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2015•2016
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
*master in de revalidatiewetenschappen en de kinesitherapie*

# Masterproef

## The impact of a physical running training program on cognitive-motor dual task performance in persons with multiple sclerosis

Promotor :
Prof. dr. Peter FEYS

Copromotor :
Dr. Carmela LEONE

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*Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie*

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# THE IMPACT OF A PHYSICAL RUNNING TRAINING PROGRAM ON COGNITIVE-MOTOR DUAL TASK PERFORMANCE IN PERSONS WITH MULTIPLE SCLEROSIS

Sarah Delva

2015-2016
Promotor: Prof. Dr. Peter Feys
Co-promotor: Dr. Carmela Leone

## Acknowledgement

Working on this master thesis was an interesting experience, during which I learnt a lot. I would like to thank especially my promotor Prof. Dr. Peter Feys, for the many challenging questions and propositions as well as for the numerous suggestions for improving my work and for the chance he gave me to participate in his research team at the REVAL centre of the University of Hasselt. Also the support of Mr. Paul Van Asch is highly appreciated. During the different phases of this thesis project, I really enjoyed working with dr. Carmela Leone, drs. Lousin Moumdjian and dr. Florian Van Halewyck in the research team as well as with the MS patients participating in the study.

Leuven, May, 23 2016 SD

## Research context

Patients with multiple sclerosis (pwMS) are often confronted with motor impairments as well as cognitive deficits. Physical and cognitive training are expected to have a beneficial effect on patient’s motor and cognitive capacity, thereby reducing impairments or slowing down their progression. In evaluating the impact of rehabilitation, as well as in research, most often motor and cognitive function are measured separately, whereas in daily life, people often have to perform both functions at the same moment. Furthermore, in evaluating the physical and cognitive status of patients simultaneously, it is important to realise that cognitive motor interference (CMI) may be present. When at least two tasks are performed at the same moment, outcomes may be worse than when single tasks are performed.

Dual tasking is often the case in daily life. Therefore, not only physiotherapists, but also patients, medical doctors, other health care providers and patients’ family and friends should understand the impact of CMI. It is of importance to physiotherapists who are in direct contact with pwMS. Physiotherapists tend to practice for example gait as a single task, without asking the patient to do something else simultaneously, e.g. walking while talking. However, in daily life, people very often simultaneously use both functions. Therapists should be aware of this CMI and should not only practice with the patient under single but also under dual task conditions. Also other health care providers who are in touch with pwMS, such as nurses and medical doctors, should be aware of the possibility of CMI and its impact on training outcomes. Finally, pwMS, their families and friends should be made aware of CMI, and its impact of patients’ motor and cognitive functioning.

While it is established that training may improve fitness in pwMS, it is important to investigate the impact of training on CMI, since dual tasking is more common in daily life than single tasking. The focus of this thesis is on physical running training and its impact on motor dual task performance. Other parts of the project deal with cognitive dual task performance.

The specific patient group in the study is persons with mild MS, being patients with only limited impairments and hence limited deterioration of physical functioning. Dual task assessment in these patients may even be considered as an early marker of impairment in daily life motor performance.

The specific focus on this thesis project is on the impact of physical (running) training on dual task performance in patients with mild MS.

This master thesis part 2 was done in Diepenbeek at the research centre REVAL of UHasselt. It is part of a broader research project, about the influence of rehabilitation therapy on the cognitive and motor functioning and on neuroplasticity of pwMS, performed under the supervision of Prof. Dr. Peter Feys and Prof. Dr. Bert Op 't Eijnde, at the rehabilitation research centre REVAL of UHasselt in Diepenbeek.

This master thesis contributed to the research design with a critical appraisal of this design (part I of master thesis). Recruitment of participants in the clinical study was performed by other team members, but part of the data acquisition (baseline and post training measurements in most of the participants) for the single and dual tasks was performed during the master thesis work. The thesis work also involved active participation in the two group training (team building) sessions as well as in the MS Run organised in Antwerp. Data processing for the outcome measures reported in this thesis was performed as part of the thesis work, with methodological support of the research team about the statistical techniques to be used. The research paper was written entirely by the student, with, of course, several feedback moments from the promotor.

## Abstract

**Background**: Patients with multiple sclerosis (pwMS) are often confronted with motor as well as cognitive deficits. These may already show up during the early disease phases. Physical and cognitive training may reduce impairments or slow down progression. In daily life, cognitive motor interference (CMI) may be present: when at least two tasks are performed simultaneously, outcomes may be worse than when single tasks are performed. The impact of physical training on dual task performance should be studied, since this setting is more relevant for daily life than single tasking. This study deals specifically with persons with mild MS, being patients with little impairments,

**Objectives**: the impact of a 12 weeks home based running training program on motor dual task performance in patients with mild MS is investigated.

**Participants**: 21 MS patients were assigned to the experimental group (running training) and an equal number to a control group (no training).

**Measurements**: motor and cognitive performance under single and dual task conditions were measured at baseline and twelve weeks later. Dual task cost (DTC) was calculated.

