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Masterproef deel 2

Cognitive-motor interference in persons with MS: test-retest reliability of dual task assessment.

Highlights

The digit span walk, vigilance walk and subtraction walk have a good reliability in persons with MS and are recommended to use in clinical settings

There are various theories about the variability in DTC.

Adding a motor task to a mental task worsens performance by over 50% in PwMS not in controls

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CONTEXT OF THE MASTER THESIS

This master thesis is part of the research domain neurological rehabilitation, more specific neurological examination in Persons with Multiple Sclerosis (PwMS). A wide range of symptoms is found in PwMS. They suffer from cognitive impairments, walking dysfunctions, numbness in arms and legs, fatigue etc. For PwMS, it can be problematic to perform dual tasks in daily life activities. For example, walking while texting. Performing dual tasks can typically lead to a decline of the performance on one or both tasks, which is called Cognitive-Motor Interference (CMI). Since there is a relative high prevalence of this disease, which affectsdi young people, it is important to recognize and treat cognitive changes that have a large impact on Quality of Life (QoL) [1].

In clinical settings, it is necessary to use valid and reliable measuring instruments for assessing CMI. These instruments are initially to recognize PwMS that present difficulties with performing dual tasks, so that they can receive an adapted rehabilitation program. Persons with MS without cognitive impairment are more likely to participate in social activities than PwMS with cognitive deficits. An effective dual task training program is needed to improve the performance of daily life activities and to enhance QoL for PwMS. The rehabilitation needs to be efficient because MS produces substantial health care costs [2].

This master thesis part 2 is performed in the second master year at the University of Hasselt in Diepenbeek. The investigation took place at the research Centre REVAL in Diepenbeek and in the Rehabilitation & MS Centre in Overpelt.
This investigation is a duo master thesis, performed by two master students from the University of UHasselt: Jessy Lebbe and Hanne Snyers, under supervision of the promotor Prof. dr. Peter Feys and co-promotor Prof. Ilse Baert.

The introduction and method were each written by one of the students, with received feedback of Prof. Ilse Baert. The data extraction is performed in association with the copromotors.

The statistical analysis was performed by the two students independently and discussed until an agreement was reached.

The results and discussion was written by both students. Under supervision of Renee Veldkamp, the two students accompanied measurement moments in the Rehabilitation & MS centre in Overpelt and in the National MS Centre in Melsbroek.

In agreement with the promotor, the central format was applied for this thesis.

ACKNOWLEDGMENTS

We want to thank everyone who contributed to this master thesis. Dr. Ilse Baert for introducing us to the ongoing research. Also for helping us through the process, for the suggestions and the feedback. Renee Veldkamp for the guidance in measurement moments in the National MS Centre in Melsbroek and in the Rehabilitation & MS Centre In Overpelt. At last, we want to thank Prof. Dr. Peter Feys for overviewing this project and for the last modifications of the master thesis.

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Abstract

Background: Persons with Multiple Sclerosis (PwMS) have difficulties with performing dual tasks (DT) in daily life. This can lead to a decline in performance of one of the tasks, called Cognitive-Motor Interference (CMI).

Objective: The purpose of this study was to objectify the test-retest reliability of the DTC. The investigated dual tasks were walking activities while performing diverse cognitive tasks in PwMS and age-gender matched healthy controls (HC).

Design: A single-measures design was used.

Methods: Persons with MS, still working and being active in daily life, performed three cognitive tasks (titrated digit span backward, auditory vigilance and subtraction) and four walking tasks. Inclusion criteria were: Expanded Disability Status Scale score ≥2 and ≤ 6, Mini-Mental State Examination score ≥26 and no relapse or corticoid-therapy within the last 30 days. Tasks were assessed at two-time points with an interval of three to five days.

Results: Thirty-three patients with MS, between 38 and 65 years old, were included in the study. As for the reliability of DT motor parameters; subtraction walk, vigilance walk and digit span walk showed good Intraclass Correlations Coefficients (ICCs) and Spearman correlations coefficients. For the reliability of DT cognitive parameters, all test-retest reliability coefficients indicated a poor reliability.

Discussion and conclusion: The values of test-retest reliability of the cognitive DTC are lower compared to the motor DTC Cognitive performance showed lower test-retest reliability than motor in DT conditions. The digit span walk, vigilance walk and subtraction walk in the motor DT conditions have a good reliability and are recommended to use in clinical settings.

Introduction

Multiple Sclerosis (MS) is an autoimmune [3], chronic and degenerative disorder of the Central Nervous System (CNS) [4]. It affects the spinal cord, cerebellar pathways, the cerebellum, the brainstem and the optic nerve [5]. The disorder is characterized by inflammation, demyelination and neuronal degeneration [6] and is most prevalent in women and young adults age between 20 and 40 years old [7-11]. For the past three decades the total estimated prevalence rate of Persons with Multiple Sclerosis (PwMS) is 83 per 100.000 in Europe [6] and 2.3 million worldwide [12].

Multiple sclerosis has a wide variety of symptoms including, among others, fatigue, weakness or numbness in one or more limbs, impaired manual dexterity, lack of coordination, tremor and ataxia [13], bowel and bladder dysfunction [14] and visual disorders [15]. Cognitive impairment is present in 40-65% of PwMS (numbers vary between clinic and community based studies) and has a great impact on daily life beyond the physical aspect. Thus, cognitive deficits can disrupt the ability to maintain employment [16].

These cognitive impairments are domain-specific deficits; most frequently involved are long-term, explicit and episodic memory, complex attention, information processing speed and executive functions [17, 18]. Attentional capacity is with 22-25% the most common impaired cognitive domain in PwMS. They show slower and less accurate divided and sustained attention when compared to healthy controls (HC) [19]. Cognitive impairment was found in all disease stages and in all clinical phenotypes, although RR patients show less cognitive deficits compared to the PP and the SP phenotype [20]. Furthermore, walking dysfunctions are a major restriction in daily life for approximately 85% of the PwMS [21]. Persons with MS have, compared to HC, a reduced gait speed [22], a slower cadence, a shorter stride length [23] and a longer double support time [24]. They also show elevated gait variability and reduced knee and ankle motion [23, 25, 26].

In daily life, people are often required to combine walking and cognitive abilities. For example, walking on the street while talking on the phone or counting the money in your wallet while walking in the house [27].

