Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effects of cognitive-motor dual task training compared to single motor training in Multiple Sclerosis: a multicentre randomized clinical trial

Mieke Goetschalckx
Kathleen Grieten

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

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Acknowledgement

We would like to thank prof. Dr. Peter Feys and dra. Renee Veldkamp to guide us through our master thesis. We acknowledge the medical MS centers in Belgium (National MS Center Melsbroek, De Mick AZ Klina Brasschaat, Revalidatie & MS centrum Overpelt), Israel (Sheba Medical Center), Italy (Italian Multiple sclerosis society), participants and trainers to cooperate in the multicenter, single-blind randomized clinical trial.

Hasselt, 01/06/2019 G.M and G.K.

Context

It is generally accepted that persons with Multiple sclerosis (pwMS) suffer both from motor as well as cognitive impairments. Moreover, recent research reported that both cognitive and mobility impairments can have a detrimental effect on quality of life, functional independence and health perception in pwMS. Besides, pwMS have problems with dual tasking, that can be described as 'the concurrent performance of two tasks that can be executed independently, measured separately and have distinct goals.' (McIsaac, Lamberg, & Muratori, 2015). CMI has both practical and clinical consequences. Therefore, an appropriate rehabilitation strategy that incorporate both motor, cognitive as well as cognitive-motor dual task impairments in pwMS is needed. The evidence of Dual task training (DTT) in pwMS is limited, although, a recent feasibility study reported promising results of a dual task gait training program in pwMS (Sosnoff et al., 2017), but highlights the need for further research to compare the effect of dual-task training to traditional single task training. A better understanding the effect of dual task training (DTT) compared to single mobility training (SMT) in patients with multiple sclerosis can guide and improve patient specific clinical practice.

The growing interest in cognitive motor interference pwMS can be reflected by the several ongoing research projects within the neurological rehabilitation department at REVAL, university of Hasselt. A small 'research & development' pilot project was financed by the Flemish MS Society and conducted in 2015-2016 in collaboration with three MS centers (RMSC Overpelt, NMSC Melsbroek, De Mick Brasschaat) and engineering groups at Hasselt University and PXL. An electronic prototype of an assessment- and training-application has been developed together with physiotherapists and neuropsychologists. Thereafter, the application was expanded to prepare for an international multi-center approach. The international, multi-center study was funded and commenced by the European network for MS rehabilitation (RIMS) and co-funded by the Swedish PROMOBILIA Foundation and the Sailing4MS. Furthermore, a reliability study of the various cognitive-motor dual tasks used in the present randomized clinical trial was performed from September 2016 till April 2017 and the results of this study will be published in Neurorehabilitation and Neural Repair (NNR) journal soon. Subsequently, a multicentre randomized clinical trial into the effects of

integrated cognitive-motor dual task training on cognitive-motor interference in pwMS was conducted from December 2016 till July 2018.
Protocol establishment, approval of the ethical committees, patient recruitment and data collection were conducted in Belgium by Dr. Ilse Baert, Dra. Renee Veldkamp and Fanny van Geel. Mieke Goetschalckx and Kathleen Grieten attended data collection sessions in National MS Center Melsbroek. Data collection was finished by July 2018, where after the data files were checked independently by Mieke Goetschalckx, Kathleen Grieten and Dra. Renee Veldkamp. The statistical plan was composed by Dra Renee Veldkamp in cooperation with a statistician providing services to BIOMED, Mieke Goetschalckx and Kathleen Grieten. Data processing was performed independently by Mieke Goetschalckx, Kathleen Grieten and Renee Veldkamp. Whenever a discrepancy between data results existed, they reflected how they accomplished the results and discussed the possible differences until a consensus was reached.

Academical writing was conducted by Mieke Goetschalckx and Kathleen Grieten. The master thesis is constructed according to "International Committee of Medical Journal Editors – ICMJE (2015). The manuscript was written by Mieke Goetschalckx and Kathleen Grieten. Suggestions of prof. Peter Feys and PhD student Renee Veldkamp were considered.

The effects of cognitive-motor dual task training compared to single motor training in Multiple Sclerosis: a multicentre randomized clinical trial.

Goetschalckx M. and Grieten K.

26 May 2019, Hasselt University, Belgium

Research questions

What are the effects of cognitive-motor dual task training (DTT) compared to single mobility training (SMT) on cognitive-motor interference and absolute dual task performance in patients with multiple sclerosis during cognitive-motor dual tasks with different complexity levels.

What are the effects of cognitive-motor dual task training (DTT) compared to single mobility training (SMT) on functional mobility, cognition, fatigue, quality life and self-reported dual task difficulty in daily life in patients with multiple sclerosis?

Highlights

- Dual task training has a superior effect compared to single motor training, to reduce dual task cost of walking velocity while performing cognitive tasks as digit span and subtracting. This effect is observed immediately after the intervention and retained at four weeks follow-up period.
- Only dual task training was able to improve walking performance in more complex dual task conditions such as walking over obstacles while performing a cognitive task.
- The cognitive dual task cost, nor the single or dual task cognitive performance were significantly changed after dual task training or single mobility training.
- Both dual task training and single mobility training are effective in improving functional mobility and cognition.
- No significant differences were observed in self-reported secondary outcomes of quality of life, fatigue and dual tasking in daily life over time and between groups over the intervention period.

Authors: Goetschalckx Mieke and Grieten Kahtleen
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Abstract

Background: Persons with multiple sclerosis (pwMS) experience difficulties during cognitive-motor dual tasks (DT) resulting in cognitive-motor interference (CMI).

Objectives: The purpose of this multicenter randomized clinical trial is to investigate the effect of dual task training (DTT) compared to single mobility training (SMT) on cognitive-motor interference (CMI), motor, cognitive and mood characteristics.

Methods: Forty-seven pwMS participated in an eight-week single-blind, multicentre randomized clinical trial and four-week follow up. Subjects in DTT-group underwent DT training while SMT group performed gait and balance exercises. All participants performed three motor, three cognitive and nine cognitive-motor DT before training, after intervention and after follow up. To test hypothesis a linear mixed model was used. Primary outcomes were CMI, measured by dual task cost (DTC) and absolute single- and dual task performances. Secondary outcomes were functional mobility, cognition, self-reported fatigue, quality of life and DT in daily life.

Results: Multiple comparison revealed a superior effect of DTT compared to SMT to reduce DTC of walking velocity while performing cognitive tasks. Moreover, DT gait velocity during walking over obstacles with cognitive tasks improved only after DTT. No significance interaction effect, nor a main effect of time or group was found on cognitive DTC and cognitive performances. After both interventions, functional mobility, assessed by the T25FWT fast, TUG and DGI, and cognitive function, assessed by the SDMT, PASAT 3” and PASAT 2” improved significantly. No significant changes occurred in self-reported quality of life, fatigue and difficulty of dual tasking in daily life.

Conclusion: An eight-week DTT has a superior effect compared to SMT on CMI of walking while performing cognitive tasks in pwMS. Moreover, only DTT improved motor performance during more complex dual tasks. However, both DTT and SMT can be recommended to improve functional mobility and cognition in pwMS.

Keywords: Multiple sclerosis, Dual task training, dual task cost, cognitive motor interference, walking

Introduction

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system (CNS) characterized by inflammation and demyelination in multiple regions of the CNS (Selter & Hemmer, 2013). The clinical course of MS is progressive and highly variable across patients (Jacques, 2015). Motor and cognitive impairments are common in persons with MS (pwMS). Half of the pwMS in Europe experience mobility problems in the first month of diagnosis and more than 90% within 10 years of diagnosis (Kotelnikova et al., 2017; Motl & Learmonth, 2014). The prevalence of cognitive impairments in MS ranges from 40 to 70% (McIntosh-Michaelis et al., 1991; Rao, Leo, Bernardin, & Unverzagt, 1991) with memory, processing speed, attention and executive functions among the most affected domains (Rogers & Panegyres, 2007). Both cognitive and mobility impairments can have a detrimental effect on quality of life, functional independence and health perception in pwMS (Kratz et al., 2017; Paltamaa, Sarasoja, Leskinen, Wikstrom, & Malkia, 2007; Sacca et al., 2017).

Dual tasking, such as walking while talking, is a common everyday act that can be defined as 'the concurrent performance of two tasks that can be executed independently, measured separately and have distinct goals.' (McIsaac et al., 2015). Dual tasking can lead to different patterns of changes in the performance of the single tasks, with combinations of facilitation and interference (Plummer et al., 2013). A deterioration in single task performance during dual tasking is called cognitive-motor interference (CMI) (Al-Yahya et al., 2011) and can be quantified by the dual task cost (DTC), i.e. the percentage of change in dual task performance compared to the single task performance (Leone, Patti, & Feys, 2015). In healthy subjects and elderly, it is accepted that CMI assessment during walking is a good reflection of the interaction between cognition and mobility in daily life (Brustio, Magistro, Zecca, Liubicich, & Rabaglietti, 2018). Although, CMI is present in all humans, it is often greater in persons with nervous system diseases, i.e. pwMS (McIsaac, Fritz, Quinn, & Muratori, 2018). Experimental studies examining the effect of the simultaneous execution of a motor (e.g. walking) and cognitive task in pwMS report a deterioration of dual task walking performance compared to single task walking, shown by a decrease in gait speed and cognitive performance in DT conditions (Leone et al., 2015; Postigo-Alonso et al., 2018; Sirhan, Frid, & Kalron, 2018; Wajda & Sosnoff, 2015). Most of the studies assess CMI during walking. However, more complex tasks like walking over obstacles and walking while carrying a cup, are a better representation of daily life. Recently, a study of Veldkamp et al. (2019) reported that walking, walking while carrying a cup and obstacles are reliable to examine CMI during more complex tasks (Veldkamp, et al., 2019). Besides, it seems that the occurrence of CMI during walking has both practical and clinical consequences. Etamadi Y. et al. (2017) found that a higher DTC of cognitive performance during walking is related to a higher fall risk in pwMS (Etemadi, 2017). Moreover, Castelli et al. (2016) concluded that the occurrence of CMI during a dual standing balance task, may contribute to a reduced quality of life in pwMS (Castelli et al., 2016). These observations highlight the functional importance of CMI during daily life and the need for rehabilitation strategies for CMI in pwMS.

Rehabilitation programs are important to improve motor problems, cognitive dysfunctions, functional independence and quality of life (Khan & Amatya, 2017; Prosperini, Piattella, Gianni, & Pantano, 2015). In the past, motor and cognitive impairments were treated separately. Single task repetitive training may result in an increased automatization and allows a greater attention allocation toward the concurrent tasks during dual tasking (Silsupadol et al., 2009). However, evidence suggests an interaction between motor and cognitive function (Motl.R. et al. 2016; Learmonth et al.,2017) and highlights the need for training the simultaneous performance of motor and cognitive task in a dual task paradigm (Leone et al., 2015; Motl, Sandroff, & DeLuca, 2016). Two hypotheses are proposed to explain the added value of dual task training (DTT) over single task training on CMI. First, DTT might be effective in reducing CMI by producing an efficient integration of the two tasks (Hirst, S. Spelke, C. Reaves, Caharack, & Neisser, 1980; Ruthruff, Van Selst, Johnston, & Remington, 2006). Secondly, there is growing evidence for the need of task-specific training in neurological rehabilitation (Hubbard, Parsons, Neilson, & Carey, 2009; Prosperini et al., 2015). In this way specific dual task gait training can improve dual task gait performance. Studies reported positive results of dual-task training on postural stability, single and dual task gait performance in neurological diseases, fall-prone populations, older adults and dementia (Fritz, Cheek, & Nichols-Larsen, 2015; Ghai, Ghai, & Effenberg, 2017). The studies of Motl et al. (2016) and Leone et al. (2015) also highlight the need for training the simultaneous performance of motor and cognitive task in a dual task paradigm in pwMS

The evidence of DTT in pwMS is limited, although, a recent study reported promising results of a dual task gait training program in pwMS (Sosnoff et al., 2017). Specifically, a trend towards improved dual task gait speed and visuospatial memory was reported after a dual task training program involving gait and balance training while performing cognitive exercises, which was not reported in the single task training group. However, no changes in cognitive dual task performance was seen in any training groups after intervention. Caution is warranted when interpreting the results because of the small sample size and thus limited power. The lack of conclusive evidence may also be explained by the low training intensity, low disability level of the included patients and the task paradigm that may not be challenging enough.