**Results**: A 12 week running training program may have a beneficial effect on some gait parameters in patients with mild MS. At baseline, walking capacity was comparable to that of healthy subjects. Each of the gait parameters was increased for the experimental group twelve weeks after the baseline measurement. But only a few of these improvements were statistically significant, compared to the control group. This was the case for cadence and velocity for one dual task: 15 sec walking with word list generation. No significant differences were found in the DTC, which was low in all situations.

**Conclusion**: Running training may improve single and dual task performance in patients with mild MS.

## Introduction

Common symptoms of multiple sclerosis (MS), an immune-mediated neuro-degenerative disease, involve muscle weakness, extreme fatigue, imbalance, impaired speech, double vision, cognitive dysfunction and paralysis (Latimer-Cheung et al., 2013). The neuro-degenerative disease process leads to deficits in motor and cognitive functions. Motor deficits include impairments in gait and balance and appear in up to 85% of MS patients (Larocca, 2011). About 65% of persons with MS (pwMS) report cognitive deficits (Chiaravalloti & DeLuca, 2008; Wajda & Sosnoff, 2015). The cognitive impairments concern memory, visuospatial perception, executive functions, attention and information processing speed (Stoquart-ElSankari, Bottin, Roussel-Pieronne, & Godefroy, 2010). Especially cognitive processing speed and episodic memory are impaired (Motl, Gappmaier, Nelson & Benedict, 2011). Both motor and cognitive impairments lead to reduced mental, cardiovascular, neuromusculoskeletal functions, resulting in reduced walking performance such as physical activity (Motl & Pilutti, 2012). The review of the evidence on this topic, by Motl and Pilutti (2012), based on the ICF-model, showed that these impairments may further reduce participation in activities of daily living, in recreational, work or other social activities and hence in reduced quality of life. Physical inactivity can further initiate a cycle of worsening functioning and aggravating symptoms.

Previous research has shown that physical activity, especially exercise training, may benefit pwMS (Motl & Sandroff, 2015). The concept ‘exercise training’ refers to “planned, structured and repetitive physical activity undertaken over a prolonged period to maintain or improve physical fitness and functional capacity” (Motl & Pilutti, 2012, p. 488). Motl, Learmonth, Pilutti, Gappmaier, and Coote (2015) reported that the evidence suggests beneficial effects of exercise training on health-related fitness (Briken et al., 2014; Latimer-Cheun et al., 2013), walking function (Snook & Motl, 2009), balance (Paltamaa, Sjogren,Peurala & Heinonen, 2012), fatigue (Pilutti, Greenlee, Motl, Nickrent & Petruzello, 2013), depression (Ensari, Motl & Pilutti, 2014) and quality of life (Motl & Gosney, 2008). A systematic review found strong evidence that moderate intensity training, twice a week, increased aerobic capacity and muscular strength (Latimer-Cheung et al., 2013). Exercise may improve mobility, fatigue and health-related quality of life. A meta-analysis of 22 studies, focusing on the impact of exercise training on walking mobility, revealed a small improvement in walking mobility in pwMS (Snook & Motl, 2009). Also Pearson, Dieberg, and Smart (2015) identified significant improvements in walking speed after exercise training in pwMS.

Already in the early stage of the disease, pwMS may experience motor deficits manifested by reduced walking speed (Kalron, Achiron & Dvir, 2011). A number of studies explicitly report the impact of physical training, depending on the disability level. Snook and Motl (2009) concluded from their meta-analysis that physical training yielded small improvements in walking performance, but greater in patients with mild MS than in pwMS with moderate disability. Filipi, Kucera, Filipi, Ridpath, and Leuschen (2011) found parallel improvement in strength and endurance after resistance training, independent of the disability level. Likewise, Sandroff et al. (2013) found that a training intervention through internet improved walking performance, independent of the mild or moderate disability status of the pwMS. Latimer-Cheung et al. (2013) concluded from a systematic review that exercise training, performed twice a week at a moderate intensity, was effective for increasing aerobic capacity and muscular strength in pwMS with mild to moderate disability. Kalron et al. (2015) reported improvements in all walking outcome measures after a personalised 3 week intense physical rehabilitation program, whereby the pwMS with moderate and severe disability showed more improvement than the group with mild disability. In any case, all studies reported a beneficial impact of training, even in patients with mild MS, and hence little impairments.

Physical training may not only improve motor functions, but was recently suggested to also improve cognitive function (Motl, Sandroff & Benedict, 2011). A first RCT indeed demonstrated a significant improvement in cognitive function after physical training in pwMS with mild disability and a smaller impact in pwMS with moderate disability (Sandroff et al., 2014). Briken et al. (2014) demonstrated a beneficial effect of exercise on aerobic fitness, walking ability and small effects on several domains of cognitive function as visuospatial memory and alertness in patients with progressive MS and moderate disability.