However, simultaneous performance of motor and cognitive tasks can typically lead to a deterioration of the performance on one or both tasks [28]. This interaction of cognitive and motor tasks is called Cognitive-Motor Interference (CMI). There is evidence that PwMS experience CMI during dual-task walking [29] and that CMI is present in the earliest stages of MS [30]. For example, a large decrease in performance in PwMS occurs when performing dual tasks that challenge verbal fluency compared to tasks that require mental tracking [31]. In general, prioritizing a cognitive task or a motor task, depends on the patients' level of disability [25]. The CMI is usually investigated with a dual-task paradigm and is typically quantified in terms of Dual Tasks Cost (DTC). The DTC is the percentage of change in performance from single task to dual task condition [32]. Different dual task paradigms are used in which participants perform a motor task (e.g. walking or stepping over obstacles) and a cognitive task (e.g. subtracting, react on stories, word list generation (WLG)) separately and concurrently. When PwMS perform a dual task, gait parameters such as gait velocity are affected [29, 33]. Etemadi et al. [34] reported for gait velocity a dual task cost of 19.2%. Walking while performing a letter alphabet cognitive task reduced gait velocity by 15% in PwMS [35]. The addition of a cognitive task is not per se the cause of a slower walking speed, as Chien et al. reported a negative linear relation between gait variability and walking speed [36]. A slower walking speed by dual tasking, reflects to the gait speed-control areas that may be interlinked with the networks of executive functions that are necessary for multitasking [28, 37]. Hamilton et al. [33] states that in healthy controls, performing a dual task results in a lesser reduction in walking performance than PwMS. Although the review of Learmonth et al. [38] reported that CMI in both the lower and upper extremity is comparable for persons with and without MS.

Reliability is the degree to which a measurement is consistent and error-free. The reliability of different types and complexities of dual tasks paradigms to assess CMI need to be investigated, before it can be used as a clinical tool to detect impairments in PwMS. Knowledge on test-retest reliability of the measure is important and required for interpretation of changes in dual task performances. The systematic review of Yang et al. [27] concluded that the reliability of dual-task walking tests (10m walking, 5m turn walking, stepping in place etc.) was good for individuals with neurological disorders.

However, only one study revealed highly reliable outcomes when investigating the test-retest reliability of gait spatial-temporal parameters in PwMS in the cognitive motor dual-task *WLG walking* [39].

The psychometric properties (i.e., reliability, validity, responsiveness) of dual-task walking tests are understudied or unexplored in PwMS. Further examination on psychometric properties of DT walking in MS is needed.

Previously, many different types of cognitive confounders during walking were implemented without any documentation of psychometric properties of DT outcomes. Therefore, the aim of this study is to objectify the test-retest reliability of the DTC. The investigated dual tasks were walking activities with various complexity while performing diverse cognitive tasks in PwMS and age-gender matched HC.

Methods

Research design

This study is part of a multicenter study investigating cognitive-motor interference in persons with MS on dual task assessment and training. The tests for measuring cognitive motor interference, the primary outcome measure, were assessed three to five days after the test date for the demographic data and descriptive outcome measures. The CMI measures (single cognitive, single motor and dual cognitive-motor tasks) were repeated another three to five days later. Assessments took place at the same time of the day. There is a time window of maximum five plus five working days foreseen to complete the whole test battery at the different measurement points [fig 1].

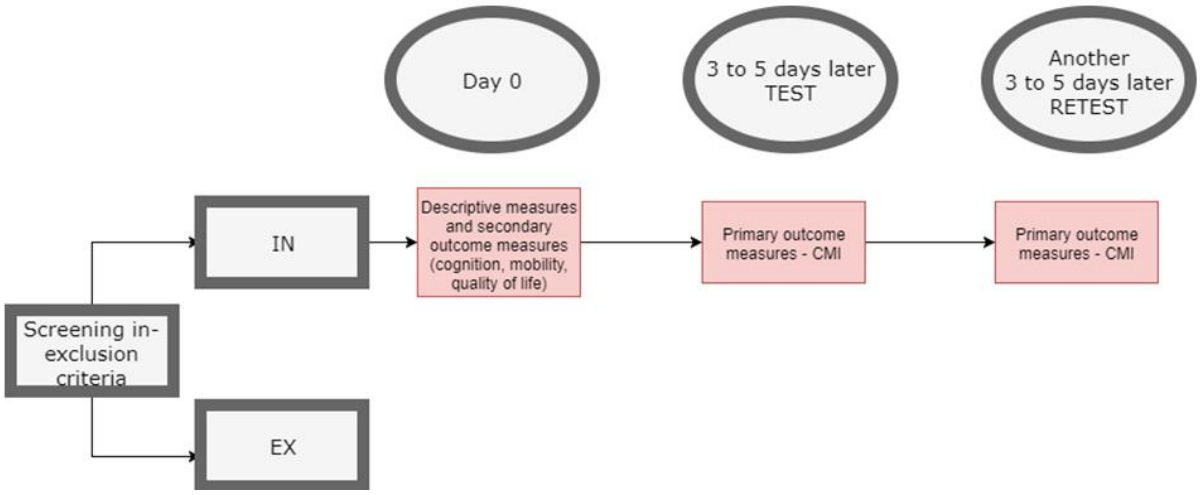

Figure 1 Overview test moments

All measures were assessed according to a standardized instruction booklet, including details on test procedures, verbal instructions and level of encouragement.

Participants

Patients diagnosed with MS, confirmed by a neurologist [5] and according to the McDonald criteria, participated in the investigation. All types of MS were included; Relapsing Remitting (RR), Primary Progressive (PP) and Secondary Progressive (SP). At least 20 PwMS are needed for a test-retest reliability study [40]. Thirty-three PwMS and 30 age-gender matched HC were assessed two times. They were recruited from the Masku Neurological Rehabilitation Centre in Finland and in Belgium in Centre Hospitalier Universitaire de Liège (CHU).

Eligibility criteria were age between 18-65 years old, an Expanded Disability Status Scale (EDSS) [41] score that was equal or larger than two and equal or smaller than five, which includes the ability to walk without an aid or rest some 200 m. The EDSS is determined by a neurologist or trained clinician. Another inclusion criterium was a score of one or more on the dual task screening list, meaning dual task interference was present.

Exclusion criteria were severely blurred vision, neuromyelitis optica, any other neurological condition (other than MS) that could interfere with the test procedure, a musculoskeletal condition interfering with mobility, a score below 26 on the Mini-Mental State Examination (MMSE), problems (even after adjustment with hearing aids or glasses) with hearing or vision interfering with the assessment, ongoing dual task training or other interfering physical therapy, cognitive training or neuropsychological rehabilitation. Participants who had a relapse within the last 30 days, who had changes in disease modifying treatment and no corticoid-therapy within the last 50 days were also excluded.

