological and social aspects in a clinical cohort	No objective measurement of cognitive fatigue
Hildebrandt et al., 2006	Memory performance in multiple sclerosis patients correlates with central brain atrophy	No objective measurement of cognitive fatigue
Deloire et al., 2006	How to detect cognitive dysfunction at early stages of multiple sclerosis?	No objective measurement of cognitive fatigue
Sartori et al., 2006	From psychometry to neuropsychological disability in multiple sclerosis: a new brief French cognitive screening battery and cognitive risk factors.	Other language than Dutch or English
Lengenfelder et al., 2006	Processing speed interacts with working memory efficiency in multiple sclerosis	No objective measurement of cognitive fatigue
Lazeron et al., 2005	Brain atrophy and lesion load as explaining parameters for cognitive impairment in multiple sclerosis	No objective measurement of cognitive fatigue
Engel et al., 2005	Cognitive dysfunctions in multiple sclerosis patients	Other language than Dutch or English

Marrie et al., 2005	Subjective cognitive complaints relate to mild impairment of cognition in multiple sclerosis	No objective measurement of cognitive fatigue
Denney et al., 2004	Cognitive impairment in relapsing and primary progressive multiple sclerosis: Mostly a matter of speed	No objective measurement of cognitive fatigue
Kesselring et al., 2004	Neurorehabilitation in multiple sclerosis what is the evidence-base?	Review
Archibald et al., 2004	Posterior fossa lesion volume and slowed information processing in multiple sclerosis	No objective measurement of cognitive fatigue
Birnboim et al., 2004	Cognitive strategies application of multiple sclerosis patients	No objective measurement of cognitive fatigue
Beatty et al., 2003	Changes in neuropsychological test performance over the workday in multiple sclerosis	No objective measurement of cognitive fatigue
Yorkston et al., 2003	Getting the work done: a qualitative study of individuals with multiple sclerosis	No comparison between baseline and follow-up
Krupp et al., 2003	Fatigue in multiple sclerosis - Definition, pathophysiology and treatment	Review
Schwid et al., 2002	Fatigue in multiple sclerosis: Current understanding and future directions	Review
Bagert et al., 2002	Cognitive dysfunction in multiple sclerosis - Natural history, pathophysiology and management	Review
Fisk et al., 2001	Limitations of the Paced Auditory Serial Addition Test as a measure of working memory in patients with multiple sclerosis	No objective measurement of cognitive fatigue
Van der Werf et al., 2000	Abnormal neuropsychological findings are not necessarily a sign of cerebral impairment: A matched comparison between chronic fatigue syndrome and multiple sclerosis	No objective measurement of cognitive fatigue

Archibald et al., 2000	Information processing efficiency in patients with multiple sclerosis	No objective measurement of cognitive fatigue
Beatty et al., 1998	Cognitive dysfunction in multiple sclerosis: natural history and impact on productive living	Review
Schwartz et al., 1996	Psychosocial correlates of fatigue in multiple sclerosis	No objective measurement of cognitive fatigue
Kujala et al., 1995	Attention related performance in 2 cognitively different subgroups of patients with multiple-sclerosis.	No objective measurement of cognitive fatigue
Syndulko et al., 1995	Preliminary evaluation of lowering tympanic temperature for the symptomatic treatment of multiple sclerosis	No objective measurement of cognitive fatigue
Deluca et al., 1995	Neuropsychological impairments in chronic fatigue syndrome, multiple-sclerosis, and depression	No objective measurement of cognitive fatigue
Shannon et al., 1994	A neuropsychological examination of multiple-sclerosis and its impact upon higher mental functions	No measurement of cognitive fatigue
Grossman et al., 1994	Patterns of cognitive impairment in relapsing-remitting and chronic progressive multiple-sclerosis	No objective measurement of cognitive fatigue
Deluca et al., 1993	Information-processing efficiency in chronic fatigue syndrome and multiple-sclerosis	No objective measurement of cognitive fatigue
Bol et al., 2010	The impact of fatigue on cognitive functioning in patients with multiple sclerosis	No objective measurement of cognitive fatigue
Fernandez-Munoz et al., 2015	Disability, quality of life, personality, cognitive and psychological variables associated with fatigue in patients with multiple sclerosis	No objective measurement of cognitive fatigue
Hamilton et al., 2009	Walking and talking: an investigation of cognitive–motor dual tasking in multiple sclerosis	No objective measurement of cognitive fatigue