The primary aim of this randomized controlled trial is to investigate the effect of dual task training (DTT) compared to single mobility training (SMT) on cognitive motor interference, measured by dual task cost, and single and dual motor and cognitive task performance in patients with multiple sclerosis during cognitive motor dual tasks.
We hypothesize that after training, an improvement in motor and cognitive DTC, and dual task performance will be observed in the DTT group, but not in the SMT group. This improvement will be seen immediately post-intervention and will be retained after a 4 week follow up period. Moreover, we hypothesize that both interventions will lead to an improvement in single task walking performance, but only the DTT group will improve single cognitive performance after the intervention period. Our secondary aim is to investigate the effect of DTT compared to SMT on functional mobility, cognition, fatigue, quality of life and self-reported dual task difficulty in daily life. We hypothesize that the functional mobility, will improve after the both interventions. However only cognition, quality of life, fatigue and self-reported dual task difficulty in daily life will improve more after DTT.

Methods

The study was multicentred, single-blind, randomized clinical control trial examining the effect of 8-weeks of DTT compared to SMT. The study was approved by the Ethical Committee of CHU Liège, Belgium, as well as by the local ethical committees from each participating centre and executed according to the Helsinki declaration.

Participants

Participants from medical MS center Belgium (National MS Center Melsbroek, AZ Klina capmpus De Mick rehabilitation Brasschaat, Revalidation & MS center Overpelt), Israel (Sheba Medical Center) and Italy (Italian Multiple sclerosis society) were enrolled in the present multicenter, randomized clinical trial between September 2016 and January 2018. Inclusion criteria were: (a) diagnosis of MS according to McDonald criteria, (b) age between 18 and 65 years old, (c) Expanded Disability Status Scale (EDSS) ≥2 and ≤ 6 as determined by neurologists or trained clinician, (d) no relapse within the last 30 days, (e) no changes in disease modifying treatment and no corticoid-therapy within the last 50 days, (f) minimal cognitive function as measured with the Mini Mental State Examination (MMSE) ≥26. Participants were excluded if they had (a) other medical conditions that could interfere with mobility, (b) other neurological diagnoses, (c) MS-like syndromes such as neuromyelitis optica, (d) major problems with hearing or vision interfering with the assessment or training or if they, (e) were not able to understand and execute simple instructions, (f) followed ongoing dual task training, interfering physical therapy, cognitive training or neuropsychological rehabilitation during the intervention period. The feasibility study of Sosnoff et al. (2017), regarding DTT in pwMS, recommended that a minimum sample of 20 participants in each intervention group to observe significant changes in dual task performance (Sosnoff et al., 2017). All participants received written information and signed informed consent.

Procedures

This study was a multicenter, randomized two-arm controlled trial consisting of an integrated dual task training (DTT) and a single mobility training group (SMT). Participants initially completed baseline assessment where after they were randomly assigned to either the DTT or SMT group through sealed envelopes by the study project coordinator (I. Baert), who was not involved in intervention delivery or outcome assessment. Stratification was used to balance the potential confounding variables (disability level (EDSS), age and gender). In both groups, participants trained under individual supervision for 8 weeks, 5 times over 2 weeks, leading to a total of 20 sessions. Blinded assessment of the primary and secondary outcome measures was performed at baseline, after 8 weeks intervention (post) and 4 weeks after the training period (follow up). To optimize inter-rater reliability of measurement procedures between participating centers, an instruction booklet has been created with the aim to standardize test procedures. Moreover, test-retest reliability of the assessment protocol was examined (Veldkamp, et al., 2019). Results of the reliability study reported a lower reliability of the crisscross condition, cognitive DTC and cognitive performances. Therefore, we do not discuss the crisscross condition and report shortly the results of the cognitive outcomes. A schematic overview of the study design is shown in figure 1.

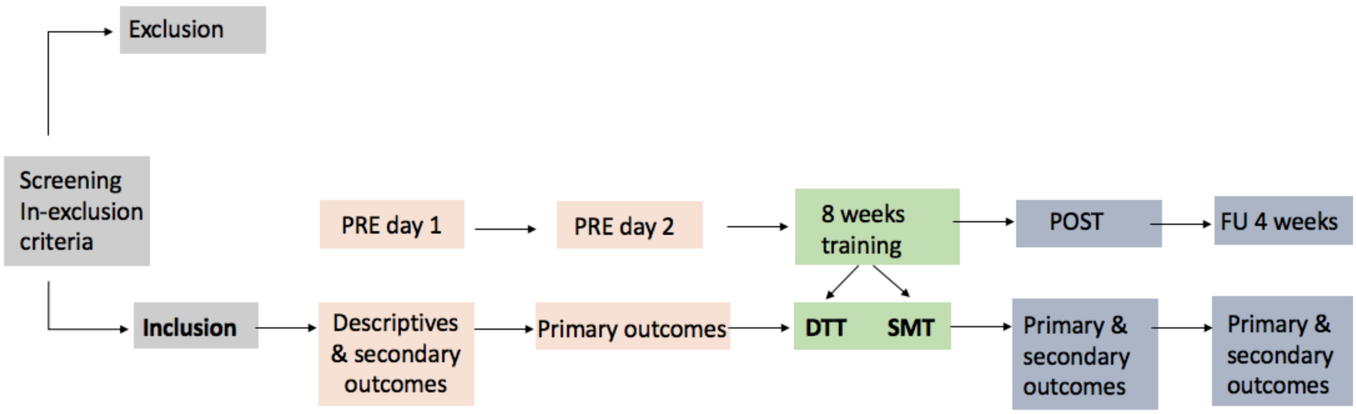

Figure 1. Study design

Outcome measures

Primary outcomes

The primary outcome measures were motor and cognitive DTC of nine integrated cognitive-motor dual tasks, as well as absolute motor and cognitive performances during single and dual tasks. CMI was expressed in terms of dual task cost (DTC), for both cognitive and motor measures, with the following formula:

$$\text{Motor DTC} = \frac{ST\ motor - DT\ motor}{ST\ motor} x\ 100$$

$$\text{Cognitive DTC} = \frac{ST\ cognitive - DT\ cognitive}{ST\ cognitive} x\ 100$$

To assess single and dual task gait and cognitive performance, participants completed three single-motor (normal walking, walking while carrying a cup and walking while stepping over obstacles), three single-cognitive (titrated digit span backwards, auditory vigilance with alphabets and serial seven subtraction), and nine integrated cognitive-motor dual tasks for one minute. During the single motor and dual cognitive-motor tasks, gait speed (m/s) was recorded by three wearable APDM sensors, placed around each ankle and in the lower lumbar region, with Mobility Lab software (Portland, USA). To support assessment and dual task training methodology, a tablet application has been developed in 2016 within a multi-disciplinary team consisting of physical and occupational therapists, neuropsychologists and rehabilitation doctors in interaction with engineers of UHasselt (EDM/IMO) and PXL in Flanders. A paper describing the development and design of the tablet application is currently being written (Tacchino, Veldkamp, Feys et al. not yet published). During the single cognitive and dual cognitive-motor tasks, cognitive stimuli were delivered by auditory speech via a headset microphone (Logitech H800 USB Wireless Headset with Noise Cancelling Microphone) with noise cancelling. Verbal responses were noted by the assessor and audio recorded on the specifically developed tablet application. Cognitive task performance was expressed as percentage of correct answers by the formula: (amount correct answers / total amount answers) x 100.

Blocks of single-cognitive, single-motor and cognitive-motor dual task as well as the order of the tasks within each block were randomized by computer randomization. This order remained the same in each test session for each participant. Participants could pause 1.5 to 2 minutes between the trials to allow time for the assessor to set up the next trial. To avoid any prioritization between the tasks, participants were instructed to perform both, motor and cognitive, tasks at the best of their ability. Halfway through the dual task assessment there was a break of 5 minutes, during which participants completed the short dual tasking questionnaire (Evans, Greenfield, Wilson, & Bateman, 2009).
For a more detailed prescription of the test setting, we refer to Supplementary figures 1-2.

Secondary outcomes

Secondary outcomes measurements included measurements of functional mobility and cognitive function, as well as self-reported quality of life, fatigue and dual task difficulty measures.

Seven functional mobility outcomes were recorded: 25-Foot Walk performed at usual speed (T25FW, seconds) (Motl et al., 2017), T25FW test fast speed (seconds), Timed Up and Go (TUG, seconds) (Podsiadlo & Richardson, 1991), Multiple sclerosis Walking Scale (MSWS-12) (Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2003), Dynamic gait index (DGI) (Shunway-Cook, 1995), Fall efficacy scale (FES) (Yardley et al., 2005), and the 2 minute walk test (2MWT) (Gijbels, Eijnde, & Feys, 2011)

Participant's cognitive function was assessed by a trained assessor who administered the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) (Boringa et al., 2001; Sepulcre et al., 2006). The BRB-NT includes eight tests that assess different domains of cognitive functioning in the following order: Selective Reminding Test (SRT), Spatial Recall Test (SPART - 10/36), Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test 3" (PASAT 3) and PASAT 2", Selective Reminding Test -Delayed (SRT-D), Spatial recall test -delayed (SPART-D-10/36) and Word List Generation test (COWAT). At post-intervention and follow-up measurements, only parallel versions of the SDMT and the PASAT were administered.

Two self-reported questionnaire, the Multiple sclerosis impact scale (MSIS-29) and the Modified fatigue impact scale (MFIS), were used to assess the impact of MS and fatigue on the quality of life, respectively (Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2004; Rietberg, Van Wegen, & Kwakkel, 2010). From both questionnaires, a total score (range MSIS-29: 29-145; range MFIS: 0-84), physical impact score and psychosocial impact score will be derived. From the MFIS, also a cognitive fatigue sub scores will be computed. Self-reported difficulty with dual tasking in daily life will be assessed by the dual task questionnaire (DTQ) (range 4-40) (Evans et al., 2009).

Intervention

All participants trained under supervision for 8 weeks, with a frequency of 5 times over 2 weeks (1 week 2*, other week 3*) leading to a total of 20 sessions. All trainers were physical therapist specialized in neurological rehabilitation. Before the start of the intervention, all trainers received the same instruction booklet with specific guidelines and internal agreements to prevent performance bias and so decrease heterogeneity in intervention between participants and centers other than the interventions of interest. The trainers and participants were not blinded.

The DTT consisted of walking or stepping on the spot while simultaneously performing a cognitive task. An interactive and adaptive application with therapist interface for dual task training was developed to support dual task training. The application contains eleven exercises in diverse cognitive domains with varying sublevels of difficulty. Each session, 5 to 6 cognitive domains were trained (8 to 15 exercises). Participants were instructed and encouraged to perform both tasks (cognitive task and walking/stepping) at their best capacity, without prioritization. During all exercises, cognitive and mobility performance were evaluated to allow progression to a higher/lower difficulty level therefore patients trained at an adequate level. For safety reasons, the therapists walked behind the patient, hereby preventing that participants adapted his speed to the therapist's walking speed. A more detailed specification of the cognitive exercise can be found in Supplementary table 1.

SMT focused on gait and dynamic balance exercises. Progression to a higher difficulty level was based on the quality judgement of performance by the therapist observation. Each session, the therapist documented which exercises the participant performed and at which level. A more detailed program can be found in Supplementary table 2.

In both groups, the perceived exertion after each training session was assessed by the Borg 15-point Ratings of Perceived Exertion Scale (Borg RPE) (Cleland, Ingraham, Pitluck, Woo, & Ng, 2016). The Borg RPE scale is a numerical scale that ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." At the end of the 8 weeks intervention period, an Intrinsic Motivation Inventory (IMI) was administered, along with open questions like strengths and weaknesses of the training and prioritization of tasks. The IMI assessed participant's interest/enjoyment, perceived competence, effort, value/usefulness, felt pressure and tension, and perceived choice while performing the training (Ryan, 1982).

