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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The difference in activation of the prefrontal cortex between a single motor task, a single cognitive task and a cognitive-motor dual task in persons with MS and healthy controls. A pilot study

Ruth Nijssen
Maxine Vos

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :

Prof. dr. Peter FEYS

BEGELEIDER :

Mevrouw Renee VELDKAMP

2020
2021

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FACULTY REHABILITATION SCIENCES

Master 2 in rehabilitation sciences and physiotherapy

The difference in activation of the prefrontal cortex between a single motor task, a single cognitive task and a cognitive-motor dual task in persons with MS and healthy controls. A pilot study.

HIGHLIGHTS

- ✓ Persons with multiple sclerosis walk slower than healthy controls, in both single tasks and dual tasks.
- ✓ Dual task cost does not differ between persons with MS and healthy controls.
- ✓ Higher left dorsolateral prefrontal cortex activation in persons with MS than in healthy controls.
- ✓ Higher brain activation of the right dorsolateral prefrontal cortex during dual task compared to single cognitive task in both groups.

Promotor:
Prof. Dr. Peter Feys

Supervisor:
Drs. Renee Veldkamp

Students:
Ruth Nijssen
Maxine Vos

AKNOWLEDGEMENTS

We want to thank everyone who made it possible to perform and write this second part of our master's thesis. Our supervisor, Drs. Renee Veldkamp, for guiding and helping us through the process, for the extensive feedback and the pleasant collaboration. Our promotor, Prof. Dr. Peter Feys, for overviewing the study and for the feedback on the last modifications of this master's thesis. Our loved ones, friends and families for all the support and feedback. Further, we want to thank the REVAL center of the faculty Rehabilitation sciences at the University of Hasselt and the National Multiple Sclerosis Centre (NMSC) Melsbroek for putting their accommodation available for our research. We also want to thank the NMSC Melsbroek for helping us with recruiting participants for the study within the centre. And of course, last but not least, special thanks to all participants who were willing to take part in this study.

Herk-de-Stad, 24/05/2021 R.N.

Bilzen, 24/05/2021 M.V.

RESEARCH CONTEXT

This master's thesis part two in rehabilitation sciences and physiotherapy is situated in the research domain of neurological rehabilitation, more specific in the research domain of multiple sclerosis (MS). Persons with MS (pwMS) present with a variety of symptoms (cognitive and motor impairments, fatigue …) and are known to have difficulties in performing dual tasks (DTs), which are often needed in ambulation and daily living in general. Measuring brain activity during dual tasking using functional near-infrared spectroscopy (fNIRS) is understudied so far. Our supervisor, Drs. Renee Veldkamp, set up the ''Learning Strategies for Improving Dual Task Performance in Multiple Sclerosis'' (StraDiMS) study to examine the influence of different learning strategies on DT performance, of which this master's thesis is part. FNIRS is a technology used in this thesis and was funded by the Belgian Charcot foundation.

After consideration with our promotor Prof. Dr. Peter Feys and supervisor Drs. Renee Veldkamp, we decided to write our second part of the master's thesis about the differences in brain activation of the prefrontal cortex (PFC) between a single motor task (SMT), a single cognitive task (SCT) and a cognitive-motor DT in pwMS and healthy controls (HCs).

This study contributes to gaining insights in the brain activation of the PFC in pwMS during performing dynamic single tasks (STs) and DTs, compared to the activation in HCs.

This master's thesis was performed in the second master year at the University of Hasselt, campus Diepenbeek. The study itself took place at the REVAL center of the faculty of Rehabilitation Sciences at the University of Hasselt in Diepenbeek and at the National Multiple Sclerosis Centre (NMSC) Melsbroek. The authors of this master's thesis are two master's students from the University of Hasselt: Maxine Vos and Ruth Nijssen, with the supervision of Drs. Renee Veldkamp and promotor Prof. Dr. Peter Feys. Both students were strongly involved in the recruitment of participants, the data collection, the data checking and in analyzing the data. The statistical analysis and writing were performed by both authors together. This master's thesis was frequently evaluated by Drs. Renee Veldkamp. The final version was evaluated by Prof. Dr. Peter Feys too.
The central format is used for this master's thesis, in agreement with the promotor and supervisor.

ABSTRACT

Background: Multiple sclerosis (MS) manifests with a variety of symptoms, including cognitive and walking impairments. While walking we are often dual tasking (f.e. walking while talking). This can lead to a further decreased balance and walking performance and higher risk of falls, called Cognitive-Motor Interference (CMI). Previous studies suggest that the PFC could contribute to DT. However, this remains understudied in walking in pwMS.

Objectives: This study aims to investigate the PFC activation and behavioural performance during a single motor task (SMT), a single cognitive task (SCT) and a DT, in persons with MS (pwMS) and healthy controls (HC).

Participants: 13 pwMS (EDSS between 2 and 5) and 17 HCs participated.

Measurements: PFC activation was measured with the functional near-infrared spectroscopy (fNIRS) system during SMT (walking), SCT (subtracting 7s) and DT (walking while subtracting 7s). Outcome measures for motor and cognitive performances during single and dual tasking were distance walked and correct answers and accuracy, respectively. Additionally, motor and cognitive dual task cost (DTC) was calculated during combined execution.

Results: No group*task interactions were found. As main effect, pwMS walked significantly slower than HCs. Further, both groups showed lower motor and cognitive (subtracting 7s) performance during DT compared to single tasks, however no differences between groups were found for the DTCs. The left dorsolateral PFC shows higher activation in pwMS and higher SMT activation compared to SCT and DT. The right dorsolateral PFC shows higher DT activations compared to SCT. No effects were found for brain activation in the frontopolar PFC.

Conclusion: We strongly recommend further research in this research domain to receive more evidence of the clinical relevance of brain activation in the PFC. Also there remains a lack of high quality studies of fNIRS measurements in pwMS.

Keywords: Multiple sclerosis, hemodynamic changes, fNIRS, prefrontal cortex, cognitive motor interference

INTRODUCTION

Multiple Sclerosis (MS) is a highly prevalent, chronic, auto-immune, inflammatory and degenerative disease of the central nervous system (CNS) in adults [1, 2], that manifests with a variety of symptoms, among which are motor impairments, cognitive disorders, fatigue and depression [1, 3]. This range of symptoms can lead to a decreased quality of the patient's life [3, 4]. Furthermore, difficulties in walking and balance disorders result in a higher risk of falls, which can lead to injuries and hospitalisation [5-7].

During community ambulation, persons with MS (pwMS) walk more slowly, with greater asymmetry and larger stride-to-stride variability than healthy controls (HCs) [8]. Motor activities performed in daily life such as walking often occur in combination with inputs from the outside (e.g., avoiding an obstacle) or with cognitive demands (e.g., talking to your companion), requiring executive functioning and attention [9, 10]. When two tasks are performed at the same time, as for example when talking while walking, this is called a dual task (DT). During the simultaneous performance of a cognitive and a motor task, there can be a decrease in performance of one or both tasks, compared to the performance of these tasks alone [11]. This interaction between cognitive and motor tasks is called cognitive-motor interference (CMI) [12]. CMI can be measured using dual task cost (DTC), which is the percentage change in performance during the DT relative to the ST [13]. Studies did not consistently demonstrate a higher DTC in pwMS than in HC [13-15], but CMI can lead to a further increased risk of falls, due to the negative effect of complex DTs on the postural stability in pwMS [16-19].

There are some theories on the mechanisms underlying CMI, but these are still debated. First of all, the capacity sharing model states that the brain capacity for the performance of tasks is limited and that CMI occurs when this capacity is exceeded during DT performance. Consequently, the performance on one or both tasks will decline [20-22]. The bottleneck theory states that CMI occurs due to competition between tasks which require the same processing structures while dual tasking, at the expense of one of the two tasks [21, 23]. Finally, the overlap hypothesis explains CMI by overlapping neural pathways which in consequence also leads to competition between the two tasks for priority. A greater DT interference will - according to the overlap hypothesis - occur with performing two more

similar tasks simultaneously, because in this case common brain areas are activated to perform the tasks individually [23-25].

Previous studies have shown that the prefrontal cortex (PFC), more specifically Brodmann Areas (BA) 9, 10 and 46, play an important role in executive function in HCs [26-28], which is found to be important in human gait, balance and DT [29-31]. Furthermore, multiple studies stated that there are processing modules in the anterolateral PFC (BA 46 and 10) which are only recruited during DT [32-35], leading to the hypothesis that the most anterior part of the lateral prefrontal cortex (LPFC) (BA 10) plays a role in DT processing. However, several other studies have reported opposite results. Whether there are some brain areas that are activated during dual-tasking and not while performing single tasks (STs) is thus still inconclusive [36].

Besides, studies also demonstrated differences in PFC activation between pwMS and HC. Three studies in pwMS using functional near-infrared spectroscopy (fNIRS) reported that for performing a DT, more activation of the PFC was seen in pwMS than in HC [37-39]. Hernandez et al. (2016) and Saleh et al. (2018) found no differences in DTC in general, nor for motor DTC individually, between pwMS and HC [37, 38]. Adversely, Chaparro et al. (2017) did demonstrate a higher DTC of walking for pwMS compared to HC [39]. Additionally, Saleh et al. (2018) showed a DTC for the cognitive component, but only in pwMS [37]. To our knowledge, this is the first study to investigate the activation in the PFC by using fNIRS while performing a single cognitive task (SCT), a single motor task (SMT) and a DT.

This study aims to examine the differences in PFC activation and in behavioural performance 1) between a SMT, a SCT and a DT, and 2) between pwMS and HC. The fNIRS system was used to measure PFC activity.

We hypothesized a higher PFC activation in pwMS compared to HC during both DT and ST performance. Further, we expected no significant difference in DTC between pwMS and HCs, although we did expect a lower absolute performance in general of the pwMS compared to HC due to the neurodegeneration in pwMS. Further, we expected to see a higher activation of BA 10 during DT performance compared to ST performance in both groups, based on the findings of previous studies.

METHODS

Participants

Participant selection

Participants were eligible for inclusion when they were between 18 and 65 years old, could walk for at least six minutes without a walking device and scored ≥ 26 on the Montreal Cognitive Assessment (MoCA) [40]. Additional criteria for the participants with MS were: being diagnosed with MS and Expanded Disability Status Scale (EDSS) score between 2 and 5.5. Participants were excluded if they had a relapse of MS in the previous month, if they were wheelchair dependent, if they had other motor or neurological impairments than MS, if participants could not understand the given instructions or if they had severe problems with vision or hearing.

Participants that were found to be eligible for inclusion were randomly allocated to the 'implicit' or to the 'explicit' group. All participants received written information and signed an informed consent. The study was approved by the Committee for medical ethics of Hasselt University, the NMSC Melsbroek and Rehabilitation & MS centre Overpelt (Belgian number: B9115202042919) and is registered at the ClinicalTrials.gov website (NCT04538872).

Recruiting

PwMS and HCs were recruited by handing out flyers in the surrounding community of the research team and via social media. PwMS were also recruited from the National Multiple Sclerosis Centre (NMSC) Melsbroek. HCs were recruited first as testing them was allowed first due to the COVID-19 circumstances compared to persons with MS. The intention was matching them with the later enrolled participants with MS by age and sex.

