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Cognitive-motor interference in people with mild to moderate multiple sclerosis, in comparison with healthy controls

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ABSTRACT

Background: Reduced motor and cognitive dual-task capacity is found to be more common among people with multiple sclerosis (MS), than among healthy populations. However, studies in larger samples of MS conducted using a more stringent methodology, which includes comparisons to healthy controls, are needed. Thus, the primary aim of this study was to explore the effects on motor and cognitive dual-tasking in people with mild to moderate overall MS-disability, in comparison to healthy controls. A second aim was to explore the differences in dual-task performance on a cognitive task between two motor tasks in people with mild to moderate MS and healthy controls.

Methods: This case-control study evaluated dual-task performance of the motor tasks *standing with eyes closed* (hereafter *standing*) and *walking* and a cognitive task assessing selective executive functions (*auditory-Stroop* test). Fifty-five people with MS (mild MS, $n = 28$; moderate MS, $n = 27$), and 30 healthy controls participated. *Standing* and *walking* were assessed using wireless inertial measurement unit sensors (APDM). *Standing* (three 30 s trials) was measured using sway area and root mean square sway, while *walking* (2 min) was measured using speed, stride length, and step time. *Auditory-Stroop* was measured using accuracy and response time. During dual-task assessments, each subject was instructed to pay equal attention to both tasks. Statistical significance was considered if $p < .05$.

Results: **In *standing*** no significant within-group differences in the *standing* measures were found between single-task and dual-task performance. However, dual-task performance differed significantly between all groups (moderate MS > mild MS > healthy controls), except between mild and moderate MS in sway area. **In *walking***, all groups slowed down speed and shortened stride length during dual-task condition compared to single-task condition. Moderate MS performed significantly poorer than mild MS and healthy controls in dual-task *walking*, but mild MS did not differ from healthy controls. **In the *cognitive task*** only mild MS increased significantly in *auditory-Stroop* response time during *walking*. In healthy controls, the performance of *auditory-Stroop* was not affected by dual-tasking. Moderate MS had significantly longer response time in dual-task *auditory-Stroop* compared to the other groups, but no differences were observed between mild MS and healthy controls. Only mild MS had significantly longer response time during *walking* than during *standing*.

Conclusion: This study showed that cognitive-motor interference in people with MS is present also in the early phases of the disease. This was shown during dual-tasking with slower walking and a longer response time in the cognitive task compared to healthy controls. Moderate MS performed poorer in almost every aspect of the motor and cognitive assessments in dual-task condition, compared to mild MS and healthy controls. Furthermore,

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during *standing*, people with MS performed poorer in *standing* measures compared to healthy controls. Additionally, healthy controls showed no cognitive interference during motor tasks.

The results suggest that standardized regular assessment of dual-tasking in MS care might increase the individual's knowledge of dual-task capacity and contribute to understanding of possible related consequences. However, feasible assessment equipment and specific motor-cognitive dual-task training interventions for people with MS need to be developed.

1. Introduction

Multiple sclerosis (MS), a chronic inflammatory and neurodegenerative disease of the central nervous system (Filippi et al., 2018), commonly leads to balance and walking limitations (Comber et al., 2018,2017) and cognitive impairment (Chiaravalloti and DeLuca, 2008; Penner, 2017). To maintain balance control while standing or walking, interactions between multiple underlying physiological systems are required, including systems for movement, sensory function, and cognitive processing (Horak, 2006). In people with MS (PwMS) it has been shown that performing a simultaneous cognitive task while walking is associated with reduced walking performance (Leone et al., 2015), and vice versa (Wajda et al., 2019). Further, there is a higher risk of falling in PwMS, even in the early phases of the disease, when performing a simultaneous cognitive task while walking or standing (dual tasking) (Kalron et al., 2010; Etemadi, 2017). This highlights the need for a better understanding of how disabilities in balance control, ambulation and cognitive function interact, to then develop interventions aimed at reducing the disease burden in PwMS.

How cognitive-motor interference (CMI) affects PwMS when performing motor and cognitive dual-tasks has recently begun to be explored (Learmonth et al., 2017; Chamard Witkowski et al., 2019). Complex cognitive tasks that challenge executive functions, sustained attention, information processing speed, and those that involve conflicting stimuli are recommended for use when testing CMI in PwMS (Prosperini et al., 2015, 2016). When performing motor and cognitive tasks simultaneously, the effect of dual-tasking could either be negative (a dual-task cost) or positive (a dual-task benefit) for either of the two tasks or for both (Kelly and Janke, 2010).

In PwMS, more severe overall MS-disability, involving physical and cognitive impairments, has been shown to be associated with poorer dual-task performance (i.e., CMI) (Rooney et al., 2020). Furthermore, dual-task cost while standing and doing a cognitive task simultaneously is associated with worsened aspects of health-related quality of life (Castelli et al., 2016).