The impairments in motor functions and restrictions in cognitive functioning have frequently been studied separately (Patti, 2009; Stoquart-ElSarkani et al., 2010). However, in daily life, people very often simultaneously use both functions, e.g. walking while talking. Research on the simultaneous execution of motor and cognitive tasks has identified interactions; the so-called cognitive-motor interference (CMI) (Wajda & Sosnoff, 2015). In an overview of 14 papers dealing with walking in pwMS, Leone, Patti, and Feys (2014) consistently found that motor function declines under dual tasking conditions (e.g. reduction of gait velocity, reduced step length, increased variability). A slowing of ambulation was consistently found in most of the studies, regardless of the nature of the cognitive dual task, the stage of the disease and the disability level in the MS patients. However, some studies showed a differential impact, depending on the disability level. For instance, Sosnoff et al. (2014) found higher CMI in more disabled pwMS.

The mechanisms underlying CMI are not yet fully understood, but different theories have been proposed (Leone et al., 2014). The capacity-sharing theory argues that each task uses part of the attention resources. Since attention resources are limited, CMI will arise once the required attention resources for performing all tasks exceed the total capacity. The bottleneck model argues that if the different tasks make use of shared brain networks, a bottleneck in information processing may occur (Leone et al., 2014). Some authors propose additionally the self-awareness theory, in which people are self-aware of their limitations and therefore consciously prioritize tasks (Wajda & Sosnoff, 2015). CMI is operationalized as dual task cost (DTC), being the difference in outcomes between performance in isolation (single task) and dual tasking performance.

Assessing the impact of physical training on motor functions, while simultaneously performing a second (dual) task, may be a more valid outcome measure for functional daily ability than single task motor performance (Leone et al., 2014; Yang, Wang, Cheng & Kao, 2007). DTC may be a more relevant measure (than single task outcomes) to evaluate the effectiveness of rehabilitation strategies to improve motor and cognitive functioning of pwMS in daily life. Dual task assessment may even be considered as an early marker of impairment in daily life motor performance, even in patients with little or no physical disability (Leone et al., 2014). For instance, Kalron, Achiron, and Dvir (2010) found that a dual task performed by patients with a clinically isolated syndrome, suggestive of MS, resulted in lower performance, compared to healthy subjects. Allali et al. (2014) likewise confirmed a decrease in walking speed and stride length during dual tasking in minimally impaired pwMS (mean EDSS = 1.90 ± 1.01).

Up to now, very few studies have investigated the impact of treatment (e.g. physical training) by pwMS on their single and dual task motor outcomes and on the DTC. The pilot study of Allali et al. (2014) examined the impact of one year of medication treatment (natalizumab) on dual task motor performance (gait) in 9 pwMS. We have found no studies that investigated the impact of physical training on dual task performance, specifically in patients with mild MS. This is the focus of our study (pwMS with EDSS-score between 0.5 and 3). Our study investigated whether physical running training for pwMS with mild disability levels improves their ability to perform single and dual motor tasks and how it affects their CMI, measured in terms of the DTC for motor functioning. The impact on cognitive and motor functions itself as well as aspects of quality of life will be reported in other master theses.

## Methods

### Selection and description of participants

The study focused on pwMS, being able to walk 5 km without rest or assistive device, which is corresponding to so-called minimal disabilities (EDSS-score between 0.5 and 3). Other inclusion criteria were being older than 18 years, and having signed the informed consent documents. Exclusion criteria were being able to run 5 km or more in the six months preceding the start of the study or participating in another study on physical training. Patients were excluded when they got seriously ill or experienced a serious deterioration of MS, when the kind of medication or the dosing of their medication was altered substantially during the course of the intervention and in case of pregnancy.

Potential participants were recruited through several channels where the study was announced: MS rehabilitation centres (REVAL rehabilitation research centre in Hasselt, the Rehabilitation and MS Centre in Overpelt, De MICK in Brasschaat, National MS centre in Melsbroek and the non-for-profit organisation Move to Sport which created a network in Flanders of MS-educated health care providers), social media and the website of the Flemish MS League and other active MS groups.

Approval for this study (including the informed consent document) was obtained from the Medical Ethics Committee of the Jessa hospital in Hasselt and from the Medical Ethics Committee of the UHasselt.

### Experimental design and procedure

A controlled trial was set up to investigate the research questions. Of the 50 candidates that attended the information and 5 km walking sessions organized in December 2014 and early January 2015 in Antwerp and Hasselt, 42 patients were assigned to either the experimental group (EXP) or the 'waiting list' control group (WLC). 8 candidates were not assigned: 2 did not meet the inclusion criteria of being able to walk 5 km without rest or aid, 4 were discouraged by the extent of the training and 2 by lack of support in their environment for the self-driven community based training. For motivational reasons, assignment to one the groups was mainly based on the individual preference of each participant to run in either a public running event in April in Antwerp, or in October in Hasselt. 21 patients were willing to start with a 12 week training program, leading to participation on the MS Run in Antwerp (April 26th, 2015). They were allocated to the experimental group (EXP). 21 patients participated in a 12 weeks training program over summer with participation in the 'Dwars door Hasselt' run in Hasselt (October 11th, 2015) as a goal, and were allocated to the 'waiting list' control group (WLC). Fig. 1 gives an overview of the study design and the number of participants for whom a full data set could be collected. During the study, 7 participants dropped out, for different reasons: the combination of participation in this study with work was too exhausting, moving to another country and too much discomfort at baseline measurements.