Statistical analysis

All the data analysis was performed with the statistical program (JMP Pro 14). Distribution of continuous data was visually checked for normality using a normal quantile plot. If the assumption of normality was met, differences in baseline characteristics between DTT and SMT group was examined by an independent Student's t test. The non-parametric Wilcoxon rank sum test was used if the assumption of normality was not met. Fisher's exact test and Pearson chi square test were used for nominal data. To test the hypotheses, a per protocol analyses was used, where only participants who completed the intervention were included. A linear mixed model was applied with type of training (DTT, SMT), time (PRE, POST, FU) and the interaction between type of training and time as fixed factors. Participants were included as random factor. Two-sided p-values were set at an α level of 0.05. Bonferroni correction ($\alpha^* = \alpha$ / # tests) was applied for multiple comparisons. If the assumption of normal distribution was not met, change values for the outcome measures were calculated by subtracting the baseline data (PRE) from the post-intervention data (POST) and FU-data from POST-data. To compare change values between groups, a two-sided independent Student's t test or Wilcoxon signed rank test were applicated. A similar analysis was performed for all secondary outcomes.

Results

Participants

The participant's flow through the study period is outlined in Figure 2. A total of 47 pwMS were randomized in either DTT (n=24) or SMT (n=23) group, whereof 16 participated in Belgium, 11 in Israel and 20 in Italy. The dropout rate was 14.9%: four participants dropped out of the DTT group, while three patients dropped out of the SMT group. The main reason was time constraints, unrelated to the nature of the intervention (n=7). The participants who dropped out showed no significantly different characteristics from those who completed the study (see Table 1. Demographic characteristics). No adverse events were reported during the study period. Mean % of missing data in the motor DTC and cognitive DTC was 3%. Missing data was due to technical or human errors. Participant's characteristics as a function of group are reported in Table 1. There were no significant group differences in mean age, gender, EDSS, disease duration, type of MS or the need of a walking aid.

Table 1. Demographic characteristics of participants in the DTT and SMT groups

	DTT (n=20) (mean ± SD)	**SMT (n=20)** (mean ± SD)	**p-value DTT vs. SMT**	**Drop-outs (n=7)**	**p value drop-outs vs. participants**
Age (years)	51.4 ± 9.3	53.4 ± 9.2	n.s	49.5	n.s
Gender (F/M %)	60.0/ 40.0	55.0/45.0	n.s	85.7/14.3	n.s
MS subtype (RR/SP/PP%)	65/20/15	65/15/20	n.s	85.7 (RR) missing: n = 1	n.s
EDSS (0-10)	3.4 ± 1.0	3.7 ±1.2	n.s	3.92±1.1	n.s
Year since diagnosis	9.6±7.7	11.4±9.8	n.s	12.4 ±10.1	n.s
Walking aid (n: yes/no)	7/13	3/17	n.s	1/5 missing: n = 1	n.s

Abbreviations: DTT, dual task training; SMT, single mobility training; n, number; vs, versus; F, female; M, male; MS; Multiple Sclerosis; RR, relapsing remitting; SP, secondary progressive; PP, primary progressive; EDSS, Expanded Disability Status Scale

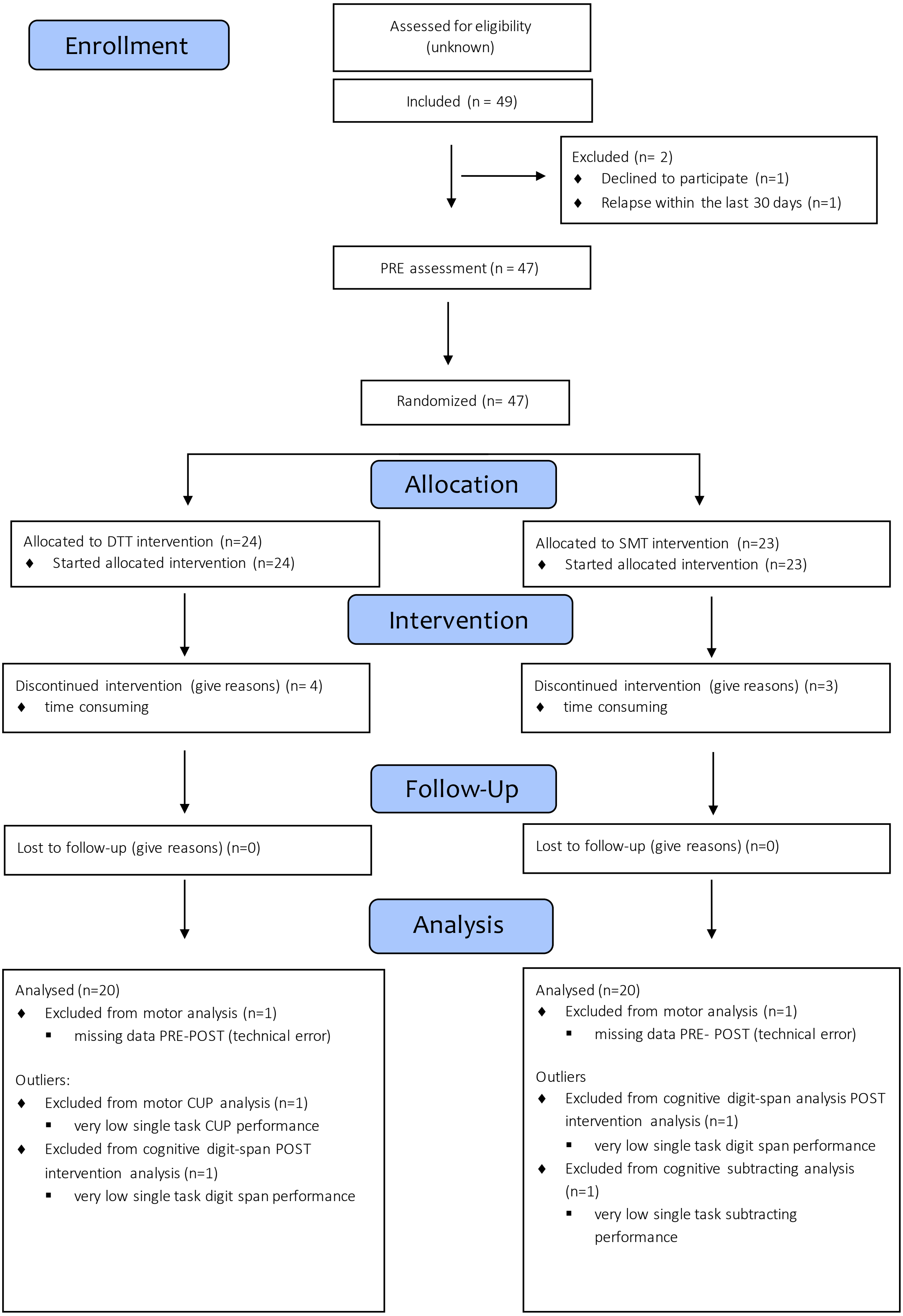

Figure 2. Consort flow diagram.

Pre-intervention

At baseline level, there were no significant differences in primary, nor in secondary outcomes between groups. Tables 2-3 and Supplementary tables 3-6 (PRE Colom) rapport mean primary and secondary outcomes as a function of group and time as well as linear mixed model analysis.

Primary outcome measures

MOTOR dual task costs

The motor DTCs as a function of group and time point, during all cognitive-motor dual tasks, and linear mixed model analysis, are shown in figure 3. and tables 2 (Walk condition), 3 (Obstacle condition) and 4 (CUP condition). An interaction effect of group*time was found for the DTC of walking velocity in the W-DS (p=.015) and W-SU (p=.006) conditions. Multiple comparisons revealed a significant improvement in favour of the DTT group in DTC for W-DS (p=.003) and W-SU (p=.003) condition after the training period. This effect was retained during the FU period. Also, an interaction effect of group*time was found in the OB-VI (p=.042) and CUP-VI (.015) conditions. After the SMT intervention, motor DTC of walking velocity deteriorated during OB-VI and CUP-VI, while no significant difference of motor DTC occurred after the DTT intervention. No interaction effects were found in the other conditions. However, a significant main effect of time was observed in the W-VI (p=.025) condition. Multiple comparisons revealed a decrease in DTC of walking velocity in the W-VI condition after both intervention programs that was retained over the FU period. A main effect of group was observed in CUP-DS (.036) and CUP-SU (.011) conditions with a significant higher motor DTC in the SMT group POST intervention and at FU compared to the DTT group.

Single and dual task MOTOR performances

The motor performances as a function of group and time point, during all single motor and cognitive-motor dual tasks, and linear mixed model analysis are reported figure 4 and tables 2 (Walk condition), 3 (Obstacle condition) and 4 (CUP condition). A significant interaction effect of intervention group*time was observed in OB-DS (p=.003), OB-SU (p=.026) and OB-VI (p=.004) conditions. Multiple comparison revealed a significantly improvement for the DTT group for all dual task OB performances (OB-DS, OB-SU, OB-VI) that was retained during the FU period. Moreover, POST intervention, a significant higher walking velocity in DTT group compared to SMT group was found in all dual task obstacles conditions. A significant effect of time was observed for all dual task walking conditions (W-DS (p=.023)**,** W-SU (p=.035) and W-VI (p=.015)), indicating that the dual task walking velocity improved after both interventions over baseline. In the CUP condition, no main effect of time, group, nor an interaction effect of time* group was observed.

COGNITIVE dual task cost, single and dual task COGNITIVE performance

No significant interaction effect of time*group, nor a main effect of time or group was found on cognitive DTC and cognitive performances in any condition. However, a significant main effect of time was found for the DS-OB (p=.006) condition. Participants' DS-OB dual task performance improved significantly at follow-up compared to baseline in both training groups. Moreover, a trend of improved cognitive single task DS performance (p = .051) after the intervention was seen in both training groups. Primary cognitive outcome measures as a function of group and time point, during all cognitive-motor dual tasks, are reported in Supplementary tables 3-5.

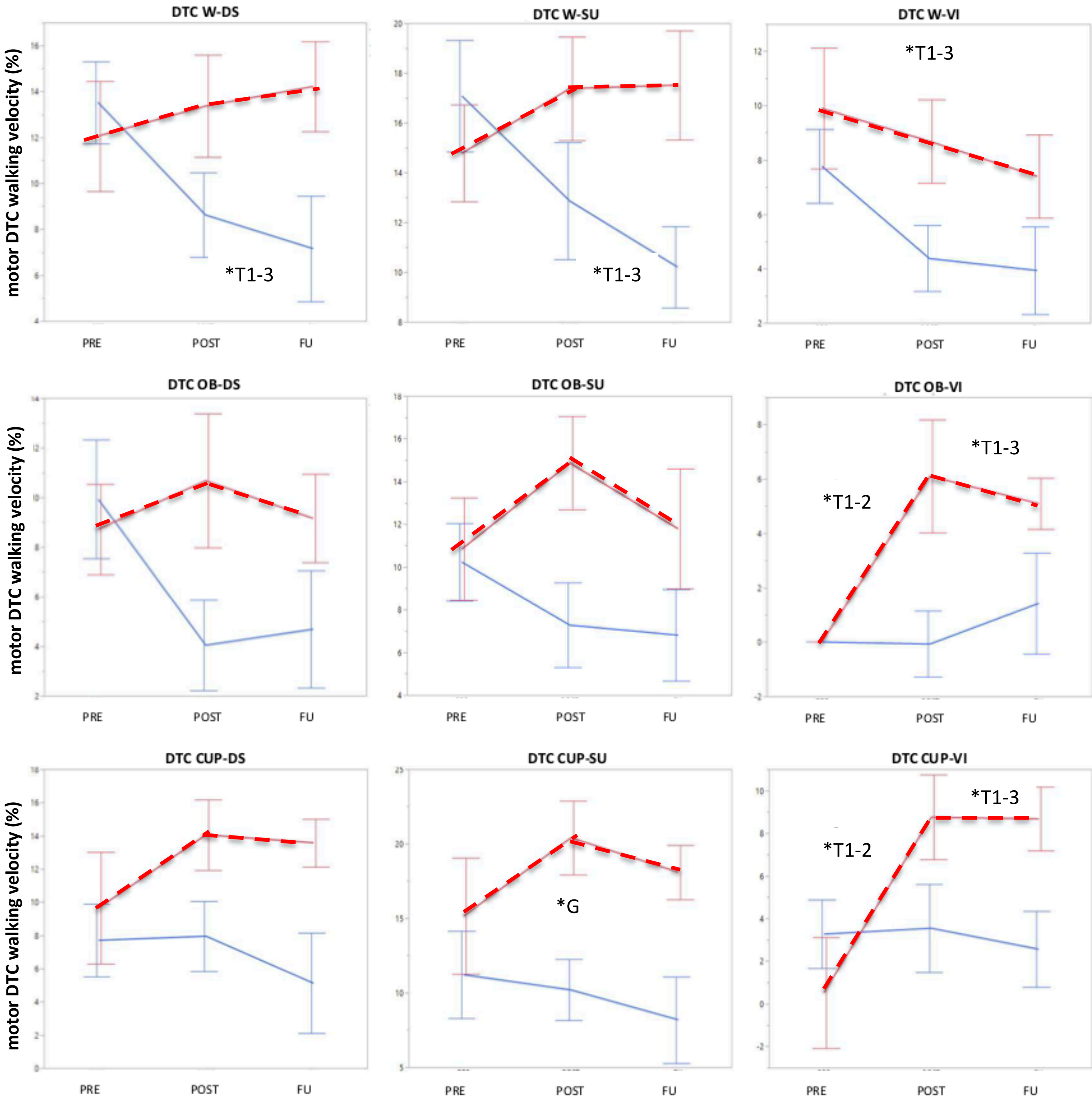

Figure 3. Linear mixed model analysis, Mean % and standard error of motor dual task cost (DTC) as a function of group over time