The inclusion criteria are focusing on PwMS who may still be working (fully or partly) and being quite active in daily life. Community living patients (outpatients) are recruited by MS societies, newsletters, neurologists, social media etc. After the procedure was explained to the participants, they signed an informed consent. The committee of medical ethics of the university of Hasselt (CME UHasselt) has agreed to this study in April 2017.

Descriptive outcome measures

Demographic data and descriptive outcome measures for QoL, cognitive and mobility performance were collected.

The population characteristics, measured at baseline, are: age, gender, disease duration since diagnosis, type of MS (RR, PP, SP), disability level (EDSS), use of foot orthoses (yes/no), history of falling past six months, employment status, education level based on Unesco International Standard Classification of Education (ISCED) and years of highest education. Intelligent Quotient (IQ) is usually normal in PwMS. Educational level was inventoried to make sure there was no difference in the level of knowledge [42].

Cognitive outcome measures

A psychologist or trained assessor assessed the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) [43]. The BRBNT incorporates the Selective Reminding test (SRT), the Spatial Recall test (SPART), the Paced Auditory Serial Addition test (PASAT), the Symbol Digit Modalities Test (SDMT) and the Controlled Oral Word Association Test (COWAT). The COWAT is called *word list generation* (WLG) in the BRB-NT. The SRT is a test of verbal memory acquisition and delayed recall. The participant is instructed to recall 12 words that the examiner reads at a rate of one word per two seconds. The participant has six trials. In every consecutive trial, only the words that are missed on the preceding trial are given. The score is the number of correct answers. Fifteen minutes after the six trials were administered, the participant is asked to recall the word list another time to test delayed recall.

In the SPART, visual memory acquisition and delayed recall are tested. A checkerboard containing a pattern of ten checkers is presented to the participant for ten seconds. After the checkerboard is removed, the participants are asked to reproduce the pattern. The participant has three trials. The score is the number of correct answers for each trial. Fifteen minutes after the first trial, a second trial is administered.

The SDMT is testing the participants sustained attention and concentration. The participant is presented with the numbers one to nine, each corresponding to a certain symbol.

Under the index, the participant is presented with rows of symbols and must fill in the correct number under each symbol. The PASAT is a test for attention, concentration, and speed of information processing. The participant is presented with single digits every three seconds using a tape to ensure standardization in the digit rate stimulus presentation. The participant is instructed to add each new digit to the one immediately prior to it. This test is also administered at a rate of two seconds per word. The scoring is the number of correct answers. Verbal fluency on sematic stimulus is tested with the WLG. The participant is asked to name as much words as possible within a given category in 90 seconds. The scoring is the number of correct answers.

Mobility outcome measures

A physiotherapist assessed diverse mobility performance scales, self-reported questionnaires and habitual walking. Performance scales quantified the mobility ability, while questionnaires give us a better insight in the participants' perception and behavioral consequences of disability problems. Mobility performance scales are: T25FW [44], the TUG [45], Dynamic Gait Index (DGI) [46] and 2 Minutes Walking Test (2MWT) [47]. The T25FW was performed at fast and usual speed to assess gait velocity. The participant is instructed to walk 25 feet as fast as possible, but also safely. The participant can use an assistive device. During the TUG, the patient is instructed to rise from a chair with armrest, walk three meters, turn back and sit down again. The DGI assess gait velocity, balance and fall risk. This is an 8-item test, including gait level surface, change in gait speed, gait with horizontal head turns, gait with vertical head turns, gait and pivot turn, step over obstacle, step around obstacle and steps. Each item is scored from zero to three. The 2MWT was assessed to capture walking endurance. Questionnaires (patient-reported outcome measures) included the Multiple Sclerosis Walking Scale-12 (MSWS-12) [48] to assess subjective walking ability and the Falls Efficacy Scale-International (FES-I) [49] to evaluate the concern about the possibility to fall.

Quality of life – participation

After the completion of the mobility measures, the psychologist or physiotherapist asked the participants to fulfill two questionnaires about the quality of life. The first one is the Multiple Sclerosis Impact Scale-29 items (MSIS-29) [50], an instrument measuring the physical (20 items) and psychological (nine items) impact of MS. The second is the Modified Fatigue Impact Scale (MFIS) [51], an instrument providing an assessment of the effects of fatigue in terms of physical, cognitive, and psychosocial functioning [52].

Experimental outcome measures

Cognitive-motor interference (primary outcome)

The interference between cognitive tasks and walking is quantified by the DTC. The DTC is calculated as a percentage of change in performance from single to dual task conditions. Single cognitive, single/dual motor and integrated cognitive-motor task were assessed. The order in which the blocks of single cognitive or single/dual motor or dual cognitive-motor tasks were performed were computer randomized, as well as the sequence of each separate task within one block (e.g. single cognitive evaluation), but remained the same in each test session for a participant. All tasks (single cognitive, single/dual motor and integrated cognitive-motor) were performed for one minute. Participants were allowed to take a break for about one and a half to two minutes between the trials to allow time for the assessor to set up the next trial. Halfway the dual task procedure, there was a break of five minutes during which participants complete the short dual tasking questionnaire developed by JJ Evans, 2009 [53].

Cognitive tasks

Three different cognitive tasks, evaluating various cognitive functions (working memory, information processing speed, sustained attention) at a high complexity level were used as cognitive distractors. The instructions were delivered by an auditory program through a developed tablet application and the participant responses were recorded via a wireless headset microphones (Logitech H800 USB Wireless Headset with Noise Cancelling Microphone) allowing the assessor to calculate afterwards the number of correct answers.

Titrated digit span backwards

Digit span loads working memory, as part of executive function. Participants listen to a titrated string of digits (e.g., 3-2-5-7-9), at the presented rate of one per second (this rate is standard in commonly used neuropsychological tests as 'Weschler Adult Intelligence Scales-III and Memory Scales'), and repeat them in the reverse order [2]. The sequence length was assessed for each patient in order to determine the participant's digit span (titrated): four trials were given at each sequence length starting from three-digit length. If three out of four trials at a given length are correct, the participant has passed that sequence length and the length was increase by one digit. Each participants digit span was determined as the last sequence length at which three out of four trials were correct.