Study-design and procedure

The data used in the current study was part of a study called ''Learning Strategies for Improving Dual Task Performance in Multiple Sclerosis'' (StraDiMS), in which the influence of different learning strategies on DT performance was examined. The measurements of each individual for the StraDiMS study were performed on four different days, showed in Figure 1. On day one, descriptive data (characteristics, cognitive and motor functioning and patient-reported outcome measures (PRO's) through questionnaires) of the participants were

collected. Baseline DT outcomes of a to-be-learned stepping task, a learning session concerning the stepping task, and retention of the learned stepping task plus DT measurements took place on day two, three and four, respectively. After the retention measurements on day four, participants additionally conducted a fNIRS walking task with a DT paradigm (explained below). All measurements took place at two different sites in Belgium: at the REVAL center of the faculty Rehabilitation sciences at the University of Hasselt in Diepenbeek or at the National Multiple Sclerosis Centre Melsbroek. In the current study, descriptive data of day one and data of the fNIRS walking task on day four were extracted and analysed. The current study will not further describe the stepping task on AMPEL [41], but appendix 5 contains some more information about the platform and the stepping task.

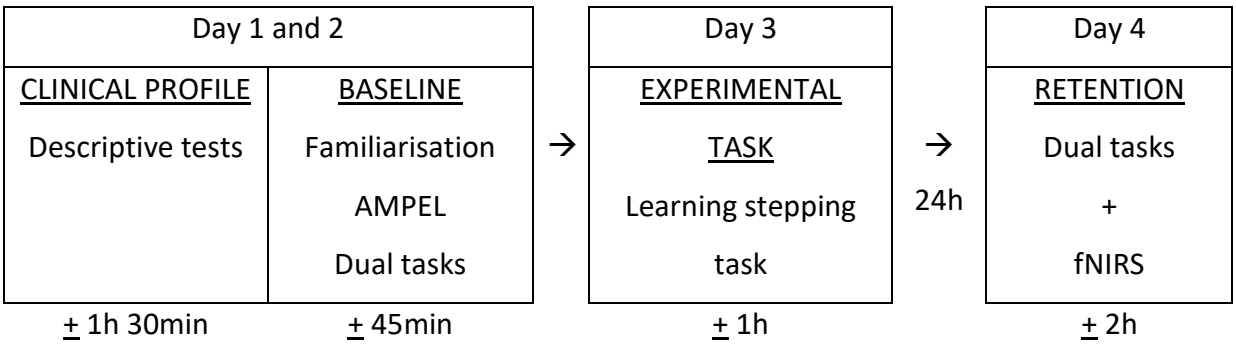

Figure 1 Study design StraDiMS

Descriptive tests

On day one, the participants were checked for eligibility based on the inclusion criteria. Characteristic parameters (age, sex, length, weight, level of education, type of MS, date of diagnosis and MS related medication) were registered and baseline measurements of the descriptive data were done. Those measurements consisted of a series of cognitive and motor tests as well as questionnaires, described below. Appendix 1 includes a detailed description of the descriptive tests.

Cognitive tests

Brief Visuospatial Memory Test-Revised (BVMT-R)

The BVMT-r was used for assessing visuospatial learning and memory. Six abstract drawings were shown for ten seconds to the participant. Afterwards, the participant was asked to try to reproduce them as correct as possible on an empty sheet of paper. The test consisted of

three trials. The scoring of each design could vary between 0, 1 and 2, based on preconceived criteria for accuracy and location of the drawing as described in the manual of the test [42, 43].

Corsi Block Tapping Test (CORSI)

The CORSI [44] is a visual variant of the Digit Span Forward test, used to assess visuospatial working memory. The researchers chose this variant instead of the Digit Span Forward itself to alter between auditory and visual cognitive tests. To accomplish the CORSI, a wooden board with nine cubes on it was used. Figure 2 shows the placement of the cubes (numbers were not visible for the participant). The examiner tapped the cubes in a random but preconceived sequence. Right after the examiner had finished tapping the sequence, the participant had to reproduce it in the exact same order. The sequences gradually increased in length until the participant was no longer able to correctly reproduce two sequences of the same length. The scoring of the CORSI consisted of three scores. The first score was the longest sequence the participant could reproduce correctly at least one time. Secondly, the total amount of sequences reproduced correctly was noted. At last, the third score was the CORSI product which is the multiplication of the first and second score. [45-48]

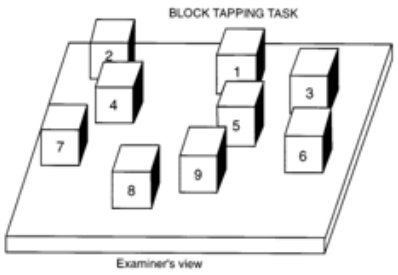

Figure 2 CORSI block tapping tests

Symbol Digit Modalities Test (SDMT)

The oral version of the SDMT was used to measure processing speed. A 'key' where symbols and numbers were coupled was shown to the participant, together with multiple rows of symbols. The participant was asked to couple as many symbols of the rows to a number corresponding to the 'key' in 90 seconds. The number of correct answers at 30, 60 and 90 seconds were noted. [49, 50]

10/36 Spatial Recall Test (SPART)

To measure visuo-spatial memory the SPART was used, in which the examiner showed a checkerboard pattern consisting of ten dots to the participant for ten seconds. Thereafter, the participant was asked to place ten checkers in the same place on an empty 6x6

checkerboard from memory. The number of correct and incorrect placed checkers was noted. This was repeated three times. [51, 52]

Paced Auditory Serial Addition Test (PASAT)

The researchers used the PASAT-3 seconds to examine sustained attention. For this test an audio file was played. The participant heard every three seconds a number between one and ten. The participant was asked to sum the last two numbers heard from the audio file (e.g., '5-7-3-2' – '12-10-5'). The total duration of the test was three minutes. The PASAT score consisted of the number of correct answers. Besides, also the dyad scores (PASAT dyad) were noted: the number of correct answers that followed after a previous correct answer. [53-55]

Digit Span Backward (DB)

The auditory DB was used to assess working memory. The examiner read a series of numbers out loud, which the participant had to repeat in the reverse order (e.g., '3-7-1' – '1-7-3'). The test consisted of seven series, each consisting of four trials with the same length. It started with a series of three numbers, which gradually increased in length as the participant answered correctly. The score of the DB was the length of the last sequence in which the participant could answer at least three out of four trials correctly. [54, 56]

Motor tests

Six Minute Walking Test (6MWT)

The 6MWT measures gait, gait speed, endurance and mobility [57]. Further, it is a strong predictor of the EDSS score of a pwMS [58]. The test took - as recommended in the guidelines [59] - place in a quiet walkway of 30 meters long. Participants were asked to walk as many meters as possible in six minutes, over and back in the 30m hallway [60]. The use of a walking aid was permitted if needed. The examiner noted the traversed meters per minute and in total.

Timed Up and Go (TUG)

With the TUG, the participant was instructed to stand up from a chair with arm-rests, walk a distance of three meters, turn around a cone, walk back to the chair and sit down as fast - but safely - as possible. The test ended when the patient's buttock touched the seat. A walking

aid was permitted to use, but the examiner did not give physical assistance. Two trials were performed of which the recorded time (in seconds) was noted and the average was used as outcome. [57, 61, 62]

Timed 25-Foot Walk (T25FW)

The T25FW is a test used to gain insight into the ambulation status of a pwMS [63]. The test is part of the Multiple Sclerosis Functional Composite (MSFC). The participant was instructed to walk 25 feet as fast, but safely, as possible Two trials were performed of which the time was noted in seconds. The mean of the two trials was calculated. [57, 64, 65]

Four Square Step Test (FSST)

The FSST is a test developed to measure if a person is able to step rapidly over obstacles while changing directions, which is needed while walking in- as well as outdoors [66]. Figure 3 FSST set-up shows the set-up of the test, derived from Dite and Temple (2002) [66]. Two canes were placed in a cross, creating four squares. The participant was instructed to stand in square number one facing square number two. Next, he or she was instructed to step as quickly - but safely - as possible in the following sequence of squares: 2-3-4-1-4-3-2-1. Both feet had to stand in the square before the participant could move on to the next square. The examiner started the stopwatch when the first foot contacted the floor in square 2 and stopped the stopwatch when the last foot touched the floor back in square 1. Two trials were completed with the best time taken as the score. [66, 67]

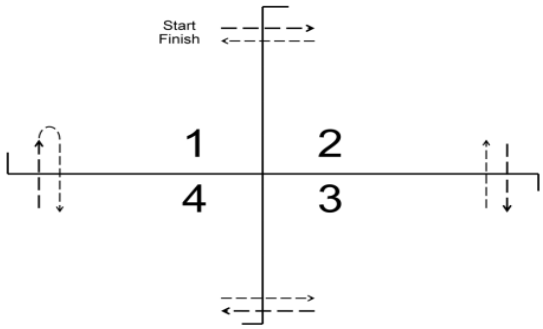

Figure 3 FSST set-up

Berg Balance Scale (BBS)

The BBS is a reliable, valid and widely-used test originally developed to assess balance in elderly people [68, 69], but has been demonstrated as a reliable instrument in pwMS too [57, 70]. The test consists of 14 items (seating balance, standing balance,…) scored on a 5-point scale (0-4) using preconceived criteria. The highest total score possible is 56 points, with a higher score indicating better balance [69].

Timed Tandem Walk-3m (TTW-3m)

The TTW-3m is a test to assess gait problems and balance during gait. The participant was asked to walk 3 meters as fast but safely as possible, with the heel of the first foot touching the toe of the last foot. The use of an assistive device was allowed. Two trials were completed, with the time of each trial noted. The second time was used in the analysis. [71]

Motricity Index (MI)

The MI is a test [72] to evaluate isometric muscle strength. In this study, the MI for lower extremity was used. The ankle dorsiflexion, knee extension and hip flexion were assessed from a seated position of the participant. Both the left and the right leg were assessed. The score for the muscle strength during each movement could vary between 0, 9, 14, 19, 25 and 33, based on the preconceived criteria. When a maximum score was allocated for each movement on both legs, one point was added so that the total score became 100. [73, 74]

Questionnaires

Dual Task Questionnaire (DTQ)

The DTQ developed by Evans et al. (2009) [75] is a questionnaire that assesses how often participants experience problems with dual tasking in daily life. The scoring for each item ranged from 0 ('never') to 4 ('very often'). The total score of all ten items was calculated.

Movement-Specific Reinvestment Scale - Dutch language version (MSRS-DLV)

The MSRS is a questionnaire developed to assess propensity for reinvestment [76, 77]. The score consisted of two parts: a 'conscious motor processing'-score and a 'movement self-consciousness'-score. [76]

Multiple Sclerosis Neuropsychology Screening Questionnaire - Patient version (MSNQ-P)

The MSNQ [78] is a reliable questionnaire consisting of 15 items and developed to screen pwMS for cognitive impairment in daily activities [79, 80]. Additionally it appears to measure depression too [81, 82]. The MSNQ-P is the patient self-report version of the original MSNQ. The score for each item could vary between 0 ('never occurs') and 4 ('occurs often/is very disturbing'). The total score of all items was counted and noted.