Although the difference in CMI between people with mild overall MS-disability and healthy controls (HC) was shown to be small in a systematic review (Learmonth et al., 2017), other studies have shown that CMI is considerably disabling also in PwMS with mild disease (Argento et al., 2021; Coghe et al., 2018). In some studies, HC did not show CMI on the cognitive task during walking, while CMI was present among PwMS, suggesting that the performance of a cognitive task during walking could serve as a marker of cognitive status in PwMS (Downer et al., 2016; Postigo-Alonso et al., 2019).

However, studies on CMI in larger samples of PwMS with a wider range of overall MS-disability, including comparisons with HC, are lacking (Leone et al., 2015). Also, studies using a more stringent methodology for the cognitive task in test procedures and in presentation of results are warranted (Leone et al., 2015; Chamard Witkowski et al., 2019), specifically that the design of the dual-task paradigm and how results on the cognitive task should be reported. Therefore, in the present study, the primary aim was to explore the effects on motor and cognitive dual tasking in people with mild to moderate MS, in comparison to HC. A second aim was to explore the difference in dual-task performance on the cognitive task between two motor tasks in people with mild to moderate MS and HC.

2. Method

2.1. Study design

A case-control study with a cross-sectional design.

2.2. Subjects

Inclusion criteria were PwMS: diagnosed according to the McDonald criteria (McDonald et al., 2001; Thompson et al., 2018) with an overall MS-disability score of 2.0 to 5.5 according to the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983); 18 to 65 years of age; able to walk 100 meters without aid. Exclusion criteria were cognitive impairment indicated by a score $<$21 in the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005); other conditions that would substantially influence balance; an MS relapse or change of disease-modifying treatment the last eight weeks; alcoholism; or pregnancy. Criterion for inclusion of HC was self-reported good health specifically related to balance and walking performance.

Eligible subjects with MS were recruited from MS specialist centers and clinical rehabilitation units in Stockholm, Sweden. PwMS who fulfilled the criteria for inclusion and exclusion, were included and categorized into two groups: mild MS (EDSS 2.0 to 3.5) and moderate MS (EDSS 4.0 to 5.5). Sex-and-age-matched HC were purposefully recruited via local press advertisement. The targeted sample size was set to 60 PwMS and 30 HC.

The Stockholm ethical review board approved the study, Nos. 2018/374-31 and 2019-01562. Procedures were conducted in accordance with the Declaration of Helsinki.

2.2.1. Data collection

Data collection was conducted from March 2019 to September 2020 at the movement laboratory at Karolinska Institutet, Stockholm, Sweden. Information on demography, fall-frequency, use of walking aid, education, years since MS diagnosis, and disease course, was collected through a structured interview. Balance control was assessed with the Mini-BESTest (Franchignoni et al., 2010).

2.3. Motor and cognitive tasks, and procedures for assessment

The two studied motor tasks were *standing with eyes closed* (hereafter *standing*) and *walking*. In *standing*, the subject was instructed to remain standing for 30 s: feet together (wearing shoes), eyes closed, hands on hips, not talking or moving. If the subject failed to remain with the feet together, *standing* was performed with feet apart. Feet together position was standardized with a 2 cm block placed between the feet, and feet apart with a 20 cm block. The subject performed three 30 s trials per condition, i.e., six trials in total.

In *walking*, the subject was instructed to walk for two minutes at a self-selected comfortable pace on a straight 25-meter indoor walkway with 180° turns at each end. For the motor task assessments, the subject was equipped with six wireless inertial measurement unit sensors (Opal sensors, APDM, Portland, OR, USA). Sensors were attached on the trunk, lumbar, wrists and feet, according to APDM Mobility Lab system manual (APDM Inc. 2017). Measures for *standing* were sway area (degrees^2) and root mean square sway (RMS-sway) (degrees). Measures for *walking* were speed (meter/second), stride length (meter), and step time (second).

The cognitive task *auditory-Stroop* (Morgan and Brandt, 1989), which challenges selective executive functions, e.g., response inhibition, has been suggested for assessment of CMI in PwMS (Learmonth et al., 2017). *Auditory-Stroop* consists of two stimulus words "high" and "low", verbally presented congruent or incongruent in a high or low pitch level through wireless headphones (Razer^{TM} ManO'War) using Audacity software (version 3.0.2). The high and low pitch frequencies used were approximately 310Hz and 90Hz, respectively. The subject was instructed to verbally respond to the stimulus pitch with the words "high" or "low", irrespective of the actual word presented, as quickly and accurately as possible. These responses were recorded through wireless