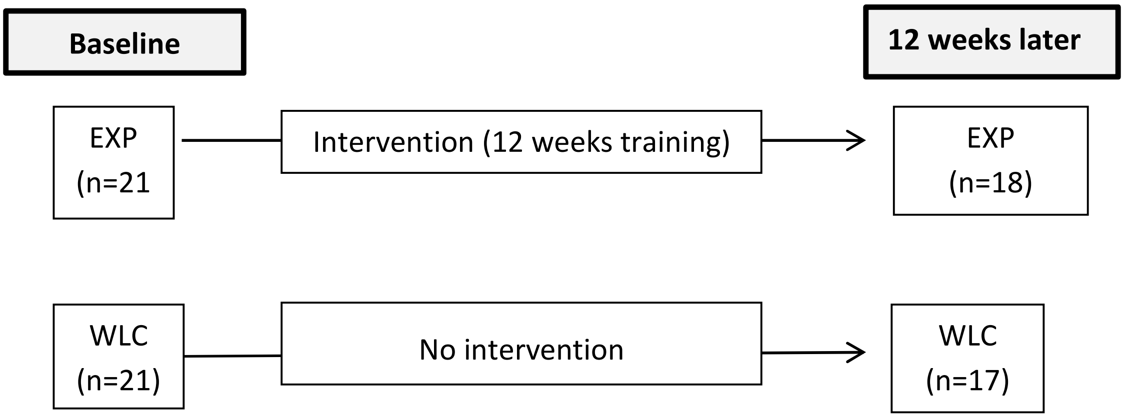

**Fig. 1**: Overview of the study design and patient flow chart.

The training that was offered consisted of a 12 week training program to be performed at home, with submaximal running training for a duration that is gradually increased, *until* the patient can run 5 km. At the start of the study, the participants received a personalized training schedule, which allowed them to train three times per week. The starting level was based on the results of a maximal endurance test. Training originally consisted of short running bouts followed by longer walking bouts, until a total distance of 5 km was covered. However, the relative amount of running gradually increased throughout the twelve weeks of training whereas the relative amount of walking gradually decreased. In the first week, the participants had to walk three times 5 km. The duration of these trainings was estimated at 60 minutes. From the second to the fourth week, the training instructions were increased to "running at 8 km/h for a couple of minutes, followed by a few minutes of walking at 5 km/h”. From week five until week twelve the running speed of 8 km/h was increased to 9 km/h.

All the participants were wearing a Withings Pulse Ox all day during the training period. This device registers the number and intensity of steps per minute and the distance covered. The participants had to upload their data at least once a week, to allow the assessors to evaluate each patient’s amount of physical activity and intensity. These data were checked weekly remotely to verify treatment adherence. If it was noticed that a participant was inactive, he or she received a call to ask for the reason. Participants themselves had also access to their data through personal web-based log-in.

This 12 week training program was offered to the EXP group. The WLC group was not immediately offered the 12 week training program. These patients participated only on the measurements at baseline and 12 weeks later. After the post measurement, the members of WLC were offered the opportunity to participate in the next 12 week training program, on a voluntary basis, but measurement of performance in, or effects of this training program was not part of the study protocol. After these 12 weeks, the participants were tested again on the same parameters as during the baseline measurement.

This master thesis focused specifically on the motor aspects of CMI – while other master theses dealt with the cognitive aspects. Hence the primary outcome measures were the single and dual motor task outcomes, enabling to calculate the dual task cost (DTC).

The primary outcome measures in this thesis were single motor and dual cognitive-motor task outcomes during walking, as well as DTC. The single motor tasks involved walking for 15 sec or for 60 sec, while holding a cup filled with water in one hand (15secW and 60secW). Participants walked at their usual speed. The outcomes of these tasks were measured in terms of gait velocity (in m/sec), stride length (in m/step) and cadence (in steps/min). The dual tasks consisted of a motor task (walking with a cup) combined with one out of 3 cognitive tasks. These tasks were: subtracting by 7, digit span forward (dsf, repeating a set of numbers) and word list generation (wlg, giving as many words as possible starting with a certain letter). Dual task performance was measured, both for motor and for cognitive tasks but analysed only for the motor tasks. Dual task cost (DTC) was operationalised with the formula DTC = (Single task outcome – dual task outcome) / single task outcome * 100. It was expressed as a ratio variable (%).

## Statistics

Statistical analyses were completed using SAS JMP version JMP pro 11.2 (SAS Institute Inc.). To check for potential differences between groups at baseline, in gait parameters, HADS and FSMC scores, an unpaired t-test was used. The main analysis of the gait parameters, the DTC and the HADs and FSMC was done with a Mixed Models ANOVA. For every parameter the mean, the standard deviation, the 95% confidence interval and the delta (difference between baseline scores and scores 12 weeks later) were calculated. The group (EXP versus WLC) effect, the time (baseline versus 12 weeks later) effect and the group*time interaction effect were studied. A significant difference was reported when $p < 0.05$ and a trend to significance was reported when $0.05 \leq p < 0.1$.

## Results

Baseline patient characteristics are reported in table 1.