12-Item Multiple Sclerosis Walking Scale (MSWS-12)

The MSWS-12 [83] is a questionnaire consisting of 12 items that demonstrates the difficulties pwMS experience during daily walking (ranging from 1 to 5 with 1 'not at all' and 5 'very much'). The questions relate to the last two weeks. The total score of all items was noted. [84, 85]

Modified Fatigue Impact Scale (MFIS)

The MFIS-21 [86, 87] was used to assess the impact of fatigue in daily life, experienced by the participant. The MFIS-21 consists of 21 items which can be aggregated into three subscales: physical, cognitive and psychosocial. The total MFIS score consists of the sum on all subscales and can range from 0 to 84. The higher the score, the more impact of fatigue the participant experiences in his or her daily living. [88]

Activities-specific Balance Confidence Scale- Nederlandse versie (ABC-NL)

The ABC scale consists of 16 items, with a total score ranging from 0 to 100, and measures balance confidence [89]. The participant was instructed to mark the percentage that corresponded with the amount of confidence they had in not falling while doing the activities described in the questions [90]. The score calculated and used in this study was the mean score of all items.

FNIRS Dual task paradigm

The procedure of the fNIRS DT paradigm on day four is depicted in Figure 4 - An example of the procedure of the fNIRS task and was explained to the participants before the start of the task. It consisted of three different tasks, namely a SMT, a SCT and a cognitive-motor DT (explained below), that were each performed five times in an alternated order with a short rest period in between the tasks. Each task had a duration of 25 seconds and the order of the tasks was randomized. The rest period had a duration of ten to 20 seconds, during which participants stood still.

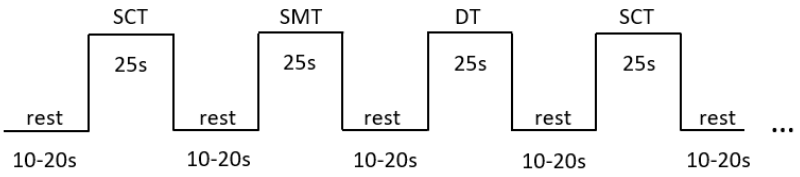

Figure 4 - An example of the procedure of the fNIRS task

The *single motor task (SMT)* consisted of walking at a comfortable pace during which participants walked up and down a 30 meters long hallway. Before the start of each SMT the command 'only walking at a comfortable pace' was given through a sound box to start the task.

The *single cognitive task (SCT)* consisted of subtracting sevens from a given starting number while standing still. The soundbox instruction for this task was 'only subtracting sevens' followed by a number (152, 165, 174, 186 or 198) as start signal of the SCT.

The *dual task (DT)* consisted of subtracting sevens while walking at a comfortable pace up and down the hallway. The soundbox instruction for this task was 'Subtracting sevens while walking at your comfortable pace' followed by a number as the start signal of the DT.

Five series of these tasks were performed. A 'beep' at the end of each task indicated the end of the task and the beginning of the rest period. The last 'end beep' was followed by the command 'end of the task' to indicate the end of the total fNIRS task. Performances of the tasks were noted and brain activity of the PFC was measured with the fNIRS system. Further description of fNIRS measurements and its technology will follow.

Configuration of the task with fNIRS technology

A script of the whole fNIRS task was made in the software PsychoPy [91]. That script consisted of: selecting the instruction that had to be read out through the soundbox, a countdown of two seconds followed by a number for the SCT and DT and a 'beep' for the SMT (indicating that the participant could start performing the given instruction), the duration of the task, another beep (marking the end of the task), a rest period and repeating this process fifteen times in total. There were six excel files created, each with the three tasks in a different order and chosen rest periods between ten and 20 seconds. PsychoPy selected the excel file

corresponding to the through randomization assigned order of tasks. Finally, PsychoPy was connected to fNIRS technology software in order to configure the performances of the tasks and the measurements of the hemodynamic changes by fNIRS.

FNIRS technology and software

NIRSport 2

NIRSport 2 (Figure 5 Nirsport2 https://nirx.net/nirsport[92]), a portable fNIRS technology, was used to measure the hemodynamic changes during the DT paradigm. We chose this system over any other neuroimaging technique, because it is a portable system and so brain activation can be measured during the execution of the different dynamic tasks.

Figure 5 Nirsport2 https://nirx.net/nirsport

NIRSport 2 has been successfully used in previous studies to measure brain activity during different tasks [37, 93]. The NIRSport 2 is a portable data platform weighing 970g and worn by the participant on the back as a little backpack. It was connected to a NIRScap attached to the head of the participant. It was used to measure hemodynamic changes in the brain by using near infrared wavelengths. Different sizes of NIRScaps (54, 56, 58, 60 centimetre), depending on the head circumference of the participants, were used in this study. The NIRScap was equipped with 16 dual tip NIRS optodes used as source or as detector. This way, channels were formed in which hemodynamic changes can be measured. To minimize interferences of external light, an additional cap was worn over the fNIRS cap on which the optodes were attached.

Location of optodes

Eight LED sources - with wavelengths between 750nm and 850nm - and seven Silicon Photodiode (SiPD) detectors, resulted in 20 channels on the PFC. An eighth detector was used to create eight short channels, important to differentiate the hemodynamic changes in superficial tissue from the hemodynamic changes in the brain area [94]. Additionally, an accelerometer was placed on top of the head, in the middle of the NIRScap (reference point Cz).

A specific location of each optode on the NIRScap was determined using fNIRS optode location decider (fOLD) toolbox [95]. This was done in order to create optimal - and standardized - channels on the brain region of interest among all participants. The location of the optodes was the same for all participants. With this toolbox, sensitivity of the channels can be calculated on which the selection of the location can be based. In this study, the dorsolateral PFC (BA 9 and BA 46) and the frontopolar area (BA 10) were covered by the sources and detectors with a varying specificity of 5-88%. In appendix 2 and 3 , a map of all possible optode locations and more detailed information about the specificity for each channel is provided.

After determining the localisation of the optodes with the fOLD software, the montage of the NIRScap was created in the NIRSsite software. The setup of the optodes in the NIRSsite software was configured with fNIRS software (Aurora) to adjust the software to the determined locations on the cap.

Aurora fNIRS software

The deoxyhemoglobin (HbR) and oxyhemoglobin (HbO_2) concentration changes measured with the NIRSport 2 system were recorded by the Aurora fNIRS software. The software PsychoPy was connected to Aurora using Lab Streaming Layer. At every 'beep' in PsychoPy, a trigger was sent into the Aurora software output, so that in the data could be seen which task started at which moment.

Outcome measures

The primary outcome measures were the hemodynamic changes (HbO_2 changes) in the PFC for each task as measured by the fNIRS system. The traversed meters during the SMT were noted. For the SCT the total of correct answers and the accuracy of correct answers was noted. During DT, both the distance and the answers were noted. Additionally, the dual task cost (DTC) was calculated for each outcome measurement with the formula: $DTC = \left(\frac{DT-ST}{ST}\right) x\ 100$. A negative DTC indicated a worse performance of the DT compared to the ST.

As secondary outcome measures, gait parameters were measured using APDM (Wearable technologies, an ERT company) sensors during the SMT and DT. During the whole fNIRS task, the participants were wearing these sensors on the dorsal side of both feet and one on their

lower lumbar spine [96]. The sensors on the feet measured different gait parameters: cadence, stride length, double limb support, single limb support, stance and swing. The sensor on the lumbar spine additionally measured the balance during gait via the coronal, sagittal and transverse range of motion (ROM), but the outcome of these last parameters were eventually not used in this study. The recordings for data via the Mobility Lab application were always started manually at the beginning of each SMT or DT by one of the researchers and ended automatically after 23 seconds.

Data analysis - Preprocessing fNIRS data

The data of the NIRSport system, saved in Aurora, was preprocessed with NIRS-toolbox functions in Matlab. First, the data of the participants was loaded into Matlab. The script can be found in appendix 4. The start markers (stimuli) of each task were adjusted so that the duration of the markers corresponded to the duration of each task (25 seconds). The different stimuli were also renamed to the corresponding task ('Motor', 'Cognitive' and 'Dual task'). Before being analysed, the data were trimmed to delete data before and after the actual task. Data was also downsampled to Fs=4 to deal with high autocorrelations. Also, the data of the short channels was taken into account with the short separation function. An estimation of HbO_2 was done by the Modified Beer Lambert Law function [97-99]. Four regions of interest (ROI's) were identified in the script (shown in Figure 6); the left frontopolar prefrontal cortex (LPFC) including the left BA 10, the right frontoportal prefrontal cortex (RPFC) including the right BA 10, the left dorsolateral prefrontal cortex (LDLPFC) including left BA 9 and 46 and the right dorsolateral prefrontal cortex (RDLPFC) including the right BA 9 and 46. With a General linear model (GLM) function transformation of the data was done, whereafter HbO_2 data of each subject (subject statistics) for each ROI was produced. To deal with the contaminations - like motion artifacts, blood pressure, respiratory or cardiac signals – the autoregressive iteratively reweighted least squares (AR-ILRS) algorithm of GLM functions was used. Hereby, sensitivity and specificity of the HbO_2 data was optimized. This data was used to run different statistics, as described below. [100-102]

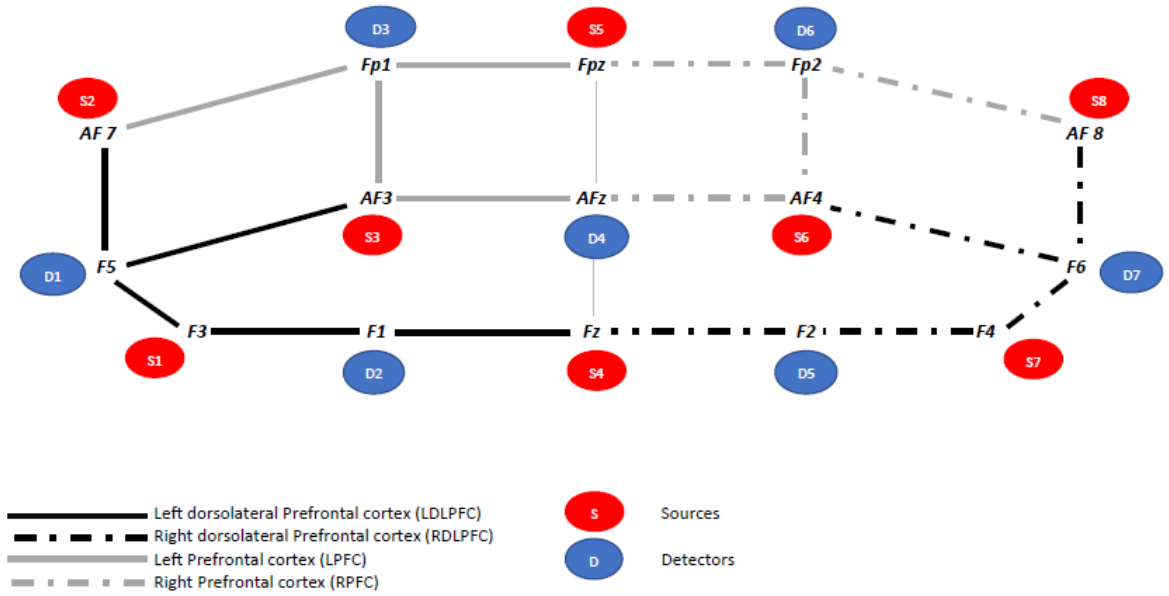

Figure 6 Regions of interest and their channels

Statistics

Descriptive outcomes

Statistics were conducted in SAS JMP, with a significance level set at 0.05. Differences between pwMS and HCs in descriptive outcomes (characteristics, cognitive tests, mobility tests and PRO's) were analysed using independent t-tests (parametric) and Wilcoxon and/or Welch tests (nonparametric). Unequal variances were checked with the Brown-Forsythe test (equal variances when $p>0.05$) and normal distribution of data was checked with the Shapiro-Wilk test (normally distributed when $p>0.05$). Fisher's exact test was used to analyse categorical descriptive data.