Provinciali et al., 1999	A multidimensional assessment of multiple sclerosis: relationships between disability domains	No objective measurement of cognitive fatigue
Paul et al., 1989	Impairments of attention in individuals with Multiple Sclerosis	No objective measurement of cognitive fatigue
Barak et al., 2006	Cognitive fatigue in multiple sclerosis: findings from a two-wave screening project	No objective measurement of cognitive fatigue
Beckerman et al., 2013	The effectiveness of aerobic training, cognitive behavioural therapy, and energy conservation management in treating MS-related fatigue: the design of the TREFAMS-ACE programme	No objective measurement of cognitive fatigue
Ben Ari Shevil et al., 2014	How are cognitive impairment, fatigue and signs of depression related to participation in daily life among persons with multiple sclerosis?	No objective measurement of cognitive fatigue
Berard et al., 2014	Cognitive fatigue in individuals with multiple sclerosis undergoing immunoablative therapy and hematopoietic stem cell transplantation	No objective measurement of cognitive fatigue
Genova et al., 2013	Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging	No objective measurement of cognitive fatigue
Hanken et al., 2015	Integrity of hypothalamic fibers and cognitive fatigue in multiple sclerosis	No objective measurement of cognitive fatigue
Hanken et al., 2016	On the relation between self-reported cognitive fatigue and the posterior hypothalamic-brainstem network	No objective measurement of cognitive fatigue
Heesen et al., 2005	Altered cytokine responses to cognitive stress in multiple sclerosis patients with fatigue	No objective measurement of cognitive fatigue
Huolman et al., 2011	The effects of rivastigmine on processing speed and brain activation in patients with multiple sclerosis and subjective cognitive fatigue	No objective measurement of cognitive fatigue
Knoop et al., 2012	Which cognitions and behaviours mediate the positive effect of cognitive behavioural therapy on fatigue in patients with multiple sclerosis?	No objective measurement of cognitive fatigue
Kos et al., 2004	Cognitive fatigue in multiple sclerosis: comment on Schwid SR, Tyler CM, Scheid EA, Weinstein A, Goodman AD and McDermott MR	Review
Krupp et al., 1994	Cognitive functioning and depression in patients with chronic fatigue syndrome and multiple sclerosis	No objective measurement of cognitive fatigue
Moss-Morris et al., 2012	A pilot randomised controlled trial of an Internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue	No objective measurement of cognitive fatigue
Padua et al., 2007	Reply to "Motor assessment of upper extremity function and its relation with fatigue, cognitive function and quality of life in multiple sclerosis patients"	Review
Patti et al., 2011	Quality of life, depression and fatigue in mildly disabled patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: 3-year results from the COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study	No objective measurement of cognitive fatigue
Penner et al., 2009	The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue	No objective measurement of cognitive fatigue

Sandi et al., 2015	The Hungarian validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery and the correlation of cognitive impairment with fatigue and quality of life	No objective measurement of cognitive fatigue
Sandyk et al., 1997	Immediate recovery of cognitive functions and resolution of fatigue by treatment with weak electromagnetic fields in a patient with multiple sclerosis	Case report
Yozbatiran et al., 2006	Motor assessment of upper extremity function and its relation with fatigue, cognitive function and quality of life in multiple sclerosis patients	No objective measurement of cognitive fatigue
van Kessel et al., 2008	A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue	No objective measurement of cognitive fatigue
Van Ettinger-Veenstra et al., 2016	Cumulative evidence for MS as a neural network disconnection syndrome consistent with cognitive impairment mechanisms and the confounding role of fatigue and depression-outlook from the Fourth Nordic MS symposium	Review
Thomas et al., 2010	Development and preliminary evaluation of a cognitive behavioural approach to fatigue management in people with multiple sclerosis	No objective measurement of cognitive fatigue
Thomas et al., 2010	Multi-centre parallel arm randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based cognitive behavioural approach to managing fatigue in people with multiple sclerosis	No objective measurement of cognitive fatigue
Skerrett et al., 2006	Fatigue and social impairment in multiple sclerosis: the role of patients' cognitive and behavioral responses to their symptoms	No objective measurement of cognitive fatigue
Parmenter et al., 2003	The cognitive performance of patients with multiple sclerosis during periods of high and low fatigue	No objective measurement of cognitive fatigue
Van der Hiele et al., 2015	Work Participation and Executive Abilities in patients with Relapsing-Remitting Multiple Sclerosis	No objective measurement of cognitive fatigue
Barhgav et al., 2016	Immediate effect of two yoga-based relaxation techniques on cognitive functions in patients suffering from relapsing remitting multiple sclerosis: A comparative study	No objective measurement of cognitive fatigue
Feinstein et al., 2015	is there a cognitive signature for multiple sclerosis-related fatigue?	No objective measurement of cognitive fatigue
Hanken et al., 2015	Is there a cognitive signature for MS-related fatigue?	Review
Hanken et al., 2016	Is there a cognitive signature for MS-related fatigue? Response to Feinstein	No objective measurement of cognitive fatigue
Morrow et al., 2017	The effect of Fampridine-SR on cognitive fatigue in a randomized double-blind crossover trial in patients with MS	No objective measurement of cognitive fatigue
Niino et al., 2014	Apathy/depression, but not subjective fatigue, is related with cognitive dysfunction in patients with multiple sclerosis	No objective measurement of cognitive fatigue