**Table 1**: Baseline characteristics of participants

| Variable | | EXP | WLC | p-value |
|---|---|---|---|---|
| Age (yrs) | | 36.64 ± 8.53 (19.5-51.3) | 44.35 ± 8.54 (29.2-62.4) | n.s. |
| Height (cm) | | 168 ± 6 (157-179) | 169 ± 7 (155-180) | n.s. |
| Weight (kg) | | 67.20 ± 15.22 (50.105.0) | 76.13 ± 9.55 (58.0-92.0) | n.s. |
| Sex (M/F) | | 1/20 | 3/18 | n.s. |
| HADS | Anxiety | 5.71 ± 4.42 (3.70-7.73) | 5.95 ± 4.17 (4.06-7.85) | n.s. |
| | Depression | 5.33 ± 4.70 (3.19-7.47) | 3.52 ± 2.99 (2.16-4.89) | n.s. |
| | Total | 10.43 ± 6.67 (7.39-13.46) | 9.48 ± 6.58 (6.48-12.47) | n.s. |
| FSMC | Physical | 32.29 ± 8.81 (28.28-36.30) | 29.29 ± 9.41 (25.00-33.57) | n.s. |
| | Mental | 33.38 ± 9.99 (28.84-37.93) | 28.86 ± 10.00 (24.31-33.41) | n.s. |
| | Total | 65.67 ± 18.31 (57.34-74.00) | 58.14 ± 18.92 (49.53-66.75) | n.s. |

p value: ** $p < 0.05$; * $0.05 \le p < 0.1$ or n.s. (not significant)

Table 1 shows the results of the comparison for the demographic factors and for quality of life indicators between the EXP and the WLC group at baseline. The participants in EXP were on average younger (average of 36.64 years) than in WLC (average of 44.35 years), but this difference was not significant. There was no significant difference in length nor weight between both groups either. The majority of participants in both groups were women. There were no significant differences in quality of life, as measured by the HADS (hospital anxiety and depression scale) and the FSMC (fatigue scale for motor and cognitive function) either.

At baseline (cf. table 2), for the two single tasks, significant differences were found for velocity and cadence. The WLC group walked faster and at higher cadence than the EXP group. Both groups were comparable for stride length in the single task conditions. It must be noticed that, on average, participants in this study had baseline gait parameters that were comparable to those of healthy subjects under normal walking conditions. Peterson, Perry, and Montgomery (1985) report for healthy subjects a velocity of about 1.4m/sec, a cadence 120 steps/min and a stride length of 1.4m.

At baseline, there were almost no significant differences between the EXP and the WLC group for every dual task outcome. Only for the parameter cadence, there was a trend towards significance for two dual tasks, 60secW-dsf and 15secW-wlg.
The DTC differed only significantly between the EXP and the WLC group at baseline for stride length during the 60secW-dsf task.

Table 2 further reports the results of the EXP and the WLC group, at baseline and 12 weeks later of running training for the EXP group or unchanged therapy for the WLC group. When inspecting the numbers, comparing the baseline measurement and the measurements 12 weeks later, the EXP group improved its average gait performance after the training, in all of the single and dual task conditions. For about half of the parameters and half of the cognitive distractors, in the EXP group, the DTC decreased, while for the other half, the DTC increased. For the WLC group, at twelve weeks after the baseline measurement, some outcomes were better than at baseline, while others were worse.

Next, the statistical results are reported, first regarding a group effect followed by a time effect. Lastly, the time*group interaction effect is described.

The group effect describes whether there is a significant difference between the EXP and the WLC group in terms of the gait parameters across the measurements at baseline versus 12 weeks later.
Both groups were significantly different for the 60secW single task, for the gait parameters velocity and cadence, but not for stride length. The post-hoc (Tuckey's) tests showed that both gait parameters were better in the EXP than in the WLC group. Under the other single task setting (15secW), there was only a trend towards significance for cadence (p=0.09).
There was no significant difference between both groups under the dual task settings.
Concerning the DTC, there was a significant difference, for the parameter stride length under the dual task 60 secW-dsf. The post-hoc test showed that the DTC was larger for the EXP group than for the WLC group.