*Abbreviations: Dotted red line represents Single mobility training (SMT); Solid blue line represents dual task training (DTT), Error bars represents standard deviation, walk (W), Obstacles (OB), Digit span (DS), Subtracting (SU), Vigilance (VI), Significant interaction effect of the linear Mixed models are indicated by *, Significant time effect of the linear Mixed models are indicated by *T, 1 = PRE, 2=POST, 3=Follow up (FU), Significant group effect of the linear Mixed models are indicated by *G*

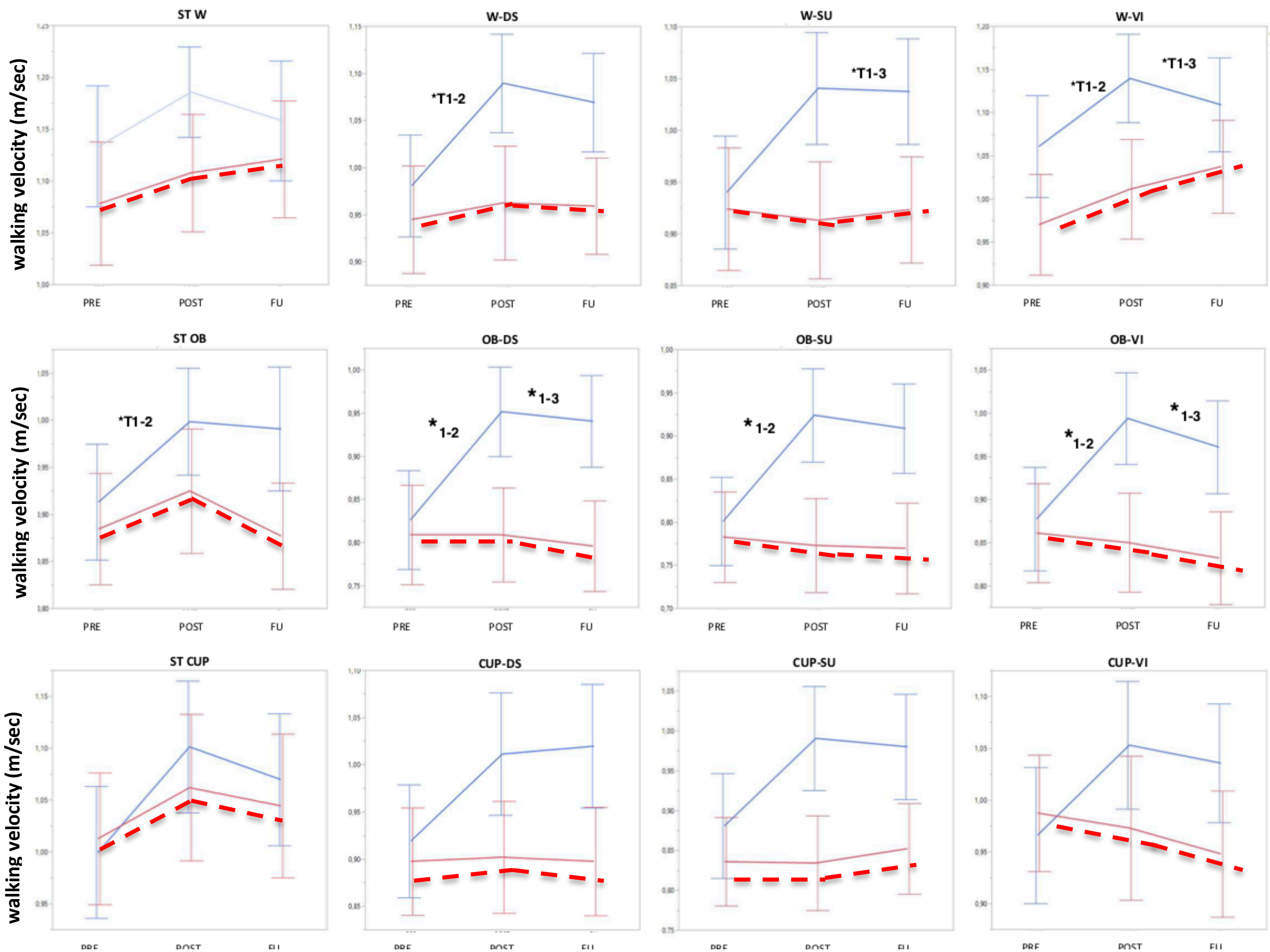

Figure 4. Linear mixed model analysis, Mean % and standard error of motor performances (walking velocity, m/sec) as a function of group over time

*Abbreviations: Dotted red line represents Single mobility training (SMT); Solid blue line represents dual task training (DTT), Error bars represents standard deviation, Single task (ST), Walk (W), Obstacles (OB), Digit span (DS), Subtracting (SU), Vigilance (VI), Significant interaction effect of the linear Mixed models are indicated by *, Significant time effect of the linear Mixed models are indicated by *T, 1 = PRE, 2=POST, 3=Follow up (FU)*

Table 2. Means and standard deviation of motor dual task cost and performances during “Walk” condition as a function of group over time

Condition	Outcomes	Group	PRE Mean± SD	POST Mean± SD	FU Mean± SD	Mixed model analysis Time	 Group	 Time*Group	Multiple comparison		
W	**velocity (m/s)**	**DTT**	1.13± 0.25 (n=18)	1.19± 0.18 (n=18)	1.16± 0.25 (n=19)	n.s.	n.s.	n.s.			
		SMT	1.08± 0.26 (n=19)	1.11± 0.23 (n=17)	1.12± 0.25 (n=19)						
W-DS	**velocity (m/s)**	**DTT**	0.98± 0.23 (n=18)	1.09± 0.22 (n=18)	1.07± 0.23 (n=19)	**0.023**	n.s.	n.s.	**T1-2** **0.012**	T1-3 0.028	T2-3 0.678
		SMT	0.95± 0.25 (n=19)	0.96± 0.25 (n=17)	0±96± 0.23 (n=19)						
	DTC	**DTT**	13.53± 7.90 (n=18)	8.62±7.81 (n=18)	7.15± 9.99 (n=19)	n.s.	n.s.	**0.015**	**DTT 1-2** **0.024**	**DTT 1-3** **0.003**	DTT 2-3 n.s.
		SMT	12.06±10.45 (n=19)	13.37± 9.46 (n=18)	14.22± 8.58 (n=19)				SMT 1-2 n.s.	SMT 1-3 n.s.	SMT 2-3 n.s
									DTT-SMT 1 n.s.	DTT-SMT 2 n.s.	**DTT-SMT 3** **0.016**
W-SU	**velocity (m/s)**	**DTT**	0.94± 0.23 (n=18)	1.04± 0.23 (n=18)	1.04± 0.22 (n=19)	**0.035**	n.s.	n.s.	**T1-2** **0.037**	**T1-3** **0.017**	T2-3 n.s.
		SMT	0.92± 0.25 (n=18)	0.91± 0.23 (n=17)	0.92± 0.22 (n=19)						
	DTC	**DTT**	17.08± 9.55 (n=18)	12.86± 9.99 (n=18)	10.21± 7.10 (n=19)	n.s.	n.s.	**0.006**	**DTT 1-2** **0.026**	**DTT 1-3** **0.003**	DTT 2-3 n.s.
		SMT	14.78± 8.26 (n=18)	17.38± 8.84 (n=18)	17.52± 9.53 (n=19)				SMT 1-2 n.s.	SMT 1-3 n.s.	SMT 2-3 n.s
									DTT-SMT 1 n.s.	DTT-SMT 2 n.s.	**DTT-SMT 3** **0.016**
W-VI	**velocity (m/s)**	**DTT**	1.06± 0.24 (n=17)	1.14± 0.22 (n=18)	1±11±0.24 (n=19)	**0.015**	n.s.	n.s.	**T1-2** **0.014**	**T1-3** **0.009**	n.s.
		SMT	0.97± 0.26 (n=19)	1.01± 0.24 (n=17)	1.04± 0.23 (n=19)						
	DTC	**DTT**	7.78± 5.61 (n=17)	4.371± 5.167 (n=18)	3.93± 7.04 (n=19)	**0.025**	n.s.	n.s.	**T1-2** **0.045**	**T1-3** **0.010**	T2-3 n.s.
		SMT	9.91± 9.68 (n=19)	8.69± 6.51 (n=18)	7.40± 6.68 (n=19)						

Abbreviations: Single mobility training (SMT); Dual task training (DTT), Dual task cost (DTC), Walk (W), Digit span (DS), Subtracting (SU), Vigilance (VI), amount of data present in each group (n), not significant (n.s.), significant effects after Bonferroni correction (0.05/3 = 0.016) are indicated ***red*** *and bold, p values in* ***bold*** *are not significant after Bonferroni correction, comparison between outcome measures at pre-post intervention are indicated by T1-2, comparison between outcome measures at pre intervention and follow-up are indicated by T1-3, comparison between outcome measures at post intervention and follow-up are indicated by T1-2*

Table 3. Means and standard deviation of motor dual task cost and performances during "Obstacle" condition as a function of group over time

Condition	Outcomes	Group	PRE	POST	FU	Mixed model analysis			Multiple comparisons		
			Mean± SD	Mean± SD	Mean± SD	Time	Group	Time*Group			
OB	**velocity (m/s)**	**DTT**	0.91± 0.26 (n=18)	1.00± 0.24 (n=18)	0.99± 0.06 (n=19)	**0.018**	n.s.	n.s.	**T1-2: 0.005**		
		SMT	0.88± 0.26 (n=19)	0.93± 0.27 (n=17)	0.88± 0.25 (n=19)						
OB -DS	**velocity (m/s)**	**DTT**	0.83± 0.24 (n=17)	0.952± 0.220 (n=18)	0.94± 0.22 (n=18)	**0.016**	n.s.	**0.003**	**DTT 1-2** **<0.0001** SMT 1-2 n.s. DTT-SMT 1 n.s.	**DTT 1-3** **0.001** SMT 1-3 n.s. **DTT-SMT 2** **0.042**	DTT 2-3 n.s. SMT 2-3 n.s DTT-SMT 3 n.s.
		SMT	0.81±0.25 (n=19)	0.81± 0.22 (n=17)	0.80± 0.23 (n=19)						
	DTC	**DTT**	9.93± 9.86 (n=17)	4.04± 7.69 (n=18)	4.69± 10.01 (n=18)	n.s.	n.s.	n.s.			
		SMT	8.72± 7.94 (n=19)	10.68± 11.46 (n=18)	9.16± 7.81 (n=19)						
OB -SU	**velocity (m/s)**	**DTT**	0.80± 0.21 (n=17)	0.92± 0.23 (n=18)	0.91± 0.23 (n=19)	n.s.	n.s.	**0.026**	**DTT 1-2** **0.002** SMT 1-2 n.s. DTT-SMT 1 n.s.	**DTT 1-3** **0.014** SMT 1-3 n.s. **DTT-SMT 2** **0.032**	DTT 2-3 n.s. SMT 2-3 n.s DTT-SMT 3 n.s.
		SMT	0.78± 0.23 (n=19)	0.77± 0.22 (n=17)	0.77± 0±23 (n=19)						
	DTC	**DTT**	10.23± 7.44 (n=17)	7.27± 8.45 (n=18)	6.81± 9.40 (n=19)	n.s.	n.s.	n.s.			
		SMT	10.84± 10.423 (n=19)	14.86± 9.31 (n=18)	11.79± 12.28 (n=19)						
OB -VI	**velocity (m/s)**	**DTT**	0.88± 0.26 (n=18)	0.99± 0.23 (n=18)	0.96± 0.23 (n=19)	n.s.	n.s.	**0.004**	**DTT 1-2** **0.000** SMT 1-2 n.s. DTT-SMT 1 n.s.	**DTT 1-3** **0.013** SMT 1-3 n.s. **DTT-SMT 2** **0.045**	DTT 2-3 n.s. SMT 2-3 n.s DTT-SMT 3 n.s.
		SMT	0.86± 0±25 (n=19)	0.85± 0.24 (n=17)	0.83± 0.23 (n=19)						
	DTC	**DTT**	0.00± 0.00 (n=18)	-0±07± 5.13 (n=18)	1.43± 8.08 (n=19)	**0.010**	**0.010**	**0.042**	DTT 1-2 n.s **SMT 1-2** **0.001** DTT-SMT 1 n.s.	DTT 1-3 n.s. **SMT 1-3** **0.003** **DTT-SMT 2** **0.001**	DTT 2-3 n.s. SMT 2-3 n.s **DTT-SMT 3** **0.043**
		SMT	0.00± 0.00 (n=19)	6.10± 8.81 (n=18)	5.09± 4.11 (n=19)						

Abbreviations: Single mobility training (SMT); Dual task training (DTT), Dual task cost (DTC), Obstacle (OB), Digit span (DS), Subtracting (SU), Vigilance (VI), amount of data present in each group (n), not significant (n.s.), significant effects after Bonferroni correction are indicated ***red*** *and bold, p values in* ***bold*** *are not significant after Bonferroni correction, comparison between outcome measures at pre-post intervention are indicated by T1-2, comparison between outcome measures at pre intervention and follow-up are indicated by T1-3, comparison between outcome measures at post intervention and follow-up are indicated by T1-2*

Table 4. **Means and standard deviation of motor dual task cost and performances during "CUP" condition as a function of group over time**

Condition	Outcomes	Group	PRE	POST	FU	Mixed model analysis			Multiple comparisons		
			Mean± SD	Mean± SD	Mean± SD	Time	Group	Time*Group			
CUP	**velocity (m/s)**	**DTT**	1.00± 0.26 (n=17)	1.10± 0.26 (n=17)	1.07± 0.27 (n=18)	n.s.	n.s.	n.s.			
		SMT	1.01± 0.28 (n=19)	1.06± 0.29 (n=17)	1.04± 0.30 (n=19)						
CUP -DS	**velocity (m/s)**	**DTT**	0.92± 0.25 (n=17)	1.01± 0.27 (n=17)	1.02± 0.28 (n=18)	n.s.	n.s.	n.s.			
		SMT	0.90± 0.25 (n=19)	0.90± 0.25 (n=17)	0.90± 0.25 (n=19)						
	DTC	**DTT**	7.70± 8.96 (n=17)	7.95± 8.69 (n=17)	5.12± 12.80 (n=18)	n.s.	**0.036**	n.s.	**DTT-SMT** **0.036**		
		SMT	9.66± 14.66 (n=19)	14.06± 8.99 (n=18)	13.58± 6.27 (n=19)						
CUP -SU	**velocity (m/s)**	**DTT**	0.88± 0.26 (n=16)	0.99± 0.27 (n=17)	0.98± 0±27 (n=17)	n.s.	n.s.	n.s.			
		SMT	0.84± 0.24 (n=19)	0.83± 0.25 (n=17)	0.85± 0.25 (n=19)						
	DTC	**DTT**	11.21± 11.78 (n=16)	10.20± 8.41 (n=17)	8.19± 11.99 (n=17)	n.s.	**0.011**	n.s.	**DTT-SMT** **0.011**		
		SMT	15.16± 17.03 (n=19)	20.40± 10.51 (n=18)	18.098± 7.99 (n=19)						
CUP -VI	**velocity (m/s)**	**DTT**	0.97± 0.27 (n=17)	1.05± 0.26 (n=17)	1.04± 0.24 (n=18)	n.s.	n.s.	n.s.			
		SMT	0.99± 0.25 (n=19)	0.97± 0.29 (n=17)	0.95± 0.27 (n=19)						
	DTC	**DTT**	3.27± 6.62 (n=17)	3.55± 8.47 (n=17)	2.56± 7.56 (n=18)	**0.032**	n.s.	**0.015**	DTT 1-2 n.s.	DTT 1-3 n.s.	DTT 2-3 n.s.
		SMT	0.53± 11.35 (n=19)	8.76± 8.40 (n=18)	8.67± 6.51 (n=19)				**SMT 1-2** **0.001**	**SMT 1-3** **0.001**	SMT 2-3 n.s
									DTT-SMT 1 n.s.	DTT-SMT 2 n.s.	**DTT-SMT 3** **0.029**

Abbreviations: Single mobility training (SMT); Dual task training (DTT), Dual task cost (DTC), Walking while carrying a cup of water (CUP), Digit span (DS), Subtracting (SU), Vigilance (VI), amount of data present in each group (n), not significant (n.s.), significant effects after Bonferroni correction are indicated ***red*** *and bold, p values in* ***bold*** *are not significant after Bonferroni correction, comparison between outcome measures at pre-post intervention are indicated by T1-2, comparison between outcome measures at pre intervention and follow-up are indicated by T1-3, comparison between outcome measures at post intervention and follow-up are indicated by T1-2*

Secondary outcome measures

No significant interaction effect was observed, however, both groups improved their functional mobility, assessed by the 25FWT fast, TUG and DGI after the training period compared to baseline, as seen by a time effect. Besides, cognitive function, measured by the SDMT (p=.023) and PASAT 3”; PASAT 2”(p=.001; p=.041), improved significantly in both groups over time. No significant differences were observed in self-reported secondary outcomes of quality of life, fatigue and dual task difficulty between groups over the intervention period. Results of the mixed model analysis of the secondary outcome measures are reported in Supplementary table 6.

Perceived training intensity and intrinsic motivation

The 20 participants in the DTT and SMT group who finished the intervention, completed 94% and 96% of the prescribed training sessions, respectively. After each training session, the Borg RPE scale was used to evaluate the participant’s perceived exertion. Perceived exertion and the intrinsic motivation inventory did not differ between groups. The mean RPE of all training sessions was 12.29 and 12.09 for the DTT and SMT, respectively, indicating that the participants perceived the training intensity as light to somewhat hard. Results concerning adherence rate, perceived exertion and intrinsic motivation as a function of group are reported in table 5.

Table 5. Training intensity and intrinsic motivation in the DTT and SMT groups

	DTT (mean ± SD)	**SMT** (mean ± SD)	**p-value**
n completed sessions	18.85±1.73	19.20±1.61	0.511
RPE Borg	12.29±1.89	12.09±2.67	0.783
Intrinsic Motivation Inventory (IMI)			
IMI interest / enjoyment	27.26±5.36	27.50±5.84	0.896
IMI perceived competence	28.11±5.07	28.15±3.98	0.171
IMI effort / importance	23.84±7.62	25.50±6.98	0.484
IMI pressure / tension	9.42±4.81	11.25±6.00	0.299
IMI perceived choice	19.58±6.37	20.10±5.28	0.783
IMI value / usefulness	30.53±9.24	34.55±6.57	0.129

Abbreviations: RPE, Rating of Perceived Exertion; IMI, Intrinsic Motivation Inventory
Statistical analysis: independent two-sided t-test or Wilcoxon-signed rank test

Discussion

To our knowledge, this study presents the first multicentered, single-blind, randomized clinical trial that investigated the effects of cognitive-motor dual task training compared to single motor training in pwMS. The principal finding of this multicenter clinical trial was a superior effect of DTT on motor DTC of walking while performing cognitive tasks such as digit span and subtracting. Moreover, only after the DTT, a significant improvement in dual task walking performance in all obstacle dual task conditions occurred. However, DTT is as effective as SMT to improve functional mobility and cognition.

These observations confirm our first hypothesis, namely, that there will be a greater improvement in DTC of cognitive-motor dual tasks and dual task performance after DTT, not observed in the SMT group. Post-hoc analysis revealed a significant decrease in motor DTC of W-DS and W-SU in the DTT group, not seen in the SMT group, after the intervention which was retained during the four-week follow up period. However, absolute dual task walking velocity during normal walking improved after both interventions. This finding supported the “Automatization theory”, which indicates that single task repetitive training results in an increased automatization and allows a greater attention allocation toward the concurrent tasks during dual tasking (Silsupadol et al., 2009). However, the fact that both training programs were capable of improving absolute dual task motor performances of the simplest motor condition, “walk”, but not of more challenging condition “obstacles”, suggests the need for a better task integration in more difficult motor dual tasks, obtained only by DTT. Besides, the interaction effect observed in motor DTC in the “Walk” condition, support our hypotheses of a better task integration after DTT compared to SMT.

Results of the secondary mobility outcomes are in accordance with our second hypothesis. Participants improved their 25FWT fast and TUG after the training period compared to baseline. These clinical tests assess walking ability and maximal gait speed. Although the motor part of the DTT group consisted only of walking and stepping on the spot, while participants in the SMT group performed a more expanded motor programme, both interventions improved their DGI, an indicator of fall risk and the ability to adjust their walking performance to changing environments. However, no significant changes were reported in walking endurance, measured by the 2MWT, and fall efficacy.

The results of this study are in accordance with the systematic reviews of Fritz et al. (2015) and Wajda et al. (2017), who reported that patients with a variety of neurological disorders , e.g. Alzheimer Disease, Dementia, Parkinson Disease, brain injury and Multiple sclerosis, improved their dual task walking performances more after DTT, compared to single task motor training (Fritz et al., 2015; Sosnoff et al., 2017; Wajda, Mirelman, Hausdorff, & Sosnoff, 2017). Besides, the observation that absolute dual task walking performance improved both after DTT and SMT in the “WALK” condition is consistent with results of the study of Monjezi et al. (2017) and Sosnoff et al. (2017), in which dual task balance training was as effective as single task training in pwMS (Monjezi, Negahban, Tajali, Yadollahpour, & Majdinasab, 2017; Sosnoff et al., 2017). Moreover, integrated motor and cognitive DTT in pwMS reported positive results on general walking ability, assessed by TUG and Tinetti test. (Barbarulo et al., 2018; Felippe, Salgado, de Souza Silvestre, Smaili, & Christofoletti, 2019).

In contrast to the significant interaction effect on motor DTC, no significant superior effect of DTT was observed in cognitive DTC and cognitive performances. These results are in contradiction with our hypothesis that only the DTT group will improve cognitive DTC and single cognitive performance after the intervention period. The absence of any significant interaction or main effect on cognitive DTC or performances is in contrast with a recent study of Lofgren et al. (2019), who demonstrated that patients with PD in a DTT program had a significant improvement in cognitive DTC, when compared to SMT. However, they did not find a difference in motor DTC between training groups (Lofgren, Conradsson, Rennie, Moe-Nilssen, & Franzen, 2019).

The inconsistency in cognitive DTC between studies might be explained by task prioritization instructions. In this study, participants were instructed to divide their attention equally over both tasks, however, Yogev-Seligmann et al. (2012) demonstrated that explicit prioritization plays an important role in dual task performance outcomes (Yogev-Seligmann, Rotem-Galili, Dickstein, Giladi, & Hausdorff, 2012). Moreover, the type, difficulty, cognitive domain and reliability of added cognitive task can also influence the results. The test-retest reliability study for the various cognitive-motor dual tasks used in this study appeared to have a poor reliability of the cognitive DTC and performances (Veldkamp, et al., 2019).

Results of the secondary outcomes do not support are last hypothesis, that only cognition, quality of life, fatigue and self-reported dual task difficulty in daily life will improve more after DTT. As secondary cognitive measures, SDMT and PASAT”, improved significantly in both groups over time. The study of Barbarulo et al. (2018) also observed significant improvement in different cognitive tests after integrated cognitive-motor dual task training. In contrast to our results, the single motor training group in the study of Barbarulo et. al (2018) did not improved significantly on the PASAT3” performance after the intervention period while the DTT group did (Barbarulo et al., 2018). The inconsistency might be explained by difference in training protocol and complexity of the exercises between the studies. Moreover, in both groups, no significant changes in self-reported quality of life, fatigue and dual task difficulty in daily life were observed.

This study has several strengths concerning the interpretation of the results. First, the assessment of both motor and cognitive DTC during cognitive-motor dual tasks with different levels of complexity. This enabled us to demonstrate the need for a better task integration in more difficult cognitive-motor dual tasks, such as the dual task obstacle condition, that was only obtained by DTT. Moreover, we implemented a four-week follow-up assessment to examine the long-term retention effect of the interventions and found that the positive effects of DTT were maintained at four weeks follow up.

Despite the promising results of this study regarding the effect of DTT in pwMS, this study had some limitations. First, the motor part of both training groups was not identical. Therefore, one could argue that that a performance bias occurred, confounding the observed superior training effects of DTT. However, we expect only a minimal confounding effect because the motor ability on clinical tests improved equally in both groups over the intervention period and the perceived training intensity, measured by Borg scores, was no different between groups. Moreover, there was no difference in intrinsic motivation as both groups scored similarly on the IMI. Second, because no power analysis was performed, an increase in type I error and decrease power might be expected. The sample size of 20 participants in each group, was based on the recommendation of the feasibility study of Sosnoff et al. (2017) (Sosnoff et al., 2017). Therefore, further research with more power is warranted to confirm our results. Third, only participants with mild to moderate disability (EDSS score: range 2-6) participated, thereby decreasing external generalizability of the study. Besides, studies exploring the influence of different patient characteristics (e.g. EDSS, age, educational level, cognitive function, mobility function, disease duration, type of MS) on the effect of DTT compared to SMT can broaden the knowledge of the effect of DTT in pwMS.

Conclusion

Overall, this multicenter, randomized clinical trial did show a superior effect of DTT compared to SMT, on cognitive-motor interference of walking velocity while performing cognitive tasks as digit span and subtracting, that was retained at four weeks follow-up period. Moreover, only DTT was able to improve walking performance in more complex dual task conditions. However, both DTT is as effective as SMT to improve functional mobility and cognition. These findings broaden the knowledge of the effect of DTT compared to SMT in pwMS. The promising results of DTT can inspire therapist to include DTT in the rehabilitation program of pwMS who suffer from dual task difficulties to improve and maintain motor and cognitive single and dual task performances and to decrease motor DTC.

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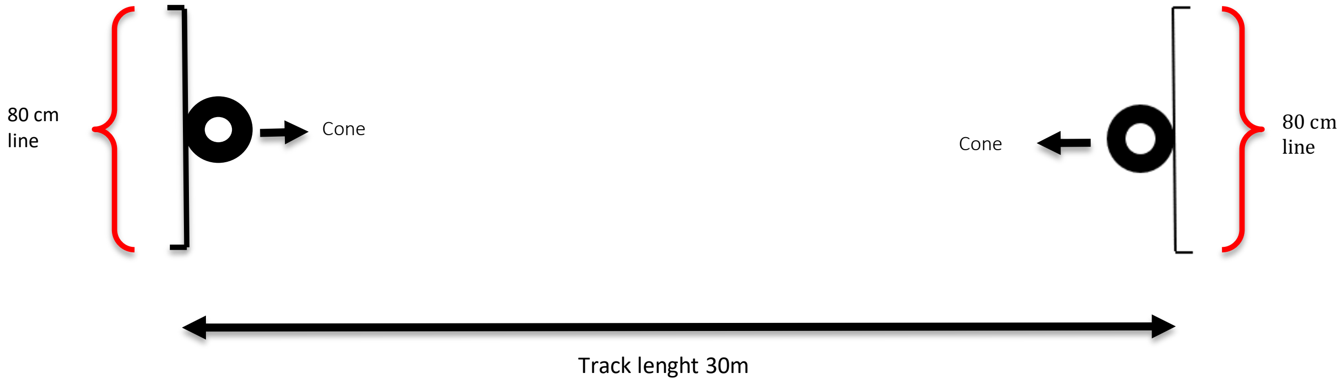
Supplementary Figure 1.Test setting motor task

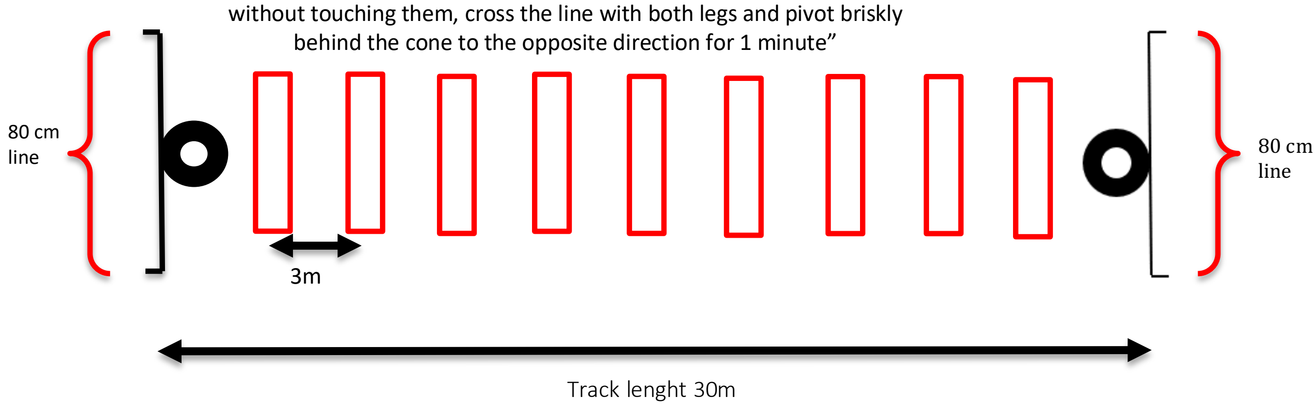
A. Walk

"walk at preferred (usual) walking speed, cross the line with both legs and pivot briskly behind the cone to the opposite direction for 1 minute"



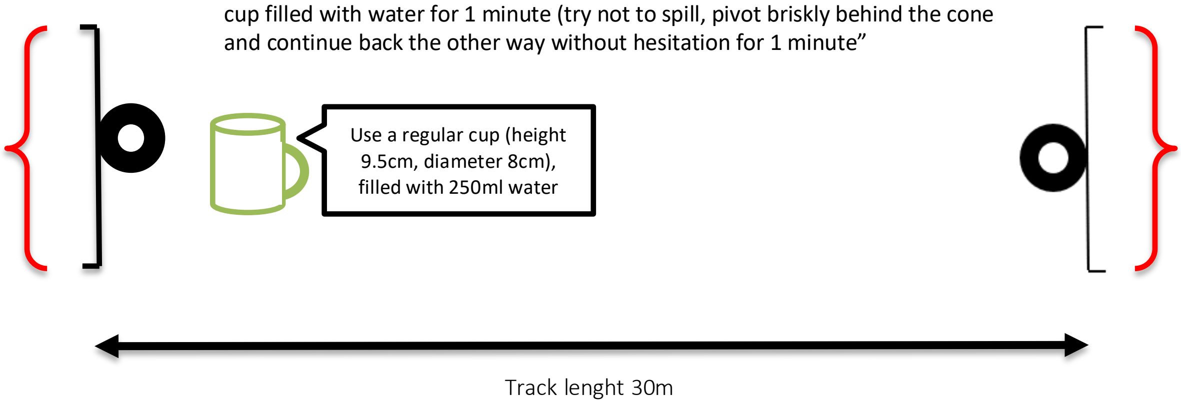
B. Obstacle

"walk at preferred (usual) walking speed and step over the obstacles without touching them, cross the line with both legs and pivot briskly behind the cone to the opposite direction for 1 minute"



C. Cup

"walk with your preferred (usual) walking speed back and forth while holding a cup filled with water for 1 minute (try not to spill, pivot briskly behind the cone and continue back the other way without hesitation for 1 minute"



Supplementary Figure 2: Test setting cognitive tasks

A. Titrated digit span backwards:

- Sequence length: personal (digit span determined as last sequence length with three out of four trials correct)
- Rate: 1 digit /sec
- Delivery: auditory program
- Score: response accuracy (%)

Sequence length	Digit span	Correct answer
3	3-2-8	8-2-3
4	2-9-4-1	1-4-9-2
5	2-5-9-7-6	6-7-9-5-2
6	4-3-1-9-2-5	5-2-9-1-3-4
7	5-3-2-4-1-6-8	8-6-1-4-2-3-5
8	6-8-4-7-5-3-9-2	2-9-3-5-7-4-8-6

B. Auditory vigilance with alphabets

- Rate: one letter per 1,5 seconds (40 letters all together of which 16 target letters),
- Target letter chosen are different per country, based on some common rules
- Delivery: Auditory program
- Score: response accuracy (%) and reaction time

Letter	Response
D	*Silence*
S	*Silence*
L	YES
M	*Silence*

C. The Serial Sevens Subtraction Test

- Counting backwards by 7, starting from '100' ('102', '144', 165', '198').
- Score: response accuracy (ratio of correct answers to total answers)

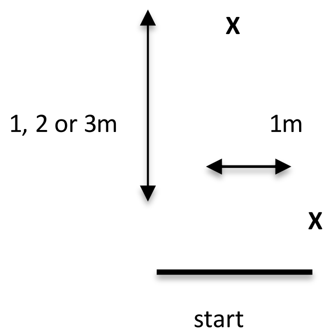
START: 100	102	144	165	198
93	95	137	158	191
86	88	130	151	184
79	81	123	144	177
72	74	116	137	170
…	…	…	…	…

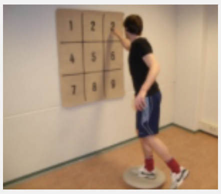
Supplementary Table 1. Dual task training cognitive exercises

Cognitive Exercise	Difficulty level
1. Noise exercise	
The participant familiarises with target sounds. While walking, the patient will hear different sounds and answer “yes” if the sound corresponds to the target sounds.	1. two target sounds 2. three target sounds 3. four target sounds
2. Words exercise	
The participant will hear a word while walking and needs to give a new word using the nth letter of the given word as first letter for the answer.	1. first letter 2. last letter 3. 2nd letter 4. 4th letter
3. Apple exercise	
The participant will first hear the particular target word. When the exercise starts, the patient will hear different words while walking and answer “yes” if the sound corresponds to the target word.	1. one target word – hear semantically different noise words 2. one target word – hear words from the same category or semantically different noise words 3. two target words - hear words from the same category or semantically different noise words
4. Reverse exercise	
The participant will hear a word while walking and need to spell this given word letter by letter in the reverse order.	1. 3/4 letter word – time 10 seconds 2. 5/6 letter word – time 20 seconds 3. 7+ letter word – time 30 seconds
5. Listen exercise	
The participant will hear words at a presenting rate of 6sec while walking and need to say if he heard this word before or not (heard / not heard), before the next word is played.	1. 30 words 2. 35 words 3. 40 words and counting how many times a specific word is played
6. Taboo exercise	
The participant will hear while walking a target word and taboo words with some time interval between. The participant needs to describe the target word without using the taboo words and respecting the rules: 1. you cannot use the word itself nor parts of this word. 2. You cannot use words that are derived from the word 3. Gestures and noises are forbidden 4. Abbreviations, initials nor clues like ‘sound as’, ‘rhymes like’ are allowed.	1. describe the target word within 20 sec 2. describe the target word within 30 sec 3. describe the target word within 40 sec
7. Story exercise	
The participant will hear a story while walking. When the story is completed, the participant can sit down and respond to three questions about the story by selecting the right answer option within 45 seconds.	1. question with three answer options 2. question with four simple answer options 3. question with four difficult answer options
8. Difference exercise	
The participant will see two images and need to answer if these images are the same or different.	1. images may contain more than one difference – time frame 15 sec 2. images may contain one difference – time frame 20 sec 3. images may contain one small difference - time frame 30 sec
9. See exercise	
The participant will see an avatar smiley and needs to remember this for later. Afterwards, three smileys are presented, and the participant needs to tell which smiley he/she just saw within the time limit.	1. three clearly different smileys– time frame 10 sec 2. three smileys of which two smileys have smaller differences - time frame 15 sec 3. three smileys of which two smileys have one small difference - time frame 20 sec

10. **Think exercise**	
- The participant will see four images in the middle of the screen that need to match with one of the images in the right bar. - The participant will see a calculation assignment on the screen and need to solve this assignment. - The participant will see a logical reasoning task, consisting of a series of symbols and one question mark, and need to tell the which symbol needs to be placed instead of the question mark.	
11. **Roadmap exercise**	
The participant will see the roadmap with seven locations. His current location is given by a blue circle. The participant will navigate himself to the target location by telling the therapist what direction he wants to go on the map.	1. roadmap with seven locations 2. roadmap with seven locations, roundabouts, houses and trees 3. roadmap with seven locations, roundabouts, houses, trees and one-way streets

Supplementary table 2: Single Mobility training exercises

Exercise on	Exercise description / instruction	Difficulty levels
Normal gait speed	Walk at your normal speed	1. for 2 min 2. over uneven underground for 2 min 3. backwards for 1 min
Fast gait speed	Walk as fast as you can (not running)	1. for 30sec 2. for 60sec 3. for 90sec
Gait quality	Depending on clinical need: walking while focus on - heel strike - knee raise - hip flexion	1. for 2 min 2. for 2 min, increase amplitude 3. for 2 min, increase speed
Change in gait speed	Begin walking at your normal pace. When I tell you "Go", walk as fast as you can. When I tell you "Slow", walk as slowly as you can.	1. for 2 min with fixed presentation interval (every 30sec) and execution time (5sec) 2. for 2 min with variable presentation interval (10-30sec) and execution time (10sec) 3. for 3 min with variable presentation interval (10-30sec) and execution time (10sec)
Gait with shoving obstacles	Begin walking at your normal speed. When you come to the first wooden block, shove it over the line with your right leg (±10cm). When you come to the second wooden block, shove it over the line with your left leg, and so on, alternately right/left foot and medial/lateral side of the feet.  	1. straight line, every 3m a wooden block (length) with a width of 1m between left and right blocks, for 2 min 2. straight line, every 1m a wooden block (length) with a width of 1m between left and right blocks, for 2 min 3. straight line, variable length (1,2,3m) between the wooden blocks with a width of 1m between left and right blocks, for 2 min
Gait with horizontal head turning	Begin walking at your normal pace. When I tell you "Look right", keep walking straight, but turn your head to the right. Keep looking to the right until I tell you,	1. While standing, turn to look directly behind you toward left

	"Look left". Then keep walking straight and turn your head to the left until I tell you "Look straight". Where after you keep walking straight, but return your head to the center.	shoulder for 10sec. Repeat to the right. For 2 min 2. While walking, every 15 sec head turn, for 2 min 3. While walking, every 10 sec head turn, for 2 min
Gait with vertical head turning	Begin walking at your normal pace. When I tell you "Look up", keep walking straight, but tip your head up. Keep looking up until I tell you, "Look down". Then keep walking straight and tip your head down. Keep your head down until I tell you "Look straight", then keep walking straight, but return your head to the center.	1. While standing, turn to look up for 10sec. Repeat to look down. For 2 min 2. While walking, every 15 sec head up-down, for 2 min 3. While walking, every 10 sec head up-down, for 2 min
Pivot turning	Begin walking at your normal pace. When I tell you "Turn and stop", turn as quickly as you can to face the opposite direction and stop.	1. 3 turns at 15sec, at 30sec and at 45sec for 1 min 2. 6 turns at 10, 30, 50, 70, 90, 110 sec for 2 min 3. 6 turns with a variable time interval, for 2 min
Reaching forwards 	The patient is standing at a distance from a wall with a poster with 9 numbers (40*40cm squares) so that number 5 is on the level of the patient's sternum and the patient can reach comfortably the numbers without trunk movements or strong elevation of the shoulders. The therapist says which number (at random) the patient needs to touch with his preferable hand.	1. both feet on the floor, for 2 min 2. both feet on balance foam, for 2 min 3. both feet on bosu ball, for 2 min
Standing unsupported	Standing stable without holding.	1. feet together for 1 min on the floor 2. feet together for 1 min on an Airex balance pad 3. feet together + eyes closed for 1 min on the floor 4. feet together + eyes closed for 1 min on an Airex balance pad
Tandem stance/gait	Tandem stance: Place one foot directly in front of the other. If you feel you cannot place your foot directly in	1. tandem stand as long as possible, max 2min (2*left in front of right, 2*right in front of left)

	front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. Tandem gait: walk in a straight line while the toes of your back foot touch the heel of the front foot at each step.	2. tandem gait forwards for 2 min 3. tandem gait backwards for 1 min
Stepping on the spot	Step on the spot or on and off a bench.	1. stepping on the spot for 2 min 2. march up and down on a 15cm step for 2 min 3. march up and down on a 30cm step, for 2 min
Stepping	Stepping forwards, backwards, to the right, to the left.	1. step sideways to the left and left alternately over a cane, for 2 min 2. step forwards and backwards alternately over a cane, for 2 min 3. step forwards, to the right, backwards, to the left and counterclockwise back over canes, for 2 min
Standing on one leg	Stand on one leg as long as you can without holding.	1. on less impaired leg (3*) 2. on most impaired leg (3*) 3. on less impaired leg with eyes closed (3*) 4. on most impaired leg with eyes closed (3*)
Sit-to-stand	Standing up and sitting down from a chair.	1. allowed to use their arms to push off from the chair with armrests, for 1min 2. allowed to use their arms to push off from the chair with armrests, for 2min 3. without push off from armrests, for 2min
Stairs (15-16 steps)	Walk up these stairs. At the top, turn around and walk down.	1. with rail uses, 2* 2. without rail uses, 2* 3. without rail uses, 4*
Picking up object from the floor	From standing position: pick up a beanbag which is placed in front of your feet.	1. from standing position, for 1min 2. during walking, for 1min

	During walking: walk and pick up the bean bags from the floor (every 3m).	3. during walking, for 2min
Tapping the ground	In standing position: tap the ground lightly with the ball of your foot.	1. with less impaired leg, on the spot next to the other foot, for 1min 2. with most impaired leg, on the spot next to the other foot, for 1min 3. with the less affected leg, forwards-backwards (± 20m for/after other foot, not tandem), 2*1min 4. with the most affected leg, forwards-backwards (± 20m for/after other foot, not tandem), 2*1min
Tapping a step	In standing position: tap lightly on a step (± 15cm height) with your foot.	1. with the less affected leg, for 1min 2. with the most affected leg, for 1min 3. with the less affected leg, for 2min 4. with the most affected leg, for 2min
Hopping	Hopping on one leg.	1. on the spot, with the less impaired leg, 5* 2. on the spot, with the most impaired leg, 5* 3. on the spot, with the less impaired leg,10* 4. on the spot, with the most impaired leg, 10*
Running	Running without limping.	1. for 15sec, 5*, ± 10sec breaks between 2. for 30sec, 3*, ± 10sec breaks between 3. for 60sec, 2*, ± 10sec breaks between

Supplementary Table 3. Means and standard deviation of cognitive dual task cost and performances of Digit-span as a function of group over time								
Condition	**Outcomes**	**Group**	**PRE**	**POST**	**FU**	**Mixed model analysis**		
			Mean± SD	**Mean± SD**	**Mean± SD**	**Time**	**Group**	**Time*Group**
DS	**% Correct answers/total given answers**	**DTT**	0.76± 0.28 (n=20)	0.84± 0.21 (n=17)	0.87± 0.16 (n=20)	*0.051*	0.318	0.769
		SMT	0.82± 0.23 (n=20)	0.86± 0.15 (n=19)	0.88± 0.14 (n=20)			
DS-W	**% Correct answers/total given answers**	**DTT**	0.71± 0.19 (n=20)	0.82±0.26 (n=17)	0.82± 0.21 (n=20)	0.228	0.567	0.127
		SMT	0.82± 0.24 (n=20)	0.84± 0.16 (n=19)	0.79± 0.21 (n=20)			
	DTC	**DTT**	3.16± 41.60 (n=19)	4.45± 21.77 (n=17)	6.29± 18.42 (n=20)	n.s	n.s	n.s
		SMT	3.45± 28.17 (n=19)	1.95± 20.81 (n=19)	8.99± 29.22 (n=20)			
DS-OB	**% Correct answers/total given answers**	**DTT**	0.68± 0.17 (n=20)	0.78± 0.27 (n=17)	0.85± 0.18 (n=19)	**T1-2** **0.006**	n.s.	n.s.
		SMT	0.77± 0.21 (n=19)	0.83± 0.22 (n=19)	0.84± 0.16 (n=20)	**T1-3** **0.002**		
	DTC	**DTT**	8.86± 23.00 (n=19)	8.30± 34.30 (n=17)	0.75± 21.65 (n=19)	n.s.	n.s.	n.s.
		SMT	5.79±21.66 (n=18)	3.46± 25.53 (n=19)	2.80± 19.91 (n=20)			
DS-CUP	**% Correct answers/total given answers**	**DTT**	0.78± 0.20 (n=19)	0.75± 0.28 (n=17)	0.83± 0.26 (n=20)	0.736	0.984	0.212
		SMT	0.78± 0.24 (n=20)	0.86± 0.14 (n=19)	0.83± 0.19 (n=20)			
	DTC	**DTT**	-6.81± 52.97 (n=18)	10.88± 27.45 (n=17)	6.84± 27.92 (n=20)	n.s.	n.s.	n.s.
		SMT	7.39± 19.83 (=19)	-1.03± 14.71 (n=19)	4.99± 21.13 (n=20)			

Abbreviations: Single mobility training (SMT); Dual task training (DTT), Dual task cost (DTC), Walk condition (W), Walking over obstacles (OB), Walking while carrying a cup of water (CUP), Digit span (DS), amount of data present in each group (n), not significant (n.s.), significant effects after Bonferroni correction (0.05/3 = 0.016) are indicated ***red*** *and bold, a positive trend is indicated by inclined p values in red, comparison between outcome measures at pre-post intervention are indicated by T1-2, comparison between outcome measures at pre intervention and follow-up are indicated by T1-3, comparison between outcome measures at post intervention and follow-up are indicated by T1-2*

Supplementary Table 4. Means and standard deviation of cognitive dual task cost and performances of Subtracting (SU) as a function of group over time (								
Condition	**Outcomes**	**Group**	**PRE**	**POST**	**FU**	**Mixed model analysis**		
			Mean± SD	**Mean± SD**	**Mean± SD**	**Time**	**Group**	**Time*Group**
SU	**% Correct answers/total given answers**	**DTT**	0.90± 0.10 (n=20)	0.94± 0.08 (n=18)	0.91± 0.12 (n=20)	0.489	0.683	0.572
		SMT	0.92± 0.11 (n=19)	0.93± 0.14 (n=19)	0.95± 0.10 (n=19)			
SU-W	**% Correct answers/total given answers**	**DTT**	0.87± 0.12 (n=20)	0.94± 0.11 (n=18)	0.91± 0.12 (n=20)	0.177	0.670	0.157
		SMT	0.91± 0.08 (n=18)	0.90± 0.11 (n=19)	0.94± 0.09 (n=19)			
	DTC	**DTT**	3.54± 12.71 (n=20)	-0.51± 8.41 (n= 18)	-1.26± 16.66 (n=20)	n.s.	n.s.	n.s.
		SMT	-1.33± 17.52 (n=18)	1.19± 13.56 (n=19)	-0.36± 15.76 (n=19)			
SU-OB	**% Correct answers/total given answers**	**DTT**	0.87± 0.14 (n=20)	0.94± 0.11 (n=18)	0.87± 0.13 (n=20)	0.439	0.361	0.152
		SMT	0.91± 0.12 (n=19)	0.90± 0.14 (n=19)	0.93± 0.08 (n=19)			
	DTC	**DTT**	3.23± 17.66 (n=20)	-1.23± 14.15 (n=18)	4.00± 13.47 (n=20)	n.s.	n.s.	n.s.
		SMT	-1.20± 17.86 (n=19)	1.31± 15.18 (n=19)	0.61± 15.30 (n=19)			
SU-CUP	**% Correct answers/total given answers**	**DTT**	0.84± 0.19 (n=20)	0.88± 0.15 (n=18)	0.89± 0.13 (n=20)	0.383	0.493	0.226
		SMT	0.86± 0.17 (n=19)	0.93± 0.09 (n=19)	0.89± 0.10 (n=19)			
	DTC	**DTT**	6.90± 17.79 (n=20)	6.03± 12.60 (n=18)	1.38± 16.71 (n=20)	n.s.	n.s.	n.s.
		SMT	5.37± 17.28 (n=19)	-3.58± 23.42 (n=19)	4.21± 17.36 (n=19)			

Abbreviations: Single mobility training (SMT); Dual task training (DTT), Dual task cost (DTC), Walk condition (W), Walking over obstacles (OB), Walking while carrying a cup of water (CUP), Subtracting (SU)), amount of data present in each group (n), not significant (n.s.),

Supplementary Table 5. Means and standard deviation of cognitive dual task cost and performances of Vigilance (Vi) as a function of group over time (Pre, Post, follow-up)							
Condition	**Outcomes**	**Group**	**PRE mean±SD**	**POST mean±SD**	**FU mean±SD**	**Wilcoxon signed rank test POST-PRE**	**Wilcoxon signed rank test FU-PRE**
Vi	**% Correct answers/total given answers**	**DTT**	0.99±0.03 (n=19)	0.98±0.03 (n=18)	0.99±0.3 (n=20)	n.s.	n.s.
		SMT	0.99±0.03 (n=20)	0.99±0.02 (n=20)	0.99±0.2 (n=20)		
Vi-W	**% Correct answers/total given answers**	**DTT**	0.98±0.04 (n=20)	0.99±0.03 (n=18)	1.00±0.01 (n=20)	n.s.	n.s.
		SMT	0.98±0.5 (n=20)	0.99±0.02 (n=20)	0.98±0.04 (n=20)		
	DTC	**DTT**	1.49±4.28 (n=19)	-0.51±3.34 (n=18)	-0.51±3.65 (n=20)	n.s.	n.s.
		SMT	1.08±3.46 (n=20)	0.37±3.40 (n=20)	1.03±4.43 (n=20)		
Vi-OB	**% Correct answers/total given answers**	**DTT**	0.96±0.05 (n=20)	0.98±0.02 (n=18)	0.99±0.03 (n=20)	n.s.	n.s.
		SMT	0.97±0.04 (n=20)	0.98±0.03 (n=20)	0.99±0.02 (n=20)		
	DTC	**DTT**	2.59±5.79 (n=19)	0.17±3.52 (n=18)	0.36±3.71 (n=20)	n.s.	n.s.
		SMT	2.05±4.69 (n=20)	0.57±4.23 (n=20)	0.61±2.51 (n=20)		
Vi -CUP	**% Correct answers/total given answers**	**DTT**	0.96±0.06 (n=20)	0.98±0.02 (n=18)	0.99±0.01 (n=20)	n.s.	n.s.
		SMT	0.98±0.03 (n=20)	0.99±0.01 (n=20)	0.98±0.03 (n=20)		
	DTC	**DTT**	2.34±6.84 (n=19)	-0.30±3.19 (n=18)	0.35±3.47 (n=20)	n.s.	n.s.
		SMT	0.35±3.92 (n=20)	-0.90±2.72 (n=20)	1.00±3.91 (n=20)		

Abbreviations: Single mobility training (SMT); Dual task training (DTT), Dual task cost (DTC), Walk condition (W), Walking over obstacles (OB), Walking while carrying a cup of water (CUP), Vigilance (Vi)), amount of data present in each group (n), not significant (n.s.), change values were calculated by subtracting the baseline data (PRE) from the post-intervention data (POST) and FU-data from POST-data. To compare change values between groups, a Wilcoxon signed rank test were applicated to investigate if the change was different from zero.

Supplementary table 6. Mixed model analysis, Means and standard deviations of secondary outcomes as a function of group over time

Mobility test	Group	PRE	POST	FU	Mixed model analysis			Multiple comparison		
		Mean± SD	Mean± SD	Mean± SD	Time	Group	Time*Group			
T25FW usual	**DTT**	7.24 ± 1.54	6.45±1.14	6.94±1.65	**0.042**	n.s.	n.s.	**T1-T2: 0.038**		
	SMT	7.41± 2.34	7.01±2.27	7.25±2.16						
T25FW fast	**DTT**	6.17±1.47	5.27±1.22	5.51±1.36	**0.0055**	n.s.	n.s.	**T1-T2: 0.0256**	T2-T3: n.s.	**T1-T3: 0.0070**
	SMT	6.36±2.57	6.03±2.51	5.73±1.80						
TUG	**DTT**	8.60±2.21	7.64±1.69	8.30±2.61	**0.0043**	n.s.	n.s.	**T1-T2: 0.0031**		
	SMT	8.81±3.29	8.00±2.66	8.49±2.75						
MSWS-12	**DTT**	30.05±10.29	29.58±11.06	27.45±10.68	**0.0328**	n.s.	n.s.	T1-T2: 0.078	T2-T3: 0.98	**T1-T3: 0.047**
	SMT	31.55±11.48	26.80±12.78	28.30±14.06						
DGI	**DTT**	19.15±4.34	21.05±2.59	21.85±2.11	**<0.001**	n.s.	n.s.	**T1-2: 0.0023**	T2-3: 0.28	**T1-3: <0.001**
	SMT	20.25±3.21	21.40±3.52	21.70±2.90						
FES-I	**DTT**	30.85±11.70	28.21±8.61	27.65±9.03	n.s.	n.s.	n.s.			
	SMT	28.25±9.46	26.80±9.35	29.05±10.60						
2MWT	**DTT**	144.13±42.14	157±33.60	150.35±45.60	n.s.	n.s.	n.s.			
	SMT	141.10±37.12	142.85±36.46	143.90±39.35						
Cognitive test										
SDMT	**DTT**	46.80±11.56	48.79±14.66	46.00±14.67	**0.0230**	n.s.	n.s.	**T1-T2: 0.0436**	**T2-3: 0.0436**	T1-3: 1.00
	SMT	44.70±12.22	48.20±10.50	45.50±10.35						
PASAT 3”	**DTT**	42.15±12.76	47.42±11.98	48.20±2.77	**0.0008**	n.s.	n.s.	**T1-T2: 0.0036**	T2-T3: 1.00	**T1-T3: 0.0025**
	SMT	45.15±12.80	49.35±7.67	49.20±12.41						
PASAT 2”	**DTT**	33.95±12.14	37.74±12.62	40.15±12.50	**0.0405**	n.s.	n.s.	T1-T2: 0.22	T2-T3: 0.67	**T1-T3: 0.0344**
	SMT	38.60±12.65	40.95±11.67	41.55±11.61						
Dual task difficulty										
DTQ	**DTT**	13.80±8.69	11.82±6.76	12.53±8.96	n.s.	n.s.	n.s.			
	SMT	13.00±9.12	11.80±6.88	12.15±7.56						
Quality of life										
MSIS-29 total	**DTT**	64.00±23.94	61.36±22.01	60.55±23.58	n.s.	n.s.	n.s.			
	SMT	61.75±21.40	57.75±19.30	60.05±20.70						
physiological	**DTT**	44.30±17.52	42.10±14.86	41.15±16.57	n.s.	n.s.	n.s.			
	SMT	40.80±14.24	38.30±13.47	39.70±15.35						

psychological	**DTT**	19.70±7.65	19.26±8.43	19.4±8.51	n.s.	n.s.	n.s.	
	SMT	20.95±8.74	19.45±7.82	20.35±7.29				
Fatigue								
MFIS total	**DTT**	35.47±19.04	34.68±20.38	34.50±20.27	n.s.	n.s.	n.s.	
	SMT	29.80±19.11	27.75±18.74	27.95±18.21				
physiological	**DTT**	17.05±8.53	16.84±9.03	16.60±9.75	n.s.	n.s.	n.s.	
	SMT	14.45±8.61	13.75±8.48	13.85±8.91				
psychological	**DTT**	3.05±2.41	3.00±2.62	3.15±2.62	n.s.	n.s.	n.s.	
	SMT	2.20±2.31	2.15±2.18	1.95±2.16				
cognitive	**DTT**	15.37±10.86	14.84±10.52	14.75±9.91	n.s.	n.s.	n.s.	
	SMT	13.15±9.84	11.85±9.68	12.15±9.14				

Abbreviations: Single mobility training (SMT); Dual task training (DTT), Dual task cost (DTC), Timed 25 Foot walk test (T25FWT) at usual speed (sec), Timed 25 Foot walk test (T25FWT) at fast speed (sec), Timed Up and Go (TUG) in seconds, Multiple Sclerosis Walking Scale (MSWS-12), Dynamic gait Index (DGI), Fall Efficacy Scale (FES-I), 2 minute walk test (2MWT) in meters, Symbol Digit Modality test (SDMT), Paced auditory serial addition test at 3 seconds (PASAT 3"), Paced auditory serial addition test at 2 seconds (PASAT 2"), Multiple Sclerosis Impact Scale total score (MSIS-29 total), Dual task questionnaire (DTQ), Modified Fatigue Impact Scale total score (MFIS total), significant differences after Bonferroni correction (0.05/3 = 0.016) are indicated in ***red****. p values in* ***bold*** *are not significant after Bonferroni correction,. Comparison between outcome measures at pre-post intervention are indicated by T1-2, comparison between outcome measures at pre- intervention and follow-up are indicated by T1-3, comparison between outcome measures at post intervention and follow-up are indicated by T1-2*

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): Kathleen Giesen en Mieke Goetschalckx **Datum:** 27-05-2019

Titel Masterproef: The effects of cognitive-motor dual task training compared to single motor training in Multiple Sclerosis: a multicentre randomized clinical trial

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	NVT	1	2	3	4	5
Opstelling onderzoeksvraag	O	O	O	O	O	●
Methodologische uitwerking	O	O	O	●	O	O
Data acquisitie	●	O	O	O	O	O
Data management	O	O	O	●	O	O
Dataverwerking/Statistiek	O	O	O	O	●	O
Rapportage	O	O	O	O	●	O

2) Niet-bindend advies: Student(e) krijgt toelating/~~geen toelating~~ (schrappen wat niet past) om bovenvermelde ~~Wetenschappelijke stage/~~masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

3) Deze ~~wetenschappelijke stage/~~masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) openbaar verdedigd worden.

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening Student(e)	Datum en handtekening promotor(en)	Datum en handtekening Co-promotor(en)
27/05/2019	27/5/2019	27-05-2019

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KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
6/9/'18	Bespreking MP	Promotor: Copromotor/Begeleider: Student(e): Student(e):
9/10/'18	Bespreking data	Promotor: Copromotor/Begeleider: Student(e): Student(e):
7/11/'18	Bespreking data controle	Promotor: Copromotor/Begeleider: Student(e): Student(e):
3/12/'18	Bespreking data controle en statistiek	Promotor: Copromotor/Begeleider: Student(e): Student(e):
7/1/'19	Bespreking statistiekplan	Promotor: Copromotor/Begeleider: Student(e): Student(e):
18/3/'19	Inleiding, resultaten en methode bespreking	Promotor: Copromotor/Begeleider: Student(e): Student(e):
1/4/'19	Bespreking statistiek en results	Promotor: Copromotor/Begeleider: Student(e): Student(e):
4/5/'19	Bespreking results en discussie	Promotor: Copromotor/Begeleider: Student(e): Student(e):
15/5/'19	Bespreking MP & statistiek	Promotor: Copromotor/Begeleider: Student(e): Student(e):
21/5/'19	Bespreking voortgang MP methode - discussie - lay-out.	Promotor: Copromotor/Begeleider: Student(e): Student(e):