Table 4: Quality assessment – STROBE Statement

	Bruce et al., 2010	Claros-Salinas et al., 2010	Claros-Salinas, D.(2013)	Schwid et al., 2003	Neuman n et al., 2014	Morrow et al., 2015	Krupp et al., 2000	Holtzer et al., 2013	Bailey et al., 2007	Walker et al., 2012	Rosti et al., 2006	Bryant et al., 2004	Chinnad urai et al., 2016
1a	N	N	N	Y	N	N	N	Y	N	N	N	N	N
1b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Y	N	N	Y	N	N	N	N	N	Y	N	N	N
10	N	N	N	N	N	N	N	N	N	N	N	N	N
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12a	Y	N	N	Y	Y	Y	N	N	N	N	N	N	N
12b	N	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y
12d	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y
12e	N	N	N	N	Y	N	N	Y	N	Y	Y	Y	Y
13	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

14	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
17	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y
18	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19	Y	N	N	Y	N	N	N	N	N	Y	N	N	N
20	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
21	N	N	Y	N	N	N	N	Y	Y	N	Y	Y	Y
22	N	N	N	Y	Y	N	N	N	N	N	N	N	N
TOTAL (/25)	19	17	18	20	19	17	17	17	17	20	18	18	18

Table 5: An overview of the descriptives

Article	Aim of the study	Population	MS characteristics	Sample size and age
Claros-Salinas et al., 2013	To determine if cognitive and physical loading induce cognitive fatigue.	Inclusion criteria: Definite MS (McDonald 's criteria), and cognitive fatigue [Fatigue Scale for Motor and Cognitive Functions (FSMC ≥ 22)] Exclusion criteria: Severe depression or other neurological conditions than MS	Mean EDSS score: 3.6 (SD=1.6) Disease duration: 7.7 years (SD=5.4)	N: 32 MS patients (22f, 10m) Age: 29-64 years (M= 46.8, SD= 8.6) N: 20 healthy controls Group A: N: 10 healthy controls (6f, 4m) Age: 28–58 years (M= 39.1 years) Group B: N: 10 healthy controls (6f, 4m) Age: 36-58 years (M= 46.7 years)
Neumann et al., 2014	To investigate if cognitive load induces cognitive fatigue in persons with MS.	Inclusion criteria: MS (McDonald's criteria) and cognitive fatigue defined as ≥22 on the cognitive domain of the Fatigue Scale for Motor and Cognitive Functions (FSMC) Exclusion criteria: Other neurological or psychiatric diseases, a value of N10 on the Epworth Sleepiness Scale as well as a score of N20 in the Beck Depression Inventory II	Patients with fatigue: Mean EDSS score: 3.8 (SD= 1.2) Disease duration: 9.9 years (SD= 6.7) Patients without fatigue: Mean EDSS: 3.7 (SD= 0.6) Disease duration: 13.6 years (SD= 6.8)	Patients with fatigue N: 30 MS patients (22f, 8m) Age: 31-55 years (M= 44.7, SD= 7.1) Patients without fatigue: N: 5 MS patients (2f, 3m) Age: 42-53 years (M= 45.3, SD= 6.1) Controls: N: 15 (11f, 4m) Age: 28-56 years (M= 43.6, SD= 11)
Bruce et al., 2010	Is self-reported cognitive fatigue associated with response time variability?	Inclusion criteria: MS by McDonald et al (2001) criteria, no clinical exacerbation 1 month prior to testing Exclusion criteria: No history of drug/abuse, no neurological disease other than MS, no learning disability, motor impairments,	Mean EDSS score: 4.50 (SD= 1.57) Disease duration: 10.86 years (SD= 7.98) No patient had ever had an exacerbation	N: 87 MS patients (72f, 15m) Mean age: 47.05 years (SD= 9.05) N: 24 controls (20f, 4m) Mean age: 47.83 years (SD=12)