**Table 2**: Baseline and 12 weeks later measurements for the EXP and the WLC group

| Task | | Gait Parameter | EXP GROUP | | | WLC GROUP | | | p-values | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Baseline | 12 weeks later | Delta | Baseline | 12 weeks later | Delta | Baseline | Group | Time | Interaction |
| SINGLE MOTOR TASK | 15secW | Velocity | 1.45 ± 0.12<br>(1.39-1.51) | 1.52 ± 0.13<br>(1.45-1.59) | -0.07 | 1.55 ± 0.15<br>(1.49-1.62) | 1.53 ± 0.15<br>(1.44-1.61) | 0.03 | 0.024** | 0.107 | 0.360 | 0.126 |
| | | Stride length | 1.47 ± 0.08<br>(1.43-1.51) | 1.50 ± 0.06<br>(1.46-1.53) | -0.03 | 1.47 ± 0.09<br>(1.43-1.52) | 1.49 ± 0.07<br>(1.45-1.53) | -0.01 | 0.852 | 0.873 | 0.061* | 0.897 |
| | | Cadence | 118.84 ± 8.12<br>(115.14-122.54) | 121.93 ± 10.60<br>(116.28-127.58) | -3.09 | 126.57 ± 11.62<br>(121.28-131.86) | 12.,86 ± 9.96<br>(117.11-128.61) | 3.71 | 0.017** | 0.089* | 0.993 | 0.10* |
| | 60secW | Velocity | 1.41 ± 0.11<br>(1.36-1.46) | 1.49 ± 0.12<br>(1.42-1.55) | -0.08 | 1.52 ± 0.14<br>(1.45-1.58) | 1.51 ± 0.11<br>(1.45-1.58) | 0.00 | 0.008** | 0.027** | 0.043** | 0.159 |
| | | Stride length | 1.46 ± 0.07<br>(1.43-1.50) | 1.50 ± 0.06<br>(1.46-1.53) | -0.03 | 1.48 ± 0.08<br>(1.45-1.52) | 1.50 ± 0.06<br>(1.46-1.53) | -0.01 | 0.423 | 0.561 | 0.03** | 0.604 |
| | | Cadence | 115.29 ± 8.22<br>(111.55-119.03) | 119.19 ± 9.28<br>(114.24-124.13) | -3.90 | 122.90 ± 11.28<br>(117.62-128.18) | 121.48 ± 9.26<br>(116.13-126.82) | 1.43 | 0.019** | 0.043** | 0.224 | 0.193 |
| DUAL TASK (MOT + COG) | 15secW-by7 | Velocity | 1.37 ± 0.14<br>(1.31-1.43) | 1.46 ± 0.13<br>(1.39-1.53) | -0.09 | 1.42 ± 0.17<br>(1.35-1.50) | 1.43 ± 0.13<br>(1.36-1.51) | -0.01 | 0.266 | 0.575 | 0.026** | 0.129 |
| | | Stride length | 1.46 ± 0.08<br>(1.41-1.48) | 1.48 ± 0.06<br>(1.45-1.51) | -0.03 | 1.44 ± 0.10<br>(1.39-1.48) | 1.46 ± 0.07<br>(1.42-1.50) | -0.02 | 0.806 | 0.705 | 0.046** | 0.802 |
| | | Cadence | 113.74 ± 9.71<br>(109.32-118.16) | 118.80 ± 9.72<br>(113.62-123.98) | -5.06 | 118.96 ± 12.57<br>(113.24-124.68) | 117.90 ± 9.88<br>(112.19-123.60) | 1.06 | 0.140 | 0.362 | 0.115 | 0.079* |
| | 60secW-dsf | Velocity | 1.35 ± 0.11<br>(1.30-1.40) | 1.43 ± 0.12<br>(1.37-1.49) | -0.08 | 1.41 ± 0.16<br>(1.34-1.49) | 1.42 ± 0.12<br>(1.35-1.49) | -0.01 | 0.171 | 0.342 | 0.023** | 0.207 |
| | | Stride length | 1.45 ± 0.07<br>(1.42-1.48) | 1.48 ± 0.06<br>(1.45-1.51) | -0.03 | 1.44 ± 0.09<br>(1.39-1.48) | 1.47 ± 0.07<br>(1.43-1.51) | -0.03 | 0.673 | 0.647 | 0.006** | 0.989 |
| | | Cadence | 112.19 ± 8.05<br>(108.52-115.85) | 115.86 ± 8.63<br>(111.26-120.46) | -3.67 | 117.86 ± 11.47<br>(112.64-123.08) | 116.14 ± 9.44<br>(110.91-121.37) | 1.71 | 0.072* | 0.173 | 0.202 | 0.148 |
| | 15secW-wlg | Velocity | 1.35 ± 0.14<br>(1.29-1.42) | 1.41 ± 0.12<br>(1.35-1.47) | -0.06 | 1.42 ± 0.14<br>(1.36-1.49) | 1.38 ± 0.15<br>(1.30-1.47) | 0.04 | 0.113 | 0.504 | 0.721 | 0.030** |
| | | Stride length | 1.44 ± 0.08<br>(1.41-1.48) | 1.47 ± 0.06<br>(1.44-1.50) | -0.03 | 1.44 ± 0.09<br>(1.40-1.48) | 1.45 ± 0.07<br>(1.41-1.49) | -0.01 | 0.891 | 0.660 | 0.133 | 0.482 |
| | | Cadence | 112.84 ± 9.71<br>(108.42-117.26) | 115.33 ± 8.78<br>(110.65-120.01) | -2.49 | 118.8 ± 10.18<br>(114.25-123.51) | 114.51 ± 11.84<br>(107.95-121.07) | 4.37 | 0.056* | 0.309 | 0.577 | 0.014** |
| Dual task cost (DTC) | 15secW-by 7 | Velocity | 5.61 ± 7.68<br>(2.12-9.11) | 3.77 ±4.96<br>(1.13-6.41) | 1.84 | 8.11 ± 8.15<br>(4.40-11.83) | 5.69 ± 8.05<br>(1.04-10.34) | 2.43 | 0.312 | 0.263 | 0.128 | 0.929 |
| | | Stride length | 1.61 ± 3.20<br>(0.15-3.07) | 1.39 ± 1.74<br>(0.46-2.32) | 0.22 | 2.47 ± 3.15<br>(1.04-3.90) | 2.04 ± 2.82<br>(0.41-3.66) | 0.43 | 0.385 | 0.297 | 0.580 | 0.981 |
| | | Cadence | 4.18 ± 6.72<br>(1.12-7.24) | 2.43 ± 4.62<br>(0.04-4.89) | 1.76 | 5.92 ± 6.04<br>(3.17-8.67) | 3.84 ± 6.34<br>(0.18-7.49) | 2.09 | 0.382 | 0.340 | 0.087* | 0.926 |
| | 60secW-dsf | Velocity | 3.61 ± 6.06<br>(0.86-6.36) | 3.68 ± 5.55<br>(0.73-6.64) | -0.07 | 6.69 ± 7.19<br>(3.33-10.06) | 5.65 ± 7.13<br>(1.54-9.77) | 1.04 | 0.147 | 0.160 | 0.519 | 0.649 |
| | | Stride length | 1.03 ± 1.91<br>(0.17-1.90) | 1.09 ± 1.94<br>(0.06-2.13) | -0.06 | 2.78 ± 2.55<br>(1.59-3.97) | 2.04 ± 2.52<br>(0.59-3.49) | 0.74 | 0.019** | 0.026** | 0.451 | 0.452 |
| | | Cadence | 2.59 ± 4.64<br>(0.48-4.70) | 2.66 ± 4.55<br>(0.24-5.09) | -0.08 | 4.12 ± 5.80<br>(1.41-6.84) | 3.81 ± 5.78<br>(0.47-7.14) | 0.32 | 0.358 | 0.506 | 0.575 | 0.733 |
| | 15secW-wlg | Velocity | 6.60 ± 8.75<br>(2.61-10.56) | 6.76 ± 7.75<br>(2.63-10.89) | -0.16 | 8.10 ± 6.76<br>(5.02-11.17) | 8.44 ± 8.19<br>(3.71-13.17) | -0.34 | 0.537 | 0.350 | 0.647 | 0.606 |
| | | Stride length | 1.88 ± 2.59<br>(0.71-3.06) | 1.79 ± 2.41<br>(0.51-3.07) | 0.09 | 2.46 ± 2.56<br>(1.30-3.63) | 2.69 ± 2.62<br>(1.18-4.20) | -0.22 | 0.470 | 0.251 | 0.887 | 0.702 |
| | | Cadence | 4.88 ± 7.63<br>(1.40-8.35) | 5.11 ± 6.76<br>(1.51-8.71) | -0.23 | 5.89 ± 5.07<br>(3.58-8.19) | 6.03 ± 7.29<br>(1.82-10.24) | -0.15 | 0.617 | 0.460 | 0.633 | 0.670 |