Auditory vigilance with alphabets

Participants listened 60 seconds to recorded alphabets, at the presented rate of one letter per 2.5 seconds (24 letters all together of which ten target letters), and say aloud 'yes' every time she/he heard the targeted letter e.g. 'L' or 'R'. Target letters should be chosen as not very common or very rare in everyday speech, and are not easily confounded with other letters (each country has his own version based on some common rules). Same equipment and parameters were used as for the titrated digit span. Sustained attention is tested within this task, which is commonly affected in PwMS because 'cognitive fatigue' occurs [54].

Subtraction test

Information processing speed is measured with the subtraction task. Reduced information processing speed is an indicator for cognitive impairment in PwMS [55]. Performing the subtraction task, participants had to count backwards by seven, starting from a random number which appears on the application. Performance of this task was measured by the number of correct serial subtractions. Clear instructions, including an example were given, but no practical trial was allowed so learning effects could be avoided. Assessor should be sure the participants understand the task prior to the start of the assessment itself.

Motor tasks

This study includes common walking activities carried out in daily life. That is; walking at a self-selected speed, walking at a self-selected speed while carrying a cup of water, walking at a self-selected speed while stepping over low obstacles and walking at self-selected speed crisscross from cone to cone. The obstacles are 10 x 10 x 80 cm and lie every 3m in a straight line. The cones are placed every 2 m and stand within a fixed width of 80 cm [fig. 2]. These tasks will be called *walk*, *obstacles*, *crisscross* and *cup*. For *walk*, *obstacles* and *cup*, gait speed (m/s) will be registered. For *crisscross*, turning velocity (°/s) will be registered. The same (no by-passing persons) corridor of 30 m was used as testing location for each measurement with start and stop lines of 80 cm width where after the participants had to pivot briskly. For the safety of the participants, the examiner was walking behind the patient during the entire procedure.

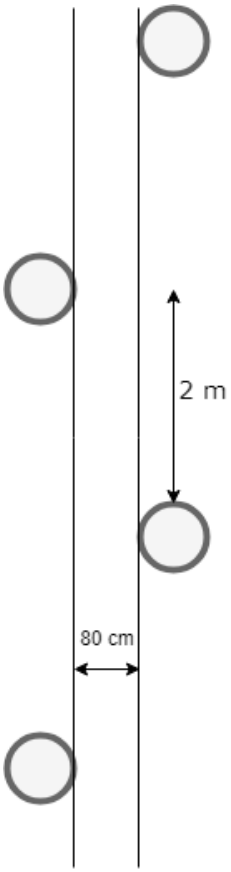

Figure 2 Setup cones

The analysis of the spatio-temporal gait parameters gait velocity and turning velocity was evaluated by wearable sensors (APDM) with the respective Mobility Lab Software. This portable technology has been used in a recent MS research study. The study showed its ability to detect mobility differences between MS and HC when traditional timed tests such as Timed 25 Foot Walk (T25FW) and Timed Up and Go (TUG) could not [56].

Dual cognitive-motor task performance

Participants were instructed to perform simultaneously the motor and cognitive task as followed: “Perform both tests at your best level”, so no prioritization of tasks was given. The combination of three cognitive and four motor tasks led to the performance of 12 dual cognitive-motor tasks. The assessments of each cognitive and motor task were performed using the same procedures described for the single cognitive or motor task conditions. The DTCs was calculated for diverse parameters of each DT paradigm as followed:

$$DTC_{cognitive}\ (\%) = \frac{(single{-}task\ cognitive\ score) - (dual{-}task\ cognitive\ score)}{single{-}task\ cognitive\ score}$$

$$DTC_{motor}\ (\%) = \frac{(single{-}task\ motor\ score) - (dual{-}task\ motor\ score)}{single{-}task\ motor\ score}$$

Statistical analysis

Data analysis was conducted for both descriptive and experimental measures. Data were analyzed using IBM SPSS Statistics for Windows version 24. Normality of the data was assessed with the Kolmogorov-Smirnov test, for both descriptive and experimental measures.

For the descriptive statistics, participant characteristics were compared between PwMS and HC using a t-test or the Mann Whitney U test. Mean and standard deviation were provided for normally distributed data, while median and interquartile range were provided for non-normally distributed data.

To assess the test-retest reliability between the DTC of test 1 and 2 (test and retest) of the PwMS and HC for normally distributed data, ICC values were calculated. Mean and standard deviation were provided. To calculate ICC values, a two-way random-effects model with absolute agreement was used. Cut-off values were used that are applied in Koo et al. 2016 [57]; values less than .5 are indicated poor, values between .5 and .75 are indicated moderate, between .75 and .9 good and values greater than .90 are indicative of excellent reliability. The Standard Error of Measurement ($SEM=SD_{pooled} X \sqrt{} [1-ICC]$) allows us to quantify the extent to which a test provides accurate scores. The Minimal Detectable Change (MDC) is calculated to determine whether a change in score can be significantly different without measurement error (Weir 2005). The MDC ($MDC=SEM X 1.96 X \sqrt{}[2]$) is used to estimate the smallest amount of change that can be detected and can be considered without measurement error. The t-tests and Cohen d effect sizes were derived from the test and retest to look for systematic differences between the tests. Effect size is a way to give an indication of the size of the difference between two groups. For non-normally distributed data, reliability was assessed using the Spearman correlation coefficient and Wilcoxon signed rank test determined differences between tests. These tests indicate the reliability and evaluate systematic differences between test, respectively. All *p* values less than .05 were considered as significant. Outliers were determined as having an absolute Z-score larger than three.

Results

Descriptive data

The clinical characteristics of the participants are presented in Table 1. Of the 63 participants, 27% were males and 73% were females. The mean age of the participants was 49.14 years. A difference can be observed in employment status between PwMS and HC. Eighteen percent of the PwMS was fully employed, while 77% of the HC was fully employed. Thirty-three participants were patients diagnosed with MS; 82% have relapsing-remitting MS, 9% have primary progressive MS and 9% have secondary progressive MS. The majority of PwMS (88%) did not use a walking aid in daily life. The mean disease duration of the 33 participants was 11.94 years. The median score of the EDSS was three (2-4) and the mean score of the MMSE was 29 (28-30) [table 1, Index 3].