fNIRS Dual Task Paradigm - behavioural

To examine differences in performance between ST and DT as well as differences between pwMS and HCs, three mixed models were conducted. Group (MS, HC) and task (SCT, SMT and DT) were set up as fixed effects and individuals as random effects. Differences in behavioural performance between ST and DT for both groups, as well as the between group differences were analysed for the correct answers and accuracy of the sub 7 and the distance walked. Furthermore, a mixed model for the DTC was set up with group (MS, HC) and outcome measure (correct answers, accuracy of answers and walked distance) as fixed effects and

individual as a random effect. Differences between the DTC of correct answers of the sub 7, the accuracy of the answers and the walked distance, for both pwMS and HCs were analysed.

fNIRS Dual Task Paradigm HbO_2 Analysis

To examine the differences in HbO_2 levels between SMT, SCT and DT as well as between pwMS and HCs, mixed models were conducted for the RPFC, the LDLPFC and the RDLPFC. Group (MS, HC) and task (SMT, SCT and DT) were set up as fixed effects and individuals as random effect. Because of the non-normal distributed data of the LPFC HbO_2 data, Wilcoxon tests were used to analyse the differences in HbO_2 levels of the LPFC. Differences between pwMS and HC were analysed separately for each task (SMT, SCT and DT).

RESULTS

Descriptive outcomes

A total of 39 participants, of which 21 pwMS and 18 HC, were recruited for the study. Two pwMS were excluded because of a low MoCa score, indicating too manifest cognitive impairment. Three of the included participants did not perform the fNIRS task. Additionally, in one HC and three pwMS the fNIRS measurement was not usable (distraction or incomplete measurement due to technical problems). After exclusion and drop-outs, data of 17 HCs and 13 pwMS (EDSS 3.1±1.3, 2–5.5) were analysed. Table 1 shows the means and standard deviations of the descriptive measures for pwMS and HCs separately. Both groups were similar in gender, age, length, weight, and education. Three types of MS participated in the study, RRMS (69.2%), PPMS (15.4%) and SPMS (15.4%). In this study, EDSS of the pwMS ranged from 2 to 5.

Table 1 - Descriptive outcomes

Characteristics			
	MS	HC	*p*
Group (n=)	13	17	
Gender (n=F)	11 (84.6%)	12 (70.6%)	0.43
MoCa (0 – 30)	28.1 ±1.5	28.41±0.9	0.70
Age (y)	43.2±12.7	44.24±12.9	0.93
Length (cm)	166.5±9.3	172.00±9.1	0.10
Weight (kg)	68.4±19.3	75.18±11.9	0.19
Years of education (y)	15.2±3.0	16.29±2.1	0.28
Level of education (1 – 6)	4.0±1.8	4.64±1.1	0.07
Type MS (%RR,PP,SP)	69.2; 15.4; 15.4		
EDSS range (0 – 10)	3.1±1.3		
	Cognitive		
	MS	HC	*p*
BVMTR (0 – 36)	23.5±8.0	26.0±5.2	0.57
CORSI pr(0 – 144)	53.4±12.8	53.8±19.8	0.46
SDMT (0 – 110)	62.8±20.9	61.6±7.9	0.86
SPART tot (0 – 30)	19.9±5.7	23.1±4.3	0.28
PASAT tot (0 – 60)	46.9±12.2	49.9±12.4	0.22
PASAT dyad (0 – 59)	37.7±18.2	43.4±17.4	0.21
DS BW (3 – 9)	4.5±1.6	4.5±1.1	0.57
	Mobility		
	MS	HC	*p*
6MWT (m)	510.2±128.1	635.7±73.9	0.01*
TUG (s)	7.2±1.8	5.6±1.2	0.01*
T25FW (s)	4.9±1.2	3.8±0.8	0.01*
FSST (s)	9.0±2.1	7.7±2.0	0.08
BBS (0 – 56)	55.5±1.3	56.0±0	0.11
TTW (s)	14.3±8.5	7.7±2.6	<0.01*
MI R (0 – 100)	85.7±20.4	99.5±2.1	<0.01*
MI L (0 – 100)	94.7±5.4	98.9±3.0	0.01*
	PRO		
	MS	HC	*p*
MSRS-tot (10-60)	38.5±9.7	25.3±9.0	<0.01*
MSNQ-P (0 – 60)	25.5±15.5	17.7±8.3	0.22
MSWS-12 (12 – 60)	32.0±15.0	12.0±0.0	<0.01*
MFIS tot (0 – 84)	43.5±20.9	15.1±14.7	<0.01*
ABC (%)	71.6±19.7	95.4±8.0	<0.01*
DTQ (0 – 40)	18.4±12.0	7.8±5.5	0.01*

*Abbreviations 1: Type MS = relapse remitting (RR), primary progressive (PP), secondary progressive (SP); expanded disability status scale (EDSS); * when p value < 0,05*

PwMS and HCs scored similar on the cognitive tests included in this study (p>0.05). For the mobility and balance related outcomes, pwMS scored worse compared to HCs (p≤0.01), except for FSST and BBS. PwMS scored higher on the PRO's (about fatigue, propensity for reinvestment, daily activities, dual tasks and balance) compared to HC (p≤0.05), except for the MSNQ-P, which is related to cognitive function in daily life.

Dual Task Paradigm performance

Figure 7 shows the performance of pwMS and HCs on the STs and DTs for distance walked, correct answers and accuracy. Also DTC of these outcome measures is shown in Figure 7. Mixed models analyses showed no interaction effects between group and task for the distance walked (p=0.30), correct answers (p=0.55) and accuracy (p=0.61), indicating no differential effect of tasks between groups. There was a significant main effect of task, with lower score on the ST compared to the DT, for number of meters walked and number of correct answers (p<0.01 for both), but not for accuracy (p=0.62). Lastly, there was a main effect of group, with a lower score in pwMS compared to HCs for distance walked (p<0.01), but not for correct answers (p=0.10) and accuracy (p=0.39).

For the DTC (both motor and cognitive), the mixed model showed no interaction effect between groups and the different outcomes of the tasks (p=0.56). There was a significant main effect of outcome measures, with a smaller cognitive DTC in accuracy than the cognitive DTC of the correct answers (p<0.01) and the motor DTC of walked distance (p<0.01). Also a smaller motor DTC of distance walked than cognitive DTC of correct answers (p<0.01) was found. The main DTC was not significantly different between pwMS and HCs.

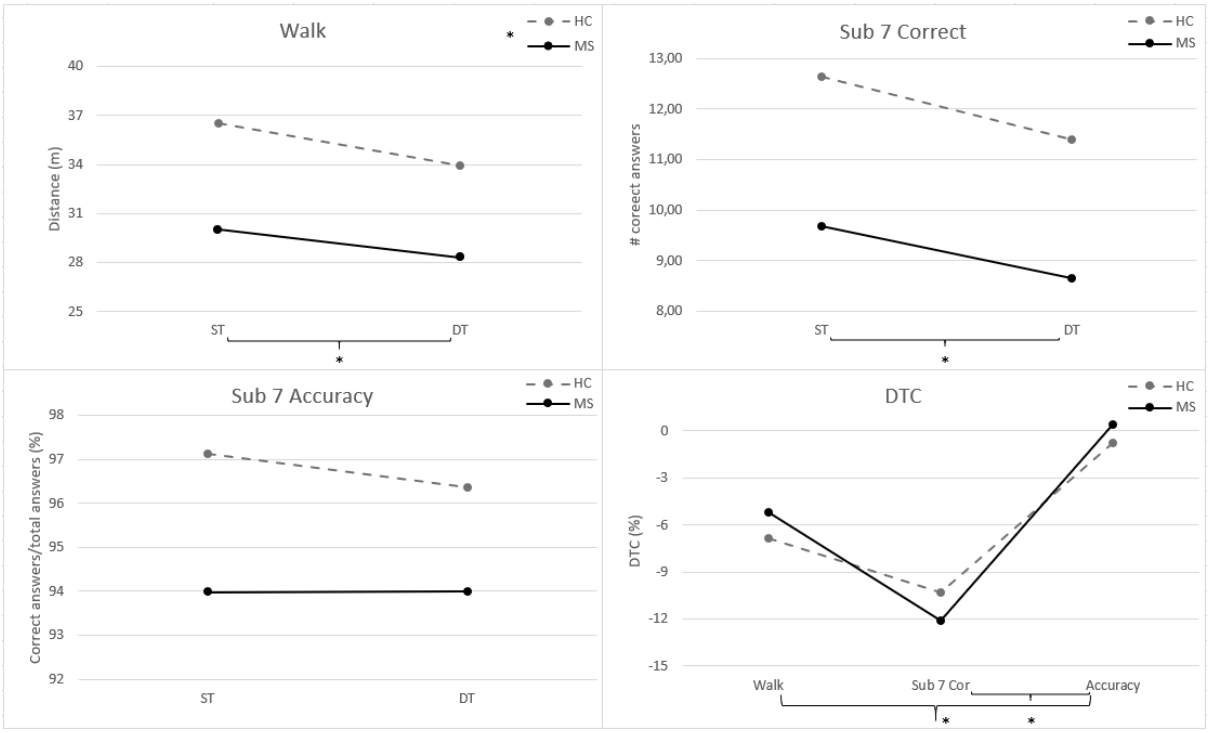

*Figure 7 - Results dual task paradigm. Significance (p≤0.05) is shown with **

Table 2 - Spatiotemporal gait parameters in pwMS and HC, during single motor and dual task conditions shows the results of the spatiotemporal gait parameters and differences between

pwMS and HCs, and DT and ST. Mixed model analyses for spatiotemporal gait parameters showed - for both left and right - no interaction effect between group and task for cadence ($p \leq 0.20$), stride length ($p \leq 0.88$), % double limb support phase ($p \leq 0.99$), % single limb support phase ($p \leq 0.81$), % stance phase ($p \leq 0.85$) and % swing phase ($p \leq 0.85$). A significant main effect for task was found for all included parameters at both sides, with a lower cadence, shorter stride length, higher % of double limb support phase, lower % of single limb support phase, higher % of stance phase and a lower % of swing phase ($p < 0.01$) during the DT compared to the ST.