* 0.05 ≤ p < 0.1 (nearly significant)
** p < 0.05 (significant)

velocity is measured in m/sec
stride length in cm/step
cadence in steps/min
DTC is expressed in %

W= walking (15 sec or 60 sec)
by7 = distracting by 7
dsf = digit span forward
wlg = word list generation

The time effect describes whether there is a significant difference in the gait parameters between the baseline measurements and twelve weeks later, across the two groups.

The baseline and 12 weeks later measurements were statistically significantly different for the 60secW single task, for the gait parameters velocity (p=0.04) and stride length (p=0.03). After the training, velocity was higher and stride length was larger than before the training. A trend to significance was observed for stride length in the 15secW single task (p=0.06).

There was likewise a significant difference under two dual task conditions (15secW-by7 and 60secW-dsf), for velocity and stride length. After the period of 12 weeks, velocity was higher and stride length was larger than before. No significant differences were detected for cadence.

There were no significant time effects  for any of the DTC either. There was only a tendency towards significance for cadence in the DTC of the 15secW-by7 task (p=0.09).

Finally, for the interaction effect, for the single tasks, a trend to significance was found for cadence during the 15secW single task (p=0.1) and no significant differences for other gait parameters.

For the dual tasks, a significant time*group interaction was found for velocity and cadence during 15secW-wlg. Post-hoc tests revealed that these gait parameters improved for the EXP group only after training. A trend to significance was found for cadence during 15secW-by7 (p=0.08). Also in this case, cadence improved after training in the EXP group only.

No significant group*time interaction effects were detected for the DTC in the different experimental conditions.

## Discussion

The study setting showed that a 12 week running training can have a beneficial effect on some gait parameters in patients with mild MS, who had a baseline walking capacity comparable to that of healthy subjects. Although for each of the gait parameters, measurements were, on average, better for the EXP group after than before the running training under all single and dual task conditions, only a few of these improvements were statistically significant, compared to the WLC group. This was the case for the gait parameters cadence and velocity in one dual task (15secW-ph). There was also a trend towards significance for cadence under the 15secW single task and the dual task 15secW-by7. No significant differences were found in the DTC, which was moreover rather low, indicating limited CMI for all study patients.

That not more significantly different results were found, may be due to the fact that no large CMI was present in this population. The average DTC for the different dual tasks and in the different settings (EXP and WLC, at baseline and 12 weeks later) ranged between 1.03% and 8.11% whereas other studies have reported higher DTCs in pwMS. The review by Leone et al. (2014) reported a DTC for velocity that ranged from 5.6% to 34.4% and 8 of the 14 included studies reported DTC of over 10%.