		visual problems or scores < 90% on Computerized Assessment of Response Bias		
Claros-Salinas 2010	Is an increase in subjective cognitive fatigue throughout the day reflected in an objective performance decrease throughout the day?	Inclusion criteria: Normal vision and hearing abilities	Disease duration: 8.19 years (SD= 7.16)	N: 20 MS patients (14f, 6m) Age: 20-53 years (M= 39.7, SD= 9.4) N: 76 controls (9f, 13m) Age control: 20-60 years (M=37.2, SD=11.7)
Schwid et al., 2003	To objectively measure cognitive fatigue as a decline in performance during tests requiring sustained attention	Inclusion criteria: Ambulatory, without significant cognitive impairment or depression	Mean EDSS score: 3.8 (SD= 1.5)	N: 20 MS patients (16f, 4m) Age: 30-61 years (M=49.8, SD= 10.7) N: 21 controls (17f, 4m) Age: 18-63 years (M= 47.2, SD= 10.7)
Morrow et al., 2015	To standardize the method used to measure cognitive fatigue in persons with MS.	Inclusion criteria: Controls must be between 18 and 55 years of age, have normal vision (≥20/70 corrected) and normal hearing, and be fluent in the English language Exclusion criteria: History of drug/alcohol use, psychiatric disorder, ADHD, other neurological condition, intake of antipsychotics, narcotics, amphetamine stimulants, marijuana, benzodiazepines other than at night Score >= 13 on the BDI, or >7.5 on the EDSS	Mean EDSS: 2.0 Disease duration: 6.6 years (SD= 1.9)	N: 100 MS patients (80f, 20m) Age: 19-55 years (M=39.2, SD= 10) N: 130 controls (92f, 38m) Age: 18-57 years (M= 37.2, SD= 11)

Krupp et al., 2000	To determine whether cognitive fatigue could be identified in persons with MS.	Inclusion criteria: All 31 women and 14 men were ambulatory and had Expanded Disability Status Scale scores of ,6.5 Exclusion criteria: Current alcohol or substance abuse, major depression or other primary psychiatric disorder, history of head injury, or history of other major medical illness, participants currently taking benzodiazepines or other agents known to affect cognitive functioning.	Mean EDSS: 3.8 (SD= 1.7)	N: 45 MS patients (31f, 14m) Mean age: 45 years (SD= 6.8) N: 14 controls (11f, 3m) Mean age: 41.8 years (SD= 6.6)
Bryant et al., 2004	Objective examination of cognitive fatigue in persons with MS.	Inclusion criteria: Classified with clinically definite MS by a board-certified neurologist with a specialization in MS. Exclusion criteria: No neurologic or psychiatric history, learning disabilities, and/or history of substance abuse.	DeLuca et al. Mean EDSS: 1.8 (SD= 0.30) Disease duration: 69.36 months (range: 15 to 288 months) (SD =18.79) Chiaravalloti et al. Mean Ambulation Index: 1.85 (SD= 0.45) disease duration: 127.82 months (range: 12 to 320 months) (SD= 21.36)	N: 56 MS patients Deluca: Mean age: 38 years (SD= 2.5) Chiaravalloti: Mean age: 45.19 years (SD=1.5) N: 39 healthy controls Deluca et al.; Mean age: 35 years (SD= 2.0) Chiaravalloti: Mean age: 41.18 years (SD=2.17)
Chinnadurai et al., 2016	To assess the prevalence and clinical/demographic profile of cognitive fatigue in MS using novel clinical and electrophysiological measures and to find their accuracy.	Inclusion criteria: Definite MS (McDonald criteria) Exclusion criteria: Stroke, major psychiatric illnesses, substance abuse, history of brain trauma, impaired colour vision, and a visual acuity of less than 20/100 in either eye	Mean EDSS: 4.6 (range: 1.0-9.0) (SD= 1.9)	N: 50 MS patients (35f, 15m) Age: 33.6 years 13-66 years (M=33.6, SD= 10.6) N: 50 healthy controls (34f, 16m) Age: 16-50 years (M= 33.6, SD= 9.6)