A significant main effect of group was found for % double limb support phase, % single limb support phase, % stance phase and % swing phase. A higher % of stance phase and double limb support phase and a lower % of swing phase and single limb support phase was found in pwMS compared to HCs ($p \leq 0.03$).

Table 2 - Spatiotemporal gait parameters in pwMS and HC, during single motor and dual task conditions

*Significance (p ≤0.05) is shown with **

Right	*Group*		*Task*		*HC*		*MS*		*Effect test*		
	HC	*MS*	*DT*	*ST*	*DT*	*ST*	*DT*	*ST*	*Group*	*Task*	*Group* Task*
Cadence (steps/min)	116,42	114,80	113,84	117,38	114,17	118,67	113,51	116,10	0,58	**<0,01***	0,19
Stride length (m)	1,34	1,23	1,26	1,31	1,32	1,37	1,20	1,25	0,06	**<0,01***	0,88
Double support (%)	18,84	21,53	20,75	19,63	19,40	18,28	22,09	20,98	**0,02***	**<0,01***	0,99
Single support (%)	40,51	39,23	39,58	40,15	40,23	40,78	38,93	39,52	**0,03***	**<0,01***	0,81
Stance (%)	59,35	60,76	60,33	59,78	59,63	59,07	61,02	60,50	**0,02***	**<0,01***	0,85
Swing (%)	40,65	39,24	39,67	40,22	40,37	40,93	38,98	39,50	**0,02***	**<0,01***	0,85

Left	*Group*		*Task*		*HC*		*MS*		*Effect test*		
	HC	*MS*	*DT*	*ST*	*DT*	*ST*	*DT*	*ST*	*Group*	*Task*	*Group* Task*
Cadence (st/min)	116,33	114,69	113,66	117,36	114,02	118,64	113,30	116,09	0,58	**<0,01***	0,20
Stride length (m)	1,35	1,23	1,27	1,31	1,32	1,37	1,21	1,26	0,07	**<0,01***	0,69
Double support (%)	18,85	21,55	20,76	19,63	19,43	18,27	22,10	20,99	**0,02***	**<0,01***	0,88
Single support (%)	40,68	39,27	39,72	40,22	40,39	40,96	39,04	39,49	**0,02***	**<0,01***	0,56
Stance (%)	59,53	60,81	60,48	59,86	59,82	59,23	61,14	60,48	**0,02***	**<0,01***	0,70
Swing (%)	40,47	39,19	39,52	40,14	40,18	40,77	38,86	39,52	**0,02***	**<0,01***	0,70

fNIRS – HbO_2 outcome

Figure 8 shows the HbO_2 levels in pwMS and HCs over the three different tasks for each ROI.

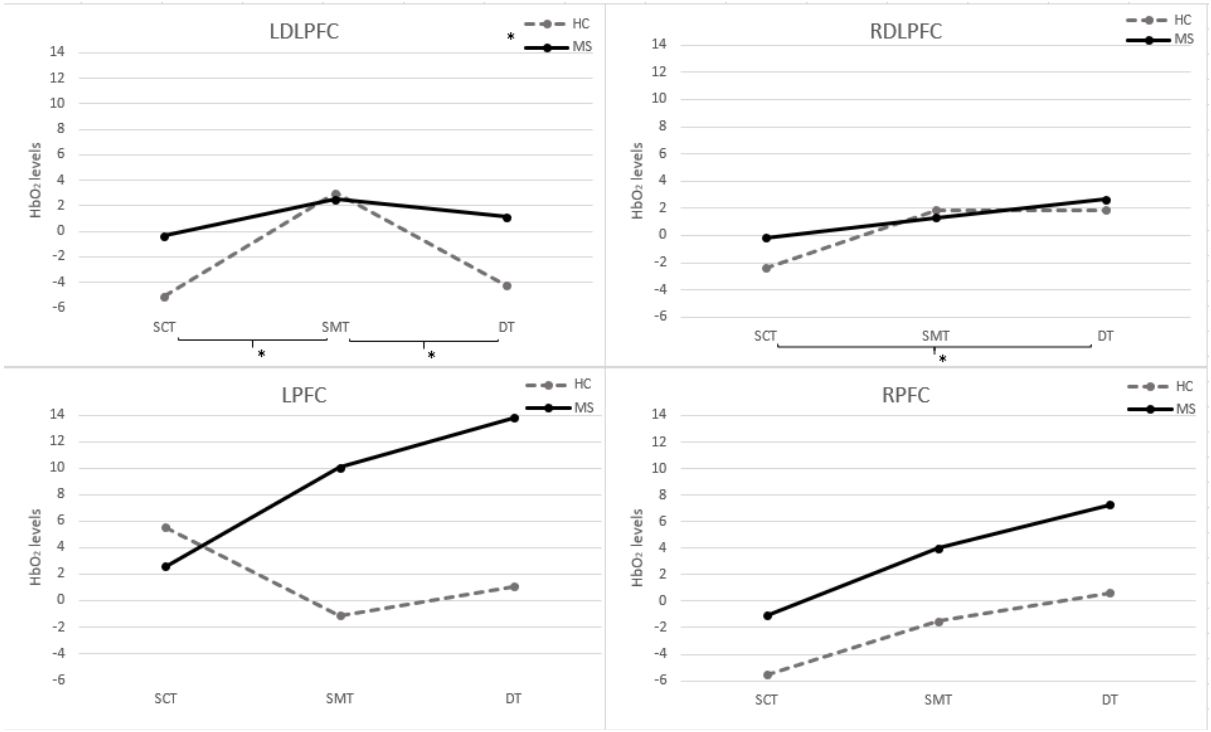

*Figure 8 - Results hemodynamic changes. Significance ($p \leq 0.05$) is shown with **

Left and Right Dorsolateral Prefrontal cortex

Mixed model analyses showed no significant interaction effects between group and tasks for LDLPFC (p=0.12) and RDLPFC (p=0.63). A significant main effect of group was found in the LDLPFC (p=0.04), not in the RDLPFC (p=0.64), indicating overall higher HbO_2 levels in pwMS compared to HCs only in the LDLPFC. Significant main effects of task were found in both LDLPFC (p<0.01) and RDLPFC (p=0.04). HbO_2 levels in the LDLPFC during the SMT were significantly higher compared to the HbO_2 levels during DT performance (p=0.02) or performing the SCT (p<0.01). In the RDLPFC, HbO_2 levels were higher during DT performance compared to the HbO_2 levels during the SCT (p=0.04), but not during the SMT (p=0.88).

Left and Right frontopolar Prefrontal Cortex

Mixed model analyses for the RPFC showed no interaction effect between group and task (p=0.96), neither a main effect for group (p=0.24) or task (p=0.12). For the LPFC, Wilcoxon tests showed no differences between pwMS and HCs for the HbO_2 levels during the SCT, the SMT and the DT in the LPFC ($p \geq 0.12$).

DISCUSSION

The objective of this study was to investigate the difference in activation of the PFC between pwMS and HCs during a walking DT paradigm using fNIRS. No interactions between group and task were found. The LDLPFC showed higher activation in pwMS compared to HCs and higher SMT activation compared to SCT and DT. The RDLPFC showed higher activation during the DT compared to the SCT. No significant differences were found for brain activation in the frontopolar PFC between pwMS and HCs. Both groups showed lower motor (walking) and cognitive (subtracting 7s) performance during DT performance and pwMS walked in general significantly slower than HCs, but no differences between groups were found for the DTCs.

Results showed that pwMS walked significantly slower than HCs during the DT paradigm, as also was found in the mobility measures at baseline. These findings confirm our hypothesis that the general performance of pwMS would be lower compared to HCs due to the neurodegeneration in MS. Both groups walked significantly slower during DT than during the SMT, which can be explained by CMI occurring in both pwMS and HCs. Also in correct answers of the subtraction by 7, DT performance was lower than the ST performance for both groups. Yet, the main DTC was not significantly different between pwMS and HCs confirming the hypothesis. These findings are consistent with the findings of Hernandez et al. (2016) and Saleh et al. (2018) [37-39], and with a systematic review on CMI in pwMS compared to HCs [14]. It supports the theory that CMI occurs both in HCs and in pwMS, with a generally similar process in both populations. Although, it should be noted that the participants with MS enrolled in this study had a MoCa score ranging from 26 to 30 and an EDSS score varying between 2 to 5. Whether the results can be generalized towards all pwMS has to be verified by further research.

There were no significant differences found in the frontopolar PFC between pwMS and HCs for the STs and DT, in contrast to what we expected to see. However, the visualization of the results (Figure 8) seemed to show a trend in accordance with our hypothesis, but this should be looked at with caution. Only further research would be able to further confirm or reject this hypothesis. Overall higher HbO_2 levels were found in the LDLPFC in pwMS compared to HCs, as hypothesized by the researchers. The finding of increased activity in the DLPFC in

pwMS compared to HCs can be supported by the compensatory cortical activation theory. This theory states that increased activity of the PFC during cognitive demands occurs with aging and neurodegenerative conditions (such as MS) in order to maintain performance while neural structures and functions degenerate [103, 104]. Next, Holtzer, Epstein, Mahoney, Izzetoglu & Blumen (2014), state that increased and sustained PFC activation during DT is congruent with the capacity sharing model [105]. This can explain our finding in the RDLPFC: higher activation was found during dual tasking compared to performing the SCT. The higher activation during a SMT compared to a DT in the LDLPFC was unexpected. Further in the discussion, some limitations of this study will be described, which could provide some explanation of this devious result.

Some methodological considerations apply. First, there was no blinding of researchers. This could possibly lead to a detection bias. However, a standard test procedure was used and it is strongly unlikely that researchers could influence the activation of the brain. Secondly, the measurements took place at two different accommodations whereby all HCs were tested at the REVAL centre and most of the participants with MS were tested in the NMSC. In the NMSC, the 6MWT was completed over a 20m path, created in an overt place. The DT paradigm was performed over a ten meter path, because of less environmental distractions and noice. In contrast, the 6MWT and the DT paradigm at the REVAL centre were performed in a 30 meter hallway. This leads to a decrease in standardisation between the measurements in the two different accommodations, but the researchers believed it would not importantly affect the outcomes in brain activity or differences in DT versus ST performances within a participant. However, it could affect the results and differences between pwMS and HCs concerning the walked distance, as for the same distance walked, one has to turn more often on a 20 or ten meter path than on a 30 meter path. Next, for the descriptive cognitive tests there were some deviations in standardisation between the application of the measurements in the NMSC and at the REVAL centre. Some pwMS performed already the PASAT and/or the SDMT during their stay in the NMSC. The scores of these tests were taken over to avoid learning effects in the performance of these cognitive tests. However, the PASAT shows an excellent inter-rater reliability which reduces the effects on the results of the study [106] and also the oral version of the SDMT is found to be a highly reliable test [107]. Also, there was a technical disturbance in one of the detectors in

the fNIRS system. Therefore, two channels were excluded from analyses (D4 – S4 & D4 – S5). In Figure 6 the concerned channels are shown with thin lines. In appendix 3 is shown that channel D4-S4 corresponds with 62% BA 9 (and 20% BA 10) and channel D4-S5 with 88% BA 10 (and 5% BA9). This can lead to some disturbances in the results of our ROI's. Further, as also reported by several articles [38, 39, 105, 108, 109], we believe that only examining the PFC is a limitation of this study. Different regions besides the PFC play important roles for locomotor functions, such as spinal cord, brainstem, cerebellum, basal ganglia, and motor cortex. But, as described, the PFC is an important area to examine in investigating brain activation during DT. Additionally, with fNIRS it is only possible to measure brain activity in the superficial brain areas (cortex). So, a total insight in brain activity wouldn't be possible with fNIRS. Finally, due to the COVID-19 pandemic, HCs had to be recruited first. Although the aim was to enrol age- and gender-matched groups, we did not succeed as good as we hoped to. Even though no statistical differences were found between groups, subtle differences could still influence the results.