Table 1 summarizes t-test scores and Mann Whitney U test scores for comparison between PwMS and HC. The t-test was used for eight descriptive measures that were normally distributed, the Mann Whitney U test was used for the other 12 descriptive measures. With regard to education level and BMI, PwMS and HC group were equal. For the cognitive descriptive measures, there was a significant difference between PwMS and HC for the SDMT and PASAT 3 seconds test. For all aspects of the mobility and QoL descriptive measures, except for the T25FW, there was a significant difference between PwMS and HC.

Reliability of DTC motor

PwMS

The ICC values of subtraction walk (.75) and vigilance walk (.80) indicated a good reliability [table 3]. The ICC values of .64 and .54 were indicative for a moderate reliability for the DT subtraction obstacles and vigilance obstacles respectively. Absolute values of effect sizes ranging from .02 to .66 were considered small. This is good, as small effect sizes mean there is no large difference between the test and the retest. The SEM for all motor DT was .01 with corresponding MDC values ranging from .02 to .04.

The Spearman correlation coefficient for DT digit span walk (.82) and vigilance cup (.73) were considered good and moderate respectively, both significant on a .01 level. The P-values, to detect systematic differences between test and retest, were larger than .05 for all DT except for the vigilance crisscross.

Healthy controls

All reliability coefficients for the motor DT were good or moderate. Ten DT conditions were normally distributed. The ICC values of digit span crisscross (.82) and digit span cup (.75) were good. The eight other ICC values ranged from .62 to .74. Absolute values of the effect sizes ranged from .03 to .50, which are all considered small. The SEM values were either .01 or .02 leading to corresponding MDC values of .02 to .05. The Spearman correlation coefficients of subtraction obstacles (.68) and subtraction cup (.86) were moderate and good. Both correlations were significant on a .01 level. The P-values of t-tests and Wilcoxon matched-pair signed-rank tests showed no systematic differences between the test and the retest, except for the DT subtraction cup.

Reliability of DTC cognitive

PwMS

For the DTC, all test-retest reliability coefficients indicated a poor reliability for the cognitive parameters. The ICC values of .18 and .04 were calculated for the DT subtraction obstacles and subtraction crisscross respectively. Effect sizes of the parametric test were small. The SEM for DT subtraction obstacles and subtraction crisscross number of correct answers was .03, leading to a MDC score of .09 number of correct answers. The Spearman correlation coefficients ranged from .01 to .37 for the other DT. Only for the DT digit span walk the Spearman Rho correlation coefficient of .37 was significantly different from 0 on a .05 level. The P-values did not show significant differences between the test and retest.

Healthy controls

For the DTC, all test-retest reliability coefficients indicated a poor reliability for the cognitive parameters. The ICC values ranged from .17 to .48 for subtraction obstacles, subtraction crisscross and subtraction cup. Effect sizes were small. The SEM for DT subtraction obstacles, subtraction crisscross and subtraction cup number of correct answers was .03. Corresponding MDC values were found to range between .08 and .09 number of correct answers. The Spearman correlation coefficients fluctuated between .08 and .44 for the other DT. Only for the DT subtraction walk, the Spearman correlation coefficient of .44 was significantly different from 0 on a .05 level. For the DT vigilance walk, vigilance obstacles and vigilance crisscross, there was a p-value smaller than .05, which indicated significant differences between the test and the retest.

Discussion

Reflection on the findings of this study

The aim of the current study was to objectify the test-retest reliability of the DTC during walking activities with various complexity while performing diverse cognitive tasks in PwMS and age-gender matched HC. Our primary findings are good reliability coefficients for the DTC that were calculated with the motor component *walking* as single task in PwMS and in HC. All DT conditions with the *crisscross* motor component in PwMS showed a poor test-retest reliability. As walking is already implemented in daily life, less attention is needed to perform this task well. In the *crisscross* task, it is possible participants need to divide their attention more between the motor and the cognitive task. There is more variability in the *crisscross* task than in the *walking* task. The reliability of the DTC including a cognitive single task were poor as well for PwMS as for HC. We also see a poor test-retest reliability in two out of the three DT conditions with the motor component *cup* and a poor reliability for one DT condition which included the *obstacles* component. Variations in gait parameters, such as step time and stride length, could have an influence on DT in individuals with neurological disorders [58], [78]. We expected lower DTC in HC and higher ICC values or Spearman Rho correlation coefficients. In eight out of twelve conditions, the ICC or Spearman Rho correlation was higher for the HC than for PwMS. We see no poor test-retest reliability values for the motor DT in HC. In most conditions, a moderate test-retest reliability was found. In the review of Sosnoff et al. [59] they argue that age, disability, walking and cognitive performance explained 17% of the variance in DTC and that the interaction between walking and cognition did not explain additional variance.

In general, the values of test-retest reliability of the cognitive DTC are lower compared to the motor DTC. All test-retest reliability coefficients for cognitive DTC are poor. It seems that for the cognitive DTC including the *vigilance* task, there is a low test-retest reliability. Almost all participants – PwMS and HC – have a maximal score of 24. The reason for this low reliability coefficient can be explained through the variability among participants or can be due to a small number of participants [60]. To demonstrate reliability, there needs to be a large variability among participants' scores. This low variability can be due to the vigilance task

itself, which has a low degree of cognitive challenge. For the subtraction task and the digit span, in which information processing speed and working memory are tested, a possible explanation could be that for these cognitive tasks it is more difficult to divide attention between the cognitive and motor task. Al-Yahya et al. and Allali et al. state that adding a motor task (walking) to a challenging mental tracking task worsens performance by over 50% in PwMS but not in controls [61, 62].

Also, gait is more a habitual behavior and cognitive tests need more goal directed control [33]. The review of Redgrave et al. [63] reported that a more pronounced learning effect may be greater for cognitive tasks than for gait tasks.

When assessing dual-tasks, outcomes are influenced by the given instructions prior to each trial, with respect to task prioritization. Instructions should be clear and understandable for the patient and each patient should be given the same instructions [44, 64]. For the cognitive and motor DT, we noticed that values for motor vigilance cup and cognitive vigilance walk in HC are lower than in PwMS. We expected a good test-retest reliability in HC, because they experience less fluctuations in their physical or cognitive performances than PwMS [65, 66].