Holtzer et al., 2013	To determine the effect of repeated exposures within and across study visits on performance measures of learning and cognitive fatigue in relapsing−remitting multiple sclerosis (RRMS).	Inclusion criteria: definite diagnosis of MS using the McDonald criteria, adequate vision and hearing. Exclusion criteria: severe motoric impairments, history of other CNS diseases and/or injuries, current clinical depression and other psychiatric disorders, and use of steroids or cholinesterase inhibitors within 30 days prior to testing. Patients not on disease modifying therapies.	EDSS range: 0 – 6 Mean EDSS: 2.45 (SD= 1.13) Disease duration: 9.48 years (SD= 1.44)	N: 30 MS patients (27f, 3m) Mean age: 43.20 years (SD= 1.73) N: 30 healthy controls (27f, 3m) Mean age: 43.57 years (SD= 1.82)
Bailey et al., 2007	To examine the cognitive performance and ratings of subjective fatigue in people with advanced MS and matched healthy control participants.	Inclusion criteria: Definite diagnosis of MS using the McDonald criteria, aged 18 or above, classified as having chronic progressive disease. The mean number of years since diagnosis: 27.21 years (range: 8 - 59). Exclusion criteria: Additional neurological disorders or major psychiatric disorder, alcohol or drug dependence, classified as 'severe' cases on the Hospital Anxiety and Depression Scale (HADS), developmental learning disabilities or a diagnosis of dyslexia.	EDSS range: 7 – 8 Mean EDSS: 7.68 (SD= 0.37) Disease duration: 27.21 years (range: 8-59)	N: 14 MS (10f, 4m) Mean age: 58.29 years (SD= 12.64) N: 17 healthy controls (12f, 5m) Mean age: 60.18 years (SD= 16.08)
Rosti et al., 2006	To assess any difference in response to the PASAT between healthy controls and MS Patients and to determine whether different scoring	Inclusion criteria: Definite MS (Poser's criteria) Exclusion criteria: Psychiatric disorders, history of substance abuse, acute	Mean EDSS: 2.9 (range: 0-7) (SD= 1.3) Disease duration: 9.0 years (range 1-27) (SD= 6.0)	N: 45 MS patients (33f, 12m) Age: 22-56 years (M= 42.7, SD= 8.3) N: 48 healthy controls (33f, 15m)

	methods influence the PASAT's sensitivity and specificity in detecting disease-associated cognitive impairment.	relapses or nervous system disorders other than MS		Age: 25-54 years (M= 42.3, SD= 7.4)
Walker et al., 2012	To examine the effectiveness of the PASAT and CTIP at detecting cognitive fatigue.	<u>Inclusion criteria:</u> Definite MS (McDonald criteria), fluent in English <u>Exclusion criteria:</u> Previous neurological, medical or psychiatric illnesses	Mean EDSS: 1.83 (SD= 1.18) Disease duration: 4.35 years (SD= 3.09)	N: 70 MS patients (57f, 13m) Mean age: 40.37 years (SD= 8.80) N: 72 healthy controls (59f, 13m) Mean age: 40.69 years (SD= 11.83)

Table 6: An overview of the strengths and limitations of included articles

Author & Journal	Limitations	Strengths
Bruce et al., 2010 Neuropsychology	- Only one (non-traditional) measure of response time variable is used - Subjects are not evenly distributed among groups (MS n=78; healthy controls n=24)	- New methods used are much less time consuming than standard neuropsychological test batteries - Motivation in patients is ensured by excluding subjects that scored beneath established cut-offs of the CARB.
Claros-Salinas et al., 2010 Journal of the Neurological Sciences	- Impairments caused by fatigue can be counteracted by practice effects - Work-related cognitive tasks between test sessions are not standardised and are individually different - Subjects are not evenly distributed among groups (MS n=20; healthy controls n=76) - All healthy controls are employed at the university of Kontstanz which may cause a performance bias of cognitive capacities	- Tests are always examined on the same moment (morning, noon, afternoon) - Diurnal differences in cognitive performance are achieved due multiple test moments
Claros-Salinas et al., 2013 Neuropsychological Rehabilitation	- A study population consisting of MS patients all suffering from severe fatigue cannot be generalised to a population suffering only from mild to moderate fatigue - Applying cognitive load in	- Different types of external load (cognitive and physical) are combined with the test battery - The order of the performed test conditions is randomised