Besides the limitations, this study also had strengths. First of all, although there was a relatively low sample size (39 participants) enrolled in this study, it should be noted that the sample sizes of previous published studies using fNIRS in pwMS were smaller, ranging from ten to 16 participants [37-39]. Secondly, in this study with the fNIRS system it was possible to gain insights in important regions for executive function (and thus in dual tasking) during walking activities, which made it a more functional measurement of brain activity [37]. Finally, this is the first study to examine the brain activation using fNIRS during a walking DT paradigm, consisting of a SMT, a SCT and a DT.

For further research, we first of all recommend developing more studies about brain activity in pwMS using fNIRS with higher sample sizes, as the few studies published enrolled very low sample sizes. That way, more evidence can be collected about brain activity during dual tasking with a walking component. This study analysed both performances of SMT, SCT and DT as well as the PFC activity of these tasks separately. It would be interesting to examine some correlations in further research, for example between DTC and the difference in PFC activation during ST and DT. We believe that the examination of such correlations would result in a higher clinical relevance. Additionally, to gain insights in the associated theories, the sum of activation of a SMT and a SCT can be compared with activation in a DT. Further,

it is possible that participants in this study demonstrated less brain activity due to a learning effect [110]. Therefore, investigating the alterations in brain activation in pwMS before and after training is an interesting and clinically relevant matter for further research too. Finally, it is recommended to investigate more of the superficial brain area than only the PFC to include more concerned areas of locomotion. We do recommend the fNIRS system because of the possibility of a real locomotor task during the measurement of these areas.

CONCLUSION

PwMS were found to walk slower than HCs, as previously demonstrated. However, DTC (both motor and cognitive) did not differ between pwMS and HCs. Next, higher LDLPFC activation in pwMS than in HCs was found. In the RDLPFC, higher activation during performance of the DT compared to the SCT. Based on the described limitations and the lack of studies that examined brain activation using fNIRS during dual tasking, we strongly recommend further research in this research domain.

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APPENDIX

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1. Detailed description of the descriptive measurements

Cognitive tests

Brief Visuospatial Memory Test-Revised (BVMT-R)

The BVMT-r was used for assessing visuospatial learning and memory. In this test the examiner showed a sheet of paper with six abstract designs to the participant at approximately 40 cm. The participant was asked to observe the designs for ten seconds and - afterwards - to try to reproduce them as correct as possible on an empty sheet of paper. There was no time limit in which the participant had to try to reproduce, but he or she should always be encouraged to try to draw as many designs as possible. The test consisted of three trials. The scoring of each design could vary between 0, 1 and 2, based on preconceived criteria for accuracy and location of the design as described in the manual of the test [42,43].

Corsi Block Tapping Test (CORSI)

The CORSI [44] is a visual variant of the Digit Span Forward test, used to assess visuospatial working memory. The researchers chose this variant instead of the Digit Span Forward itself to alter between auditory and visual cognitive tests. To accomplish the CORSI, a wooden board with nine cubes on was used. Figure 1 shows the placement of the cubes. The participant was seated in front of the examiner, who tapped with the index finger on the cubes at a rate of approximately one cube per second and in a random but preconceived sequence. Right after the examiner had finished tapping the sequence, the participant had to reproduce it in the exact same order. The following instructions were given: *"I will tap on a series of cubes on this board. When I'm done, I want you to tap on these cubes in the exact same order. Further, I will tap another sequence. The sequences will gradually increase in length."* This was continued until the participant was no longer able to correctly reproduce two sequences of the same length. The scoring of the CORSI consisted of three scores. The first score was the longest sequence the participant could reproduce correctly at least one time. Secondly, the total amount of sequences reproduced correctly was noted. At last, the third score was the CORSI product which is the multiplication of the first and second score. [45-48]

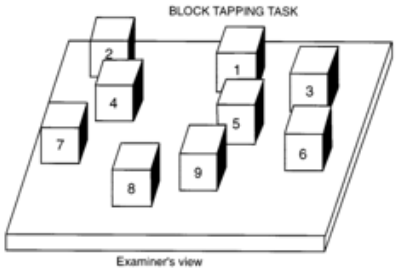


Figure 1 CORSI block tapping tests

Symbol Digit Modalities Test (SDMT)

The researchers used the verbal version of the SDMT to measure processing speed. For this test, the participant was seated in front of the examiner and was given the following instructions: *"Take a look at these boxes at the top of the page. In the upper row, you can see that every box contains a symbol. If you look at the row below, every box under the symbols contains a number. Every symbol in the upper row is different and under each symbol there is a different number. Now look at the following series of boxes just below the two upper rows. Notice that the upper boxes contain a symbol, but the boxes beneath are empty. It's up to you to fill in every empty box with the number that belongs there according to the key boxes at the top of the pages, where every symbol is linked to a number. If you look at the first symbol, for example, and then at the key, you can see that number one corresponds to the first box. So, you say "number one" for the first box out loud. Which number corresponds to the second box? You can tell me! (The participant says "number five"). Correct! So now you would say "five" to me. Which number corresponds to the third box? (The participant says "number two"). Correct! That is the idea. So, you have to fill in every empty box with the number that corresponds to the symbol above, according to the example at the top. That number, you say to me out loud."* After the instructions were given, a practice trial was given with the boxes until the double line. If the participant did not understand the task, the examiner repeated the instructions with some examples until the task was clear. Afterwards, the examiner gave the following instructions to start the real test: *"If I say "go", tell me the numbers as done before during the practice trial until I tell you to stop. I'm writing the numbers down. If you reach the end of a row, go as quickly as possible to the next row without stopping and so on. If you make a mistake, you can correct it with the correct number. Don't skip boxes and go as fast as possible. Ready? Go!"* After exactly 90 seconds, the examiner stopped the test. The number of right answers after 30 seconds, after 60 seconds and after 90 seconds was noted as a score. Also the total number of correct answers was noted. [49, 50]

10/36 Spatial Recall Test (SPART)

To measure visuo-spatial memory the SPART was used. The procedure for this test was the following. The participant was seated in front of the examiner who laid an empty 6x6 checkerboard and ten checkers in front of the participant. The following instructions were given: *"I will show you a drawing of a checkerboard where ten checkers are placed on. You can*

look at this paper for ten seconds. After ten seconds I will hide the drawing, after which you have to place as many checkers as possible at the correct place on the checkerboard in front of you." If the participant was not able to manipulate the checkers by himself, he could point to the spot where he wanted the examiner to put a checker. The participant was always motivated to place all the checkers on the board. When the participant was finished, the examiner noted the position of the checkers on the score form. The number of correct placed checkers as well as incorrect placed (referred to as "confabulations'') checkers was noted. Subsequently the checkers and the empty checkerboard were placed again in front of the participant and the same instructions were given. This was repeated three times. [51, 52]

Paced Auditory Serial Addition Test (PASAT)

The researchers used the PASAT-3seconds to examine sustained attention. The participant was seated in front of the examiner who played the audio file on her laptop which was placed next to the participant in order that he or she could hear it clearly. The following instructions were given: *"On this audio tape you will hear every three seconds a number between one and ten. Listen carefully to those two numbers, count them up and tell me the answer. When you hear the next number, you add this number to the last number you heard. Continue by each time adding the last number to the previous number you heard. Please notice: the task is not to add all the numbers, only the two last numbers mentioned. I'll give you an example. If you hear the numbers 5, 7, 3 and 2, your answers should be 12, 10 and 5. So count up the two last numbers. This is a difficult test. When you mix up, just restart by listening to the two following consecutive numbers and count them up. Try not to talk during the task, except telling me the answers. Also, try not to skip a sum."* The examiner continued to explain the task until the participant understanded the instructions. Afterwards, a practice trial was performed before the actual test was started. The examiner always tried to encourage the participant to continue the test and not to stop. The total duration of the test was three minutes. The PASAT score consists of the number of correct answers after in the first part, the second part and the third part of the test and also the total number of correct answers. Besides, also the dyad scores are noted. These scores are the number of correct answers that followed after a previous correct answer. [53-55]

Digit Span Backward (DB)

The auditory DB was used to assess working memory. The examiner read a series of numbers out loud at a rate of approximately one number per second, which the participant had to repeat the other way around. If the examiner for example said "7-3", the participant had to answer "3-7". The test consisted of seven series (from three to nine numbers), each consisting of four trials with the same length. It started with a series of three numbers, which gradually increased in length as the participant answered correctly. As long as the participant could answer at least three out of four trials correctly, the test was continued. The score of the DB was the length of the last sequence in which the participant could answer at least three out of four trials correctly. [54-56]

Motor tests

Six Minute Walking Test (6MWT)

The 6MWT measures gait, gait speed, endurance and mobility [57]. Further, it is a strong predictor of the EDSS score of a pwMS [57]. The test took - as recommended in the guidelines [59] - place in a quiet walkway of 30 meters long. The given instructions were based on the article of Goldman, Marrie, & Cohen (2008) [60] and were as follows: *"The goal of this test is to walk as far and as fast as possible within 6 minutes, by walking back and forth in this walkway. Six minutes is a long time to walk, so you will get tired. At the end of the walkway, turn around the cone as quickly as possible. Don't hesitate to continue walking. I'll show you how to turn around the cone. I will be walking behind you with a stopwatch to keep an eye on the time. Every minute, I will let you know a minute has passed and how much time is left. Fifteen seconds before the end of the test, I'll let you know the test has nearly ended. When I say "stop", stop walking and stand still. Try not to talk during the test. The goal is to walk as far and as fast as possible within 6 minutes, but don't run. Any questions?"* When the participant fully understood the task, the test was started. If the participant stopped walking, he or she was encouraged to continue walking without stopping the stopwatch. The use of a walking aid was permitted if needed. The examiner tallied during the test the traversed meters per minute. Also the total amount of traversed meters was noted.