So far, there are two theories to explain DTC. The central capacity sharing model, as well as the central bottleneck model, argue there is a central stage of information processing that is capacity limited. The central capacity sharing model states that two different tasks can be performed at the same time at the expense of both tasks. That is when both tasks require common limited resources. According to this theory, it should be possible to perform two tasks simultaneously, without dual-task interference. In contrast, the bottleneck model basically demonstrates that two tasks cannot be performed well at the same time. Automatically one task will be prioritized and therefore performing a DT, will be at the expense of one of both tasks. In regard to our results, we believe that the central capacity sharing model is more accurate, because in some participants we see a perfect performance of both tasks. In few cases e.g. for the subtraction cup cognitive DT in HC [table 3], we noticed that the dual task was even better than the single task [67, 68].

In PwMS and HC, the SEM values of both motor and cognitive parameters were low, ranging from .01 to .03. This indicates minimal variability in both groups. In the control group, the highest SEM values were found in cognitive DT 'subtraction', which is comparable to the patients' group. Clinical relevant DT changes are indicated by MDC values. The MDC values in our study range from .02 to .09, which means participants have to score 2% to 9% better or worse on the retest to attribute this change to a possible training effect. Those values are important for making clinical decisions, increasing clinical applicability and to translate from evidence to practice [69]. As it is difficult to determine whether an alteration in a person's physiological performance is due to experimental conditions or natural changes or rehabilitative interventions, MDC values are useful in finding the factor that is responsible for the change [70]. Analyzing the descriptive measures, we expected no significant differences between PwMS and HC for the cognitive measures SRT, SPART and WLG, because a minimal score on the MMSE was an inclusion criterion. However, we expected a significant difference for the PASAT and the SDMT, because participants are tested on processing speed. Processing speed is affected in PwMS, even in an early stage of MS. Only the PASAT 2 seconds did not meet the expectations, as the p-value of the performed Mann-Whitney U-test was .05. Therefore, we could not determine a significant difference between PwMS and HC. As was said in the introduction, cognitive deficits can disrupt the ability to maintain employment. In table 1, we see a large and significant difference in employment status between HC and PwMS. Although motor deficits can be challenging to maintain employment, we think cognitive impairments are a greater obstacle to be able to continue working [16].

Clinical implications

We need to be aware that PwMS experience difficulties in daily life activities, as was made clear through the dual task questionnaire. It is important that this is considered in the clinical assessment and treatment. Similar to our study, Hamilton F. et al. [33] reported that when two tasks are attempted at once, the performances of both tasks will decrease.

In the expert review of Wadja et al. [71], which included 220 articles of interventions targeting CMI, they concluded that there are promising results for improving dual tasking in MS. In our study, we see that cognitive performance is no predictor for the motor performance and vice

versa. This brings into question if we could improve DTC by adjusting only the cognitive or only the motor task.

In this study, the good reliability levels of the motor DTC in PwMS suggest that the digit span walk, vigilance walk and subtraction walk tests are reliable to be used in clinical settings. Those tests are representative to daily life activities and do not require high-technological nor expensive materials.

Reflection on the strengths and weaknesses of this study

A strength of the present study is the large sample size, with 33 PwMS and 30 HC. The HC group stimulates the understanding of the specificity of our results for PwMS. The large sample size of our study is preferable and provides more evidence regarding the test-retest reliability of the measurements. Participants would respond differently to tests reflecting other cognitive subdomains. In our study, three different cognitive tests are used. This is an advantage because different functions such as working memory, sustained attention and information processing speed are tested. The effect of these three functions on dual tasking is also being tested. Another strength of the study is the level of difficulty of the cognitive tasks (digit span and subtraction test). For example, the digit span test has the possibility to determine the ability of the patient before starting the test. It remains challenging for the patient and will keep motivating them. When assessing cognitive tasks, assessors should be cautious that learning effects do not occur. For example, in the digit span test in our study, the participants receive each test moment a different titrated string of digits. The advantage is that participants become not familiar with the position of the numbers [72].

Our study had several limitations. Firstly, our results are not based on the entire population of PwMS. Most of the included participants did not use a mobility aid (88%), reported an EDDS score between two and six and reported having relapsing-remitting MS (82%). Thus, the DT walking paradigm may not be appropriate for PwMS that are more disabled [35]. Another limitation of this study is that in some none-conditions, patients scored ‘0’ on single tasks. However, these data are valid and valuable, it is not possible to calculate the DTC.

Thereafter, cognitive performance may be affected more in PwMS with a higher EDSS stage than gait performance, because of many factors such as fatigue, emotional state, attention and a good night sleep prior to testing [73]. Fatigue is a subjective lack of physical and/or mental energy, which the participant perceives as interfering the desirable activity [74]. The prevalence of fatigue in PwMS ranges from 70% to 90%. Patients are feeling most fatigued in the afternoon or evening [75]. Another study investigated the effect of time on day on walking at five different test times, between 08:00 and 22:00. They did not find systematic changes in gait speed [76]. During a testing day, one patient was worried that her test results may not be good, because she had been drinking alcohol the night before.

Before the tests and retests were assessed, we thought learning effects would occur. Learning effects can influence DT outcomes. On the first testing day when CMI measures were assessed, the patients had no expectations from the operation of the tasks, no feeling with the different routes and could not yet estimate the height of the obstacles. Our idea was that the second testing day, the movements would be more automatically and learning effects would occur. So, the score on the retest would be better, meaning the DTC of the retest is lower. Analyzing the results of our investigation, we do not see this phenomenon and can therefore conclude no learning effects were present in this study.

Recommendations for further research

In some clinical studies, the use of medication could have a negative influence on practice effects and can affect the test-retest reliability of DT outcomes in persons with cognitive impairments such as Parkinson's disease and Huntington's disease. It is recommended to analyze how this factor could determine the reliability outcome measures [72].

At this moment, the Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modality Test (SDMT) are most frequently used to assess sustained attention and information processing speed. The PASAT and SDMT are valid screening tools for cognitive impairment, but we do not know if the PASAT and the SDMT are good predictors for the presence of CMI. Therefore, we recommend that the correlation between PASAT and SDMT on the one hand and DT on the other hand is investigated [77].

Conclusion

In our study, we found that cognitive performance showed lower test-retest reliability than motor in DT conditions. The digit span walk, vigilance walk and subtraction walk in the motor DT conditions have a good reliability and are recommended to use in clinical settings.

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Appendices

TABLES

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Table 1

Descriptive data (N=63)

T-test scores and Mann Whitney U scores for comparison PwMS and HC

		PwMS	HC	Compa-rison	t-Test value	P Valu
Demographic	**Age (y),** X (SD)	49.15 (9.17)	49.13 (9.13)		.01	.99
	Disease duration (y), X (SD)	11.94 (10.57)				
	EDSS [0-10], MED (IQR)	3 (2-4)				
	MMSE (/30), MED (IQR)	29 (28-30)				
	Gender M-F (%)	27% - 73%	27% - 73%			
	Type of MS (RR-PP-SP)	82% - 9% - 9%				
	Walking aid in PwMS (yes/no)	12% - 88%				
	Employment status, MED (IQR)	3 (2-4)	1 (1-1)	.00*		
	Education level, MED (IQR)	3 (2-3)	3 (2-4)	.37		
	Fully employed	18%	77%			
	Unemployed	12%	0%			
	Retired	46%	10%			
	Partly employed	24%	13%			
	BMI (kg/cm²), MED (IQR)	24.61 (20.52-26.88)	24.24 (22.12-28.19)	.66		
Cognitive	**SRT Longterm** [0-62], X (SD)	52.00 (10.31)	55.32 (10.85)	.12	-1.27	.21
	SRT Consistent Longterm [0-62], X (SD)	41.71 (14.10)	48.00 (14.91)	.07	-1.75	.09
	SPART [0-30], X (SD)	20.82 (5.29)	20.84 (4.42)	.92	-0.01	.99
	SDMT [0-110], X (SD)	45.91 (16.90)	55.03 (10.57)	.01	-2.58	.01*
	PASAT 3sec [0-60] , MED (IQR)	43 (37-54)	55 (43-58)	.03*		
	PASAT 2sec [0-60] , MED (IQR)	31 (27-40)	42 (27-51)	.05		
	WLG [0-50] , MED (IQR)	23 (20-35)	29 (18 -37)	.54		
Mobility	**T25FW (s)** , X (SD)	1.22 (0.22)	1.32 (0,22)	.14	-1.68	.10
	T25FW fast (s), X (SD)	1.66 (0.32)	1.86 (0,28)	.00	-2.76	.08
	TUG [0-30] , MED (IQR)	6.64 (6.21-7.69)	5.51 (5.38-5.98)	.00*		
	MSWS-12 [0-60] , MED (IQR)	27.50 (16.75-39.50)	12 (12-12)	.00*		
	DGI [0-24] , MED (IQR)	23.50 (21-24)	24 (24-24)	.00*		
	FES-I [0-64] , MED (IQR)	24.50 (19.75-32.25)	17 (16-17)	.00*		
	2MWT (m) , X (SD)	188.47 (36.30)	224.29 (25.31)	.00	-4.57	.00*
QoL	**MSIS-29** [0-145] , MED (IQR)	52.00 (45.75-68.25)	29 (29-32)	.00*		
	MFIS [0-84], MED (IQR)	35 (21-51)	0 (0-6)	.00*		
	DTQ questionnaire [0-40], X (SD)	14.06 (6.95)	5.19 (4.58)	.00	6.01	.00*

*Significant different at the 0.05 level (2-tailed)

Comparison= Mann Whitney U test p-values

Abbreviations table 1

BMI	Body Mass Index
DGI	Dynamic Gait Index
DTQ	Dual Task Questionnaire
EDSS	Expanded Disability Status Scale
FES-I	Fall Efficacy Scale International
MFIS	Modified Fatigue Impact Scale
MMSE	Mini Mental State Examination
MSIS	Multiple Sclerosis Impact Scale
MSWS	Multiple Sclerosis Walking Scale
PASAT	Paced Auditory Serial Addition Test
PP	Primary Progressive
RR	Relapsing Remitting
SDMT	Symbol Digit Modalities Test
SP	Secondary Progressive
SPART	Spatial Recall Test
SRT	Selective Reminding Test
T25FW	Timed 25 Foot Walk
TUG	Timed Up and Go
WLG	Word List Generation
2MWT	2 Minutes Walking Test

Table 2

Test-retest scores

Motor DT in PwMS	Test X (SD)	Retest X (SD)	Wilcoxon Value	t-Test Value	P Value	Spearman Rho	Effect Size (d)	ICC (95% CI)	SEM	MDC
Digit span walk	.10 (.07 - .22)	.13 (.07-.19)	214.00		.51	.82**				
Digit span obstacles	.13 (.11)	.09 (.08)		1.73	.09	.48**	.42	.45	.01	.03
Digit span crisscross	.11 (.11)	.12 (.08)		-.37	.71	.35*	-.09	.29	.01	.03
Digit span cup	.14 (.12)	.11 (.08)		1.13	.26	.76**	.28	.47	.01	.04
Subtraction walk	.16 (.09)	.15 (.08)		.59	.56	.72**	.14	.75	.01	.03
Subtraction obstacles	.15 (.09)	.12 (.07)		1.32	.19	.65**	.41	.64	.01	.03
Subtraction Crisscross	.15 (.08 - .19)	.14 (.07-.16)	177.00		.06	.34				
Subtraction cup	.12 (.11)	.12 (.08)		-.10	.92	.76**	-.02	.48	.01	.03
Vigilance walk	.08 (.08)	.09 (.06)		-.56	.58	.77**	-.14	.80	.01	.02
Vigilance obstacles	.05 (.09)	.04 (.06)		.37	.71	.61**	.09	.54	.01	.02
Vigilance crisscross	.06 (.07)	.12 (.11)		-2.66	.01*	.55**	-.66	.39	.01	.03
Vigilance cup	.06 (.01 - .11)	.06 (.03-.10)	279.00		.98	.73**				

*Correlation is significant at the 0.05 level (2-tailed)

**Correlation is significant at the 0.01 level (2-tailed)

Table 2

(Continued)

Cognitive DT in PwMS	Test X (SD)	Retest X (SD)	Wilcoxon Value	t-Test Value	P Value	Spearman Rho	Effect Size (d)	ICC (95% CI)	SEM	MDC
Digit span walk	.18 (-.03 - .50)	.10 (.00-.22)	146.00		.19	.37*				
Digit span obstacles	.17 (.00-.48)	.17 (.00-.27)	139.50		.54	.21				
Digit span crisscross	.17 (.00-.47)	.21 (.00-.28)	176.50		.76	.01				
Digit span cup	.14 (.00 - .27)	.12 (-.10-.29)	152.50		.56	.05				
Subtraction walk	.16 (-.15 - .22)	.18 (.00-.33)	371.00		.11	.16				
Subtraction cup	.13 (-.29 - .29)	.08 (.00-.24)	286.00		.46	.03				
Subtraction obstacles	.17 (.32)	.16 (.19)		.17	.87	.39*	.04	.18	.03	.09
Subtraction crisscross	.09 (.31)	.13 (.22)		-.60	.55	.14	-.15	.04	.03	.09
Vigilance walk	.00 (.00-.04)	.00 (.00-.00)	58.50		.14	.26				
Vigilance obstacles	.00 (.00-.04)	.00 (.00-.04)	94.50		.69	.05				
Vigilance crisscross	.00 (.00-.04)	.00 (.00-.04)	98.50		.81	.22				
Vigilance cup	.00 (.00-.06)	.00 (.00-.02)	64.00		.12	.07				

Table 2

(Continued)

Motor DT in HC	Test X (SD)	Retest X (SD)	Wilcoxon Value	t-Test Value	P Value	Spearman Correlation Coefficient	Effect Size (d)	ICC (95% CI)	SEM	MDC
Digit span walk	.11 (.07)	.12 (.07)		-.45	.65	.64**	-.12	.66	.01	.03
Digit span obstacles	.13 (.08)	.11 (.07)		.83	.41	.74**	.21	.70	.01	.03
Digit span crisscross	.15 (.13)	.16 (.14)		-.18	.86	.77**	-.07	.82	.02	.05
Digit span cup	.16 (.10)	.13 (.07)		1.39	.17	.86**	.36	.75	.01	.03
Subtraction walk	.16 (.08)	.15 (.07)		.48	.64	.71**	.12	.69	.01	.03
Subtraction obstacles	.12 (.10 - .21)	.12 (.08-.22)	190.00		.26	.68**				
Subtraction crisscross	.17 (.13)	.18 (.12)		-.37	.72	.75**	-.09	.69	.02	.04
Subtraction cup	.14 (.10 - .22)	.12 (.07-.18)	80.00		.00*	.86**				
Vigilance walk	.08 (.06)	.09 (.06)		-.70	.49	.78**	-.18	.74	.01	.02
Vigilance obstacles	.08 (.07)	.08 (.07)		-.41	.69	.69**	-.10	.65	.01	.03
Vigilance crisscross	.05 (.08)	.10 (.09)		-1.95	.06	.61**	-.50	.62	.01	.03
Vigilance cup	.10 (.07)	.10 (.07)		-.13	.90	.73**	-.03	.70	.01	.03

Table 2

(Continued)

Cognitive DT in HC	Test X (SD)	Retest X (SD)	Wilcoxon Value	t-Test Value	P Value	Spearman Correlation Coefficient	Effect Size (d)	ICC (95% CI)	SEM	MDC
Digit span walk	.00 (-.13 - .38)	.00 (-.13 - .10)	135.00		.30	.24				
Digit span Obstacles	.11 (.00 - .29)	.13 (.00 - .25)	186.50		.78	.11				
Digit span Crisscross	.13 (.00 - .34)	.13 (.00 - .25)	153.00		.39	.26				
Digit span Cup	.11 (.00 - .24)	.10 (.00 - .20)	128.50		.54	.08				
Subtraction walk	.11 (-.14 - .27)	.09 (-.01 - .20)	248.00		.75	.44*				
Subtraction obstacles	.04 (.28)	.11 (.19)		-1.04	.30	.18	-.27	.17	.03	.09
Subtraction crisscross	.06 (.25)	.14 (.16)		-1.46	.15	.59**	-.38	.48	.03	.08
Subtraction cup	-0,05 (.25)	.06 (.17)		-1.96	.06	.21	-.13	.25	.03	.08
Vigilance walk	.00 (.00-.04)	.00 (.00 - .00)	4.00		.03*	.16				
Vigilance obstacles	.00 (.00-.08)	.00 (.00 - .00)	5.00		.01*	.09				
Vigilance crisscross	.00 (.00-.04)	.00 (.00 - .00)	0.00		.00*	.20				
Vigilance cup	.00 (.00-.04)	.00 (.00 - .04)	56.50		.80	.26				

Index 1

Principal investigators and recruiting centers

Recruiting centers, only for assessment

- Masku Neurological Rehabilitation Centre, Finland (P.Hämäläinen and A. Romberg
- Centre Hospitalier Universitaire de Liège, Belgium (X. Giffroy)

Index 2

Employment status

- Fully employed
- Partly employed because of MS with or without disability benefits
- Unemployed looking for work, because of MS with or without disability benefits
- Retired because of health or age

Index 3

Educational level based on ISCED (Unesco International Standard Classification of Eductation, 2011)

Category 1

- Level 0 – Early childhood education
- Level 1 – Primary education
- Level 2 – Lower secondary education (general, vocational)
- Level 3 – Upper secondary education (general, vocational)
- Level 4 – Post-secondary non-tertiary education

Category 2

- Level 5 – Short-cycle tertiary education

Category 3

- Level 6 – Bachelor's or equivalent level (academic, professional)

Category 4

- Level 7 – Master's or equivalent level
- Level 8 – Doctoral or equivalent level

Category 5

- Level 9 – Not elsewhere classified

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KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
26/06/2017	Algemene uitleg protocol MP2 + uitleg gebruik van tablet met cognitieve oefeningen	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e): Snyers Hanne
07/08/2017	Uitleg protocol + doel MP2 Taakverdeling data analyse tussen Jessy en Hanne	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e): Snyers Hanne
26/09/2017	Jaarplanning MP2 overlopen Vragen m.b.t. protocol Data analyse besproken	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e): Snyers Hanne
02/10/2017	Tablet met oefeningen uitproberen	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e): Snyers Hanne
24/10/2017	Bespreking statistiek	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e): Snyers Hanne
14/11/2017	Bespreking inleiding en methodologie	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e): Snyers Hanne
06/03/2018	Bespreking methodologie en uitvoering van statistiek	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e):
20/03/2018	Bespreking resultaten en statistiek	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e):
16/04/2018	Bespreking tabellen statistiek Bespreking inleiding versie 3 Bespreking inhoud resultaten en discussie	Promotor: Feys Peter Copromotor: Baert Ilse Student(e): Lebbe Jessy Student(e): Snyers Hanne
29/05/2018	Bespreking feedback methodologie en resultaten	Promotor: Feys Peter Copromotor: Renee Veldkamp Student(e): Lebbe Jessy Student(e): Snyers Hanne

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Cognitive-motor interference in persons with MS: test-retest reliability of dual task assessment

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2018**

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Voor akkoord,

Snyers, Hanne **Lebbe, Jessy**