	combination with the test battery is very time consuming (cognitive load: 2.5 hours)	
Schwid et al., 2003 Medline	- Matching between MS patients and controls is imperfect (generally higher education of patients) - Despite a strict procedure, fluctuations between test days can still occur	- Practice effects are avoided by having the subjects perform the test twice prior to actual testing - The order in which subjects perform the tests is randomised between subjects but remained identical between visits - Patients are examined during a period of clinical stability, each day at the same time, same setting and with exact the same studies
Neumann et al., 2014 Journal of the Neurological Sciences 3	- Applying cognitive load in combination with the test battery is very time consuming (cognitive load: 2.5 hours) - All test moments are examined one the same day	- No conflict of interest occurs and no external funding can influence outcome measures - Performances are compared in resting condition and after cognitive loading
Morrow et al., 2015 Medline	- Many members of the sample are referred for a cognitive assessment. This may lead to a disproportionate number of patients with cognitive impairment - Patients take the PASAT test as part of a 90 minutes test battery whereas controls only test for 20 minutes. This longer test session may provide a higher risk for cognitive fatigue for patients - No inquiry is done to ensure patients had previous experience with the PASAT even though this test is known to have practice effects	- Large sample size (n=230) - The authors argue that patient characteristics are not different at baseline (small proportion of non-whites)
Krupp et al., 2000 Medline	- Information on precise testing conditions is very limited - Subjects are not evenly distributed among groups (MS n=45; healthy controls n=14)	- Homogenous group of patients
Holtzer et al., 2013 Medline	- Limited generalizability of the findings due to a low disease severity level (mean EDSS: 2.45) in the	- Time efficient measurement method

	population	
Bailey et al., 2007 Mult Scler	- Limited generalizability of the findings due to a high disease severity level (mean EDSS: 7.68) in the population - High risk of practice effect	- Information on precise testing conditions was elaborate
Rosti et al., 2006 Mult Scler	- Information on precise testing conditions is very limited	- Strongly matching descriptive variables between MS patients and healthy controls
Bryant et al., 2004 Rehabilitation Psychology	- Two independent subject samples that are included in the study are collected by using different protocols	- Results are consistent with earlier studies
Chinnadurai et al., 2016 Multiple Sclerosis and Related Disorders		- Strongly matching descriptive variables between MS patients and healthy controls - Modified versions (shorter, longer or more demanding) are used as measurement methods
Walker et al., 2012	- Limited generalizability of the findings due to a low disease severity level (mean EDSS: 1.83) in the population	- Strongly matching descriptive variables between MS patients and healthy controls - Authors argue about the limitations of the used measurement method - Practice effects are avoided by not including results of the first administration

Table 7: Domains of cognition tested and administration time per test

Test battery	Alertness	Selective Attention	Divided attention	Information processing speed	Working memory	Administration time
PASAT				X		72 -180s
SDMT		X	X		X	90 -180s
TAP-M	X	X	X			5 -15 min
CARB	X					?
N-back	X					15-20 min

*Excluding external load duration

Table 8: List of abbreviations

Abbreviation	Full Term
MS	Multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
HC	Healthy control
mRT	Median reaction time
RT	Reaction time
RTV	Response time variability
SDMT	Symbol Digit Modalities Test
CARB	Computerized Assessment of Response Bias
VAS	Visual Analogue Scale
PASAT	Paced Auditory Serial Addition Test
TAP-M	Test Battery for Attentional Performance
DOT	Digit Ordering Test
FSS	Fatigue Severity Scale
MFIS	Modified Fatigue Impact Scale
RFD	Rochester Fatigue Diary
SRT	Selective Reminding test
10/36	10/36 spatial recall test
TOH	Tower of Hanoi test
COWA	Controlled Oral Word Association

3DSAT	3 Digit Serial Addition Test
SDMCAT	SDMT Cum Addition Test
CTIP	Computerized Test of Information Processing
FIS	Fatigue Impact Scale
A-A	Alpha- arythmetic test
SAT	Serial addition test
3DSAT	3 digit Serial addition test
ISI	Inter-stimulus interval
CRT	Choice reaction time
SSRT	Semantic search reaction time

PART 2: RESEARCH PROTOCOL

1. Introduction

Multiple sclerosis (MS) is an autoimmune and -neurodegenerative disease. Symptoms of MS can be explained as the result of plaques of demyelination within the central nervous system (CNS) and a chronic inflammatory process[1]. This disease process leads to deficits in cognitive and motor functions. Motor deficits can include a loss of functioning and feelings in the limbs and a loss of balance and coordination[2].

In the first part, we examined objective measurement methods for cognitive fatigue in persons with multiple sclerosis (MS). We defined cognitive fatigue by the definition of Wang, Trongnetrpunya, Samuel, Ding & Kluger (2016) : “prolonged continuous performance of a cognitively demanding task induces cognitive fatigue and is associated with a time-related deterioration of objective performance, the degree of which is referred to as cognitive fatigue”. The results that were established provided an overview of methods that measured cognitive fatigue significantly by comparing results of repeated task performances or by comparing the first half of a prolonged task performance with the second half. According to the literature search cognitive fatigue can be measured objectively. We consider the PASAT and TAP-M to be superior compared to other measurement methods of cognitive fatigue. The PASAT is capable of measuring cognitive fatigue on its own due to the nature of its design. It considered to be sensitive to limitations of information processing speed and cognitive flexibility. The TAP-M has to be combined with a supplemental load in order to effectively measure cognitive fatigue. This load can be administered in the form of a physically exerting task or a cognitively demanding task. By measuring objective performance both before and after external loading, cognitive fatigue can be detected. Furthermore MS patients showed an abnormal change in objective performance during prolonged or repeated task performance compared to healthy controls, showing that cognitive fatigue in MS patients is to be expected.

Although walking is considered to be automatic or reflex controlled requiring only minimal attentional resources, some researchers suggest that it can demand attention[3]. Therefore in the second part we will examine if a relationship exists between cognitive and motor fatigue. The following definition will be used in in this protocol to describe motor fatigue[4, 5]: “the magnitude of change in a performance relative to a reference value over a given time”. Research has shown that motor fatigue can manifest during the Six Minute Walking Test (6MWT) or that the test can induce walking-related motor fatigue in persons with MS[6]. Therefore the research design of this protocol will use the 6MWT and a combination of multiple cognitive test batteries (Test Battery of Attentional Performance-Mobility version, Paced Auditory Serial Addition Test, Alertness Vigilance Test) at baseline and during the 6MWT to examine the relationship between cognitive and motor fatigue in persons with MS.

2. Aim of the study

The primary objective of this study is to examine the relationship between cognitive fatigue and motor fatigue in patients with MS.

2.1.Research questions related to the master thesis

Primary research question: "What is the relationship between cognitive fatigue and motor performance in patients with MS?"

Secondary research question: "Do changes in attention occur during the performance of the 6MWT and are these changes related to motor fatigue?"

2.2. Hypotheses

We formulated the following hypotheses: Persons with MS who suffer from cognitive fatigue will demonstrate a relationship between motor fatigue and cognitive fatigue.

3. Methods

3.1. Research design

Observational cross-sectional study. Subjects will be examined on two days within a week. Cognitive fatigue will be measured at baseline on each test day. The baseline tests include the Paced Auditory Serial Addition Test (PASAT), Test Battery of Attentional Performance-mobility version (alertness subscale) (TAP-M) and the Alertness Vigilance Test (AVT). Afterwards subjects will perform a physical exertion task: the Six Minute Walking Test (6MWT). On one day both MS patients and healthy controls will perform the 6MWT while performing the Alertness Vigilance test. On the other day subjects will only perform the 6MWT.
Performances in both the 6MWT and the AVT will be compared to each other minute by minute.

Baseline measures:

- Paced Auditory Serial Addition Test (PASAT)
- Test Battery of Attentional Performance - version Mobility (alertness subscale) (TAP-M)
- Alertness Vigilance Test (AVT)

Physical exertion task:

- Six Minute Walking Test (6MWT)

3.2. Participants

Multiple sclerosis patients will be recruited from the Rehabilitation and MS Hospital of Overpelt as well as through social media. They will be matched with healthy controls for age and gender. Healthy controls will be recruited by asking MS patients to recruit interested friends or family members.

3.2.1. Inclusion criteria

- Diagnosis of MS
- Expanded Disability Status Scale (EDSS) score between 3.0 and 6.0. A minimum score of 3.0 is chosen due to a lack of walking impairments in lower EDSS scores. A maximum score of 6.0 is chosen based on the knowledge that a score of more than 6.0 would mean that a patient is unable to walk any significant distance without assistance. Research has shown that motor fatigue is more prevalent in persons with a higher EDSS score. Using these criteria we are able to examine a variety of patients with and without motor fatigue.
- >18 years
- Ability to walk six minutes without rest or assistive device

3.2.2. Exclusion criteria

- Other neurological or psychiatric diseases
- A history of substance abuse
- Participating in another study on cognitive or physical task performance

3.2.3. Patient recruitment

The aim is to recruit 30 patients and 30 healthy controls for the study.

3.3. Medical ethics

An approval of the study will be requested from the Medical Ethics Committee of the University of Hasselt and the Rehabilitation and MS Hospital of Overpelt will be applied for in September.

3.4 Intervention

Does not apply in an observational cross-sectional study design.

3.5. Outcome measures

The relationship between cognitive fatigue and motor fatigue will be examined by determining the correlation between 6MWT (without AVT) and PASAT performance at baseline.
The relationship between alertness and motor fatigue will be examined by determining the correlation between the TAP-M and the 6MWT (without AVT) on one side and TAPM versus 6MWT combined with AVT on the other side. The AVT will also be performed in seated condition to examine the difference.

3.5.1. Primary outcome measures

6MWT

The 6MWT assesses the distance walked in a time span of six minutes. For the measurement of walking endurance in MS, it is identified as reliable, feasible and reproducible[7]. This test will be used in combination with the DWI to measure motor fatigue.

DWI (in combination with 6MWT)

The total distance covered (meters) and walking speed (meters/minute) will be registered. A decline in distance walked will be measured every minute. The change in percentage (distance walked index, DWI) will be calculated using the following formula[6]: DWI = ([Distance walked at minute n – Distance walked at minute 1]/Distance walked at minute 1) × 100. A threshold of -15% will determine if subjects show walking related fatigue. A change in performance in the AVT can be measured by calculating the change in reaction time (RT) between minute six to one. Data of the two tests will subsequently be compared to see which task will deteriorate first and if a decline in performance in one test will impact the performance in the other.

3.5.2. Secondary outcome measures

AVT

Subjects will receive auditory cues in the form of letters of the alphabet and are instructed to only respond to two specified target letters by saying “yes”. The test measures response time between presentation of the target stimuli and the response. Participants will complete this task twice per session: once while seated for a baseline measurement and once while performing the 6MWT. Total test duration will be six minutes in both cases.

TAP-M

The measuring of reaction times by means of alertness tasks can provide an effective and clinically relevant representation of fatigue[8]. The Test Battery for Attentional Performance-mobility version consists of three subscales. In this protocol only one subscale (alertness) will be used. Alertness is examined by a three minutes lasting reaction task measuring median reaction time (mRT). Subject are asked to press an external response key with their right index finger as quickly as possible after a stimulus is presented.

PASAT

It is considered to be specifically sensitive to limitations of information processing speed[9]. The PASAT will be used to examine cognitive fatigue in participants. In this test, single digits are presented every three seconds using an audio-device to ensure a standardised rate of stimulus presentation. The patient is asked to add each new digit to the one preceding it. Participants will be scored on how many correct answers, out of a maximum of 60, they are able to give. The total score will represent the degree of cognitive dysfunction present. The conversion of these results to a percentage will determine the degree of cognitive fatigue each participant suffers from. The test duration is approximately 10 min.

Descriptive outcome measures

Age, gender, disease duration, MS phenotype and EDSS-score of the participants will be noted.

The Modified Fatigue Impact Scale (MFIS) will determine the degree to which a participant suffers from fatigue in terms of physical, cognitive, and psychosocial functioning. Twenty-one items are questioned.

Participants will complete the Beck Depression Inventory 2 (BDI-II) to ensure that test results will not be influenced by motivational shortcomings.

3.6. Data analysis

Analyses will be done using the SAS JUMP software. Significance level is set at p<0,05.

The Shapiro-Wilk test will be used to verify the normal distribution of the continuous variables.

To detect differences in DWI n-1 (percentage of deceleration in minutes, compared with the first minute, starting from the second minute), a 2-way repeated-measures ANOVA will be applied, with the within subjects factor being DWI n-1 (from the second to the sixth minute) and the between-subjects factor being subgroups based on DWI 6-1. Tukey post hoc tests will be applied for contrast analysis when appropriate.

A Spearman product correlation will be used to correlate the DWI 6-1 with the MFIS total and MFIS subscores.

4. Time planning

An approval of the study will be requested from the Medical Ethics Committee of the University of Hasselt and the Rehabilitation and MS Hospital of Overpelt in September 2017. The approval is expected in November. Data collection will take place between October and March 2018. Final data-analysis is planned to be completed by April 2018. The manuscript writing will be finished by June 2018.

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6. Appendices part 2 – research protocol

Progress report UHasselt

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VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
17/10	Eerste kennismaking Contract tekenen	Promotor: Copromotor: Student(e): Student(e):
4/11.	Bespreking verdiepende literatuur	Promotor: Copromotor: Student(e): Student(e):
21/11	Literatuur search bespreking	Promotor: Copromotor: Student(e): Student(e):
[illegible]/12	Literatuur search bespreking	Promotor: Copromotor: Student(e): Student(e):
28/03	Inleiding en methode	Promotor: Copromotor: Student(e): Student(e):
9/06	Inleiding, methode en kwaliteitsbeoordeling artikels.	Promotor: Copromotor: Student(e): Student(e):
26/06	Inleiding, methode en data-extractie	Promotor: Copromotor: Student(e): Student(e):
8/08	Bespreking deel 1 + informatie Protocol	Promotor: Copromotor: Student(e): Student(e):
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Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij inwendige aandoeningen**
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