Timed Up and Go (TUG)

With the TUG, the time needed to stand up from a chair with armrests, walk a distance of three meters, turn around a cone, walk back to the chair and sit down was measured (in seconds). The test ended when the patient's buttock touched the seat. A walking aid was permitted to use, but the examiner did not give physical assistance. The participant was instructed to execute the task as fast - but safely - as possible. Two trials were performed of which the recorded time was noted. The mean of the two performances was calculated too. Additionally, it was noted if the participant was unstable when he or she turned around the cone. [57, 61, 62]

Timed 25-Foot Walk (T25FW)

The T25FW is a test used to gain insight into the ambulation status of a pwMS [63]. The test is part of the Multiple Sclerosis Functional Composite (MSFC) and measures the time needed to walk 25 feet as fast, but safely, as possible [99]. The instructions the examiner gave the participant were the following: *"Walk these 25 feet as quickly, but safely, as possible. Do not slow down until you cross the finish line. Ready? Start."* The time started running when the participant lifted the foot and crossed the start, and stopped when the first foot crossed the finish line. Two trials were performed of which the time was noted in seconds. It was also noted if the participant wore an ankle-foot orthosis, if he or she used an assistive device, if it was not possible to complete a trial and if the participant needed more than two trials to complete the test successfully. The mean of the two trials was calculated. [57, 64, 65]

Four Square Step Test (FSST)

The FSST is a test developed to measure if a person is able to step rapidly over obstacles while changing directions, which is needed while walking in- as well as outdoors [66]. Figure 2 shows the set-up of the test, derived from Dite and Temple (2002) [66]. Two canes were placed in a cross, creating four squares.

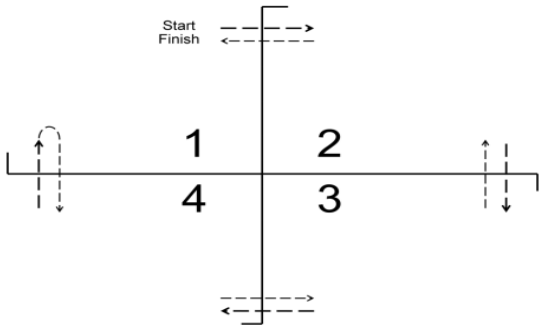


Figure 2 FSST set-up

The participant was instructed to stand in square number one facing square number two. Next, he or she was instructed to step as quickly - but safely - as possible in the following

sequence of squares: 2-3-4-1-4-3-2-1. Both feet had to stand in the square before the participant could move on to the next square. The following instructions were given: *"Try to complete the sequence as fast as possible without touching the canes. Both feet must make contact with the floor in each square. If possible, face forward during the entire sequence."* The examiner demonstrated the sequence and then gave the participant a practice trial. If needed, the practice trial was completed a second time. The examiner started the stopwatch when the first foot contacted the floor in square 2 and stopped the stopwatch when the last foot touched the floor in square 1. Two trials were completed with the best time taken as the score. [66, 67]

Berg Balance Scale (BBS)

The BBS is a reliable, valid and widely-used test originally developed to assess balance in elderly people [68, 69], but has been demonstrated as a reliable instrument in pwMS too [57, 70]. The test consists of 14 items, scored on a 5-point scale (0-4) using preconceived criteria. The highest total score possible is 56 points, with a higher score indicating better balance [68].

The following 14 items were scored; sitting to standing, unsupported standing, unsupported sitting, standing to sitting, transfers from one chair to another, standing with eyes closed, standing with feet together, reaching forward with outstretched arms, retrieving an object from the floor, turning to look behind, turning 360 degrees, placing feet alternating on a stool, standing with one foot in front and standing on one foot.

Timed Tandem Walk-3m (TTW-3m)

The TTW-3m is a test to assess gait problems and balance during gait. The instructions the examiner gave the participant to complete the TTW-3m were the following: *"Start in a standing position at the starting line. Walk these 3 meters as fast, but safely, as possible in a tandem gait. This means that you have to put the heel of your first foot against the toes of your last foot. Do not slow down until you cross the finish line. Ready? Start."* Two trials were completed. The use of an assistive device was allowed. The stopwatch was started when the participant lifted his or her foot and crossed the starting line. The time was stopped when the first foot crossed the finish line. It was also noted if certain circumstances influenced the performance, if the participant was not able to complete a trial, if the participant needed more than two trials to successfully complete two trials and - if so - the reason why. [71]

Motricity Index (MI)

The MI is a test developed by Demeurisse, Demol and Robaye (1980) [72] to evaluate isometric muscle strength. In this study, the MI for lower extremity was used. The movements assessed were ankle dorsiflexion starting from end-range plantar flexion, knee extension starting from 90° knee flexion and hip flexion starting from 90°. Both the left and the right leg were assessed. The score for the muscle strength during each movement could vary between 0, 9, 14, 19, 25 and 33, based on the preconceived criteria. When a maximum score was allocated for each movement on both legs, one point was added so that the total score became 100. [73, 74]

Questionnaires

Movement-Specific Reinvestment Scale - Dutch language version (MSRS-DLV)

The MSRS is a questionnaire developed to assess propensity for reinvestment [76] and was translated to Dutch, named the MSRS-DLV [77]. The instruction to fill in the questionnaire was the following: *"Below, you see ten statements about your moving in general. Read the statements carefully and draw a circle around the answer that fits you best."* For every statement six possible answers were provided. The score consisted of two parts: a 'conscious motor processing'-score and a 'movement self-consciousness'-score. Both scores were calculated. [76]

Multiple Sclerosis Neuropsychology Screening Questionnaire - Patient version (MSNQ-P)

The MSNQ [77] is a reliable questionnaire consisting of 15 items and developed to screen pwMS for cognitive impairment in daily activities [79, 80]. Additionally, it appears to measure depression too [80, 81]. The MSNQ-P is the patient self-report version of the original MSNQ. The instructions given were: *"The following questions investigate problems you possibly experience in daily life. Note how often these problems occur and how serious they are in the last three months. Please write down the corresponding number next to the question."* The score for each item could vary between 0 and 4, with 0 never occurs and 4 occurs often/is very disturbing. The total score of all items was counted and noted.

12-Item Multiple Sclerosis Walking Scale (MSWS-12)

The MSWS-12 [83] is a questionnaire consisting of 12 items that demonstrates the difficulties pwMS experience during daily walking. The questions relate to the last two weeks. The participant has to draw a circle around the score (ranging from 1 to 5 with 1 'not at all' and 5 'very much') that matches their answer to the question. The total score of all items was noted. [84, 85]

Modified Fatigue Impact Scale (MFIS)

The Dutch version of the MFIS-21 [86, 87] was used to assess the impact of fatigue in daily life, experienced by the participant. The MFIS-21 consists of 21 items which can be aggregated into three subscales: physical, cognitive and psychosocial. The participant is instructed to add a cross in the square corresponding to their answer on the item. The score of the three subscales and the total score of the MFIS were calculated. The score on the physical subscale can range from 0 to 36 by adding the scores on items 4, 6, 7, 10, 13, 14, 17, 20 and 21. Next, the score on the cognitive subscale can range from 0 to 40 and is the sum of the scores on items 1, 2, 3, 5, 11, 12, 15, 16, 18 and 19. Thirdly the score on the psychosocial subscale can range from 0 to 8 by adding the scores on items 8 and 9. And lastly the total MFIS score consists of the sum on all subscales and can range from 0 to 84. The higher the score, the more impact of fatigue the participant experiences in his or her daily living. [88]

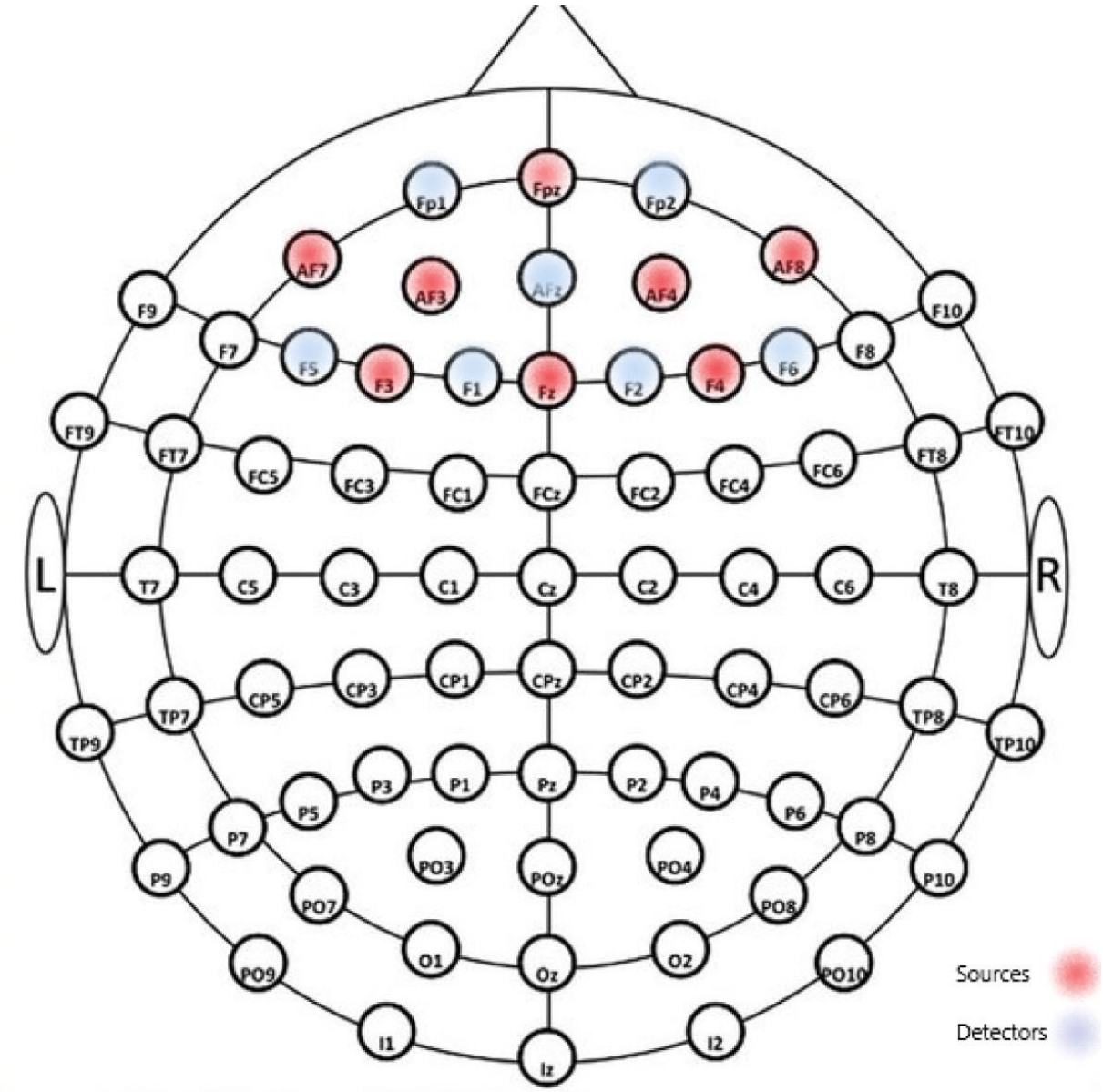
Activities-specific Balance Confidence Scale Nederlandse versie (ABC-NL)

The ABC scale consists of 16 items, with a total score ranging from 0 to 100, and measures balance confidence [89]. The participant was instructed to mark the percentage that corresponded with the amount of confidence they had in not falling while doing the activities described in the questions [90]. The score calculated and used in this study was the mean score of all items.