Also certain aspects of the study, such as the inclusion criteria, the nature of the intervention and the outcome measures may imply that the study conditions were not sensitive enough to detect relevant results.

Only pwMS with a relatively low EDSS score, who were able to walk 5 km before the start of the training were included in the study. Perhaps, the physical walking capacity of these patients is ‘too good’ to benefit from the training program involving a 12 week ‘light to moderate running’ training, compared to no training at all. In fact, the measured motor outcomes involve ‘walking at comfortable speed’ and at baseline walking speed was overall within the normal ranges for healthy subjects.

A self-selection bias may further have occurred, since all participants, both in the EXP and the WLC group were motivated to engage in physical training. In a study setting with participants highly motivated to improve their physical condition, also in the WLC group and with participants who did not have a very bad condition to start with, it may be difficult to detect significant differences in both groups. Furthermore, no randomized design was used, to be able to take into account participants' preferences regarding the timing of their training program and location for running and hence avoid drop-outs.

The training program consisted of a 12 week running training, during with patients were asked to do 3 training sessions per week. Adherence to the training scheme was only checked through random sampling of the Withing Pulse Ox measures. No information was available on the nature and intensity of exercising or other motor training in patients, neither in the EXP nor the WLC group. It is not known to what extent participants, in both the EXP and the WLC group did e.g. not, besides physical training, engage in gardening, cycling, … or other activities that may improve fitness. Hence it is not sure that there was indeed a 'true difference' in training intensity of 3 weekly sessions between the EXP and the WLC group. Future research could compare training programs, supervised in a lab or clinic setting with the unsupervised, self-motivated community training setting that was used in our set up. Supervised training in a lab setting may give more certainty about the intensity of training in the EXP group. In a previous meta-analysis, it was suggested that effect of exercise on walking was smaller in unsupervised compared to supervised settings (Snook & Motl 2009). However, we are confident that the EXP group has performed the running intervention based on the remote accelerometry monitoring as well as the fact that this group had improved its physical fitness levels during V02max testing in contrast to the WLC group (data reported in other master thesis).

Some of the single and dual task tests may not be specific nor sensitive enough to detect a relevant impact of physical training. Perhaps a 15 sec, or even a 60 sec walking test at normal speed is too short to find significant differences between both groups and between pre- and post-measurements in people with mild MS. Kalron et al. (2015) found only a minimal detectable change in the 2 min walking test, but not in the 10m and 20m walking test, which lead them to conclude that short walking tests may obscure the effectiveness of a training program. This may even be more the case in our study, dealing with persons with mild MS, who had a baseline capacity for normal walking, comparable to healthy subjects. A test where patients walk longer (e.g. the 6MWT) is recommended and was indeed performed for one of the other master thesis projects.

For the dual tasks, no specific instructions were given to the participants as to the sequence in which they had to perform both tasks. This approach assured that each participant implicitly decided for himself on how to give attention to and perform the dual tasks simultaneously. But it had the disadvantage that the results might be affected by the way in which participants learn to prioritize these tasks. The way participants learnt may be unaffected by the physical training, but may be a personal characteristic that was not evenly distributed among the EXP and the WLC group. Hence, for future research it is recommended to give more precise instructions as to how the participants should perform their dual tasks.

Finally, physical training may not only improve motor function, but also cognitive functioning of pwMS (cf. other master thesis), but it is surely also worthwhile to further investigate the reverse impact. Interventions to improve cognitive function may potentially improve motor performance of pwMS, be it through medication or cognitive exercising (Kalron, 2015). More specifically, also the impact of dual task training, with both physical and cognitive training, on CMI could be investigated. Kramer, Dettmers, and Gruber (2014) is the only study, to our knowledge, that focused on the impact of dual task training on 70 pwMS. The training consisted of posture control on an unstable surface, combined with either conventional balance training or playing exergames, which were considered as dual tasks. They reported a reduction in DTC between 10 and 20% after dual task training. Their study however, focused on a combination of two motor training tasks. We did not find other studies that focused on dual task training in pwMS. Future research should focus on the impact of combined motor-cognitive training on dual task performance.

## Conclusions

The study setting showed that a 12 week running training can have a beneficial effect on some gait parameters in patients with mild MS, with a baseline walking capacity comparable to that of healthy subjects. Although for each of the gait parameters, measurements were, on average, better for the EXP group after than before the running training under all single and dual task conditions, only a few of these improvements were statistically significant, compared to the WLC group. No significant differences were found in the DTC, which was moreover rather low.

The lack of significant results may be due to a number of characteristics of the study: the target group consisted of persons with mild MS with a normal baseline walking capacity, the mild to moderate training program was unsupervised and the outcome measures may not have been sensitive or specific enough to detect a training impact in pwMS with mild impairments. Future research should investigate the precise impact of these factors as well as the impact of combined motor and cognitive training on dual task performance.

## Conflict of interests

None.

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Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
**The impact of a physical running training program on cognitive-motor dual task performance in persons with multiple sclerosis**

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2016**

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