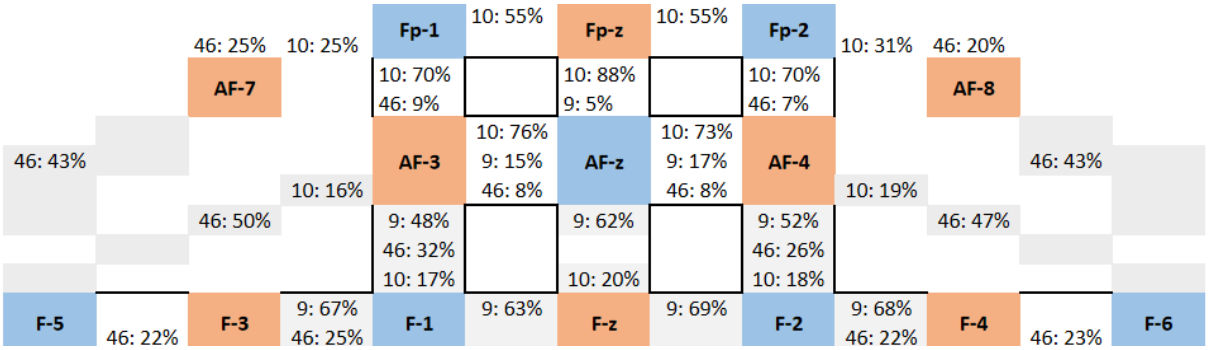
Dual Task Questionnaire (DTQ)

The DTQ developed by [75] is a questionnaire that assesses how often participants experience problems with dual tasking in daily life. Participants were asked to tick the box that best describes their answer to the question-items. The scoring for each item ranged from 0 ('never') to 4 ('very often'). The total score of all ten items was calculated.

2. Nirscap locations and locations of the sources and detectors [94]



3. Specificity of the fNIRS channels



Specificity (%) of the channels for BA 10, 9 and 46

4. Matlab script

Load data

```
raw=nirs.io.loadDirectory(['C:\Users\maxine\Desktop\Data_StraDiMS'],{'group','subject'});
```

Preprocessing data

- *Visualize demographics*

```
demographics = nirs.createDemographicsTable(raw);
```

- Changing stimulus duration

```
raw=nirs.design.change_stimulus_duration(raw,[],25);
```

- *Changing stimulus names*

```
jobs=nirs.modules.RenameStims(); %change names of stimuli
jobs.listOfChanges={...
    'stim_channel1' 'Motor'
    'stim_channel2' 'Cognitive'
    'stim_channel3' 'Dual'
    };
```

- *Trim fiels to remove irrelevant data before and after testing*

```
jobs=nirs.modules.TrimBaseline(jobs);
jobs.preBaseline = 20;
jobs.postBaseline = 20;
```

- *Resampling data – to deal with high autocorrelations in fNIRS-signals*

```
jobs=nirs.modules.Resample(jobs);
jobs.Fs=4;

raw_prep = jobs.run(raw);
```

- *Short-separation information*

```
jobs=nirs.modules.LabelShortSeperation();
jobs.max_distance=15;
```

- *Change to Hb-values*

  Converts raw data to optical density

```
jobs=nirs.modules.OpticalDensity(jobs);
```

  Converts optical density to hemoglobin

```
jobs=nirs.modules.BeerLambertLaw(jobs);
hb = jobs.run(raw_prep);
```

Define ROIs

```
source = [1 1 2 3 4]';
detector = [1 2 1 1 2]';
ROI_LDLPFC = table(source,detector);

source = [4 6 7 7 8]';
detector = [5 7 5 7 7]';
ROI_RDLPFC=table(source,detector);

source = [2 3 3 5]';
detector = [3 3 4 3]';
ROI_LPFC=table(source,detector);

source = [5 6 6 8]';
detector = [6 4 6 6]';
ROI_RPFC=table(source,detector);
```

Analyze subject level

```
jobs=nirs.modules.GLM();
jobs.AddShortSepRegressors=true;
```

```
jobs.trend_func = @(t) nirs.design.trend.legendre(t, 3);
SubjStats=jobs.run(hb);

disp(jobs);
```

Make ROIs based on SubjStats

```
SubjStatsNew=SubjStats';
LDLPFC_SubjStats = nirs.util.roiAverage(SubjStatsNew,ROI_LDLPFC);
RDLPFC_SubjStats = nirs.util.roiAverage(SubjStatsNew,ROI_RDLPFC);
LPFC_SubjStats = nirs.util.roiAverage(SubjStatsNew,ROI_LPFC);
RPFC_SubjStats = nirs.util.roiAverage(SubjStatsNew,ROI_RPFC);
```

5. StraDiMS

Day 1 and 2			Day 3		Day 4
CLINICAL PROFILE	BASELINE	→	EXPERIMENTAL TASK	→ 24h	RETENTION
Descriptive tests	Familiarisation AMPEL Dual tasks		Learning stepping task		Dual tasks + fNIRS
± 1h 30min	± 45min		± 1h		± 2h

Figure 3 Study design StraDiMS

The StraDiMS study, which means ''Learning Strategies for Improving Dual Task Performance in Multiple Sclerosis'', examined the influence of different learning strategies (implicit and explicit) on DT performance. The measurements of each individual for the StraDiMS study were performed on four different days, shown in Figure 3. On day one, descriptive data (characteristics, cognitive and motor functioning and patient-reported outcome measures (PRO's) through questionnaires) of the participants were collected. Baseline DT outcomes of a to-be-learned stepping task a learning session concerning the stepping task, and retention of the learned stepping task plus DT measurements took place on day two, three and four, respectively. The stepping task was performed on Augmented Movement Platform for Embodied Learning (AMPEL) [41]. AMPEL is visualised in Figure 4. Participants were asked to complete a stepping pattern on the lightened tiles, with the right foot and left foot alternating. After each step on a lightened tile, the next tile would light up. The time from a tile lighting up to stepping on it was measured by the platform to measure the motor performance of this task [41]. Additionally, the participants performed the stepping task as a single task, as well as combined with the subtracting 7s, the word list generation task and a vigilance task on AMPEL. Performance of stepping and de results of the cognitive tasks were measured at baseline and retention. On day three - which is the experimental day - participants practiced the stepping pattern. The explicit group was informed of a recurrent pattern of the stepping task, the implicit group was not informed. Differences in learning strategies between implicit and explicit learning as well as between pwMS and HCs can be analysed with the baseline and retention performances.

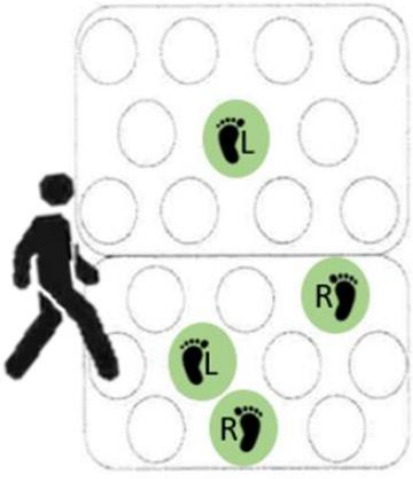


Figure 4 visualisation of AMPEL

Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - *INFORMATION STUDENT*

Faculteit/School: **Faculteit Revalidatiewetenschappen**
Faculty/School: ***Rehabilitation Sciences***

Stamnummer + naam: **1643136 Vos Maxine**
Student number + name

Opleiding/*Programme*: **2 ma revalid. & kine musc.**

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PART A - MANDATORY - TO BE FILLED* OUT *BY THE STUDENT

Titel van Masterproef/*Title of Master's thesis:* THE DIFFERENCE IN ACTIVATION OF THE PREFRONTAL CORTEX BETWEEN A SINGLE MOTOR TASK, A SINGLE COGNITIVE TASK AND A COGNITVE-MOTOR DUAL TASK IN PERSONS WITH MS AND HEALTHY CONTROLS. A PILOT STUDY

☒ behouden - *keep*

O wijzigen - *change to*:

/:

O behouden - *keep*

O wijzigen - *change to*:

In geval van samenwerking tussen studenten, naam van de medestudent(en)/*In case of group work, name of fellow student(s)*: RUTH NIJSSEN

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PART B - MANDATORY - TO BE FILLED OUT BY THE SUPERVISOR(S)

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O goedgekeurd mits wijziging van - *approved if modification of:*

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Datum en handtekening student(en)
Date and signature student(s)

24/05/2021
Maxine Vos

Datum en handtekening promotor(en)
Date and signature supervisor(s)

Peter Feys

29/05/2021

24/05/2021
Ruth Nijssen

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Registration form jury Master's thesis academic year 2020-2021,

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Faculty/School: ***Rehabilitation Sciences***

Stamnummer + naam: **1643333 Nijssen Ruth**
Student number + name

Opleiding/*Programme*: **2 ma revalid. & kine musc.**

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PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)
Date and signature student(s)

24/05/2021

Maxine Vos

Datum en handtekening promotor(en)
Date and signature supervisor(s)

Type text here

29/05/2021

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KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	BETROKKENEN
06/07/2020	Bespreking studie StraDiMS + afspraken metingen	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
01/09/2020	Bespreking onderwerpen Masterproef 2	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
17/09/2020	Bespreking en bepaling onderzoeksvraag	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
02/11/2020	Doorsturen van eerste versie gedeelte methode + inhoud introductie	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
04/11/2020	Tussentijdse data-check + bespreking/verdere uitleg fNIRS systeem	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
23/11/2020	Doorsturen van eerste versie introductie + aangepaste versie methode + inhoud data-analyse	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
08/12/2020	Bespreking feedback introductie en methode	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
08/02/2021	Doorsturen van eerste versie statistiek plan + voorlopig script Matlab	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
17/02/2021	Bespreking en feedback statistiek plan + overlopen script Matlab	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos

04/05/2021	Bespreking data-analyse, statistiek, script Matlab	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
06/05/2021	Oplossen van problemen: Verwerken script Matlab	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
08/05/2021	Doorsturen van voorlopige versie introductie, methode, deel resultaten	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
18/05/2021	Doorsturen van feedback-verwerking; intro, methode, resultaten, appendix + ideeën discussie	Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
24/05/2021	Doorsturen van voorlopige versie hele masterproef	Promotor: Prof. Dr. Peter Feys Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
Voor 07/05/2021	Feedback-verwerking masterproef deel 2	Promotor: Prof. Dr. Peter Feys Begeleider: Drs. Renee Veldkamp Student(e): Ruth Nijssen Student(e): Maxine Vos
HANDTEKENINGEN		

PROMOTOR

BEGELEIDER

STUDENTEN

Maxine Vos

24/05/2021
Ruth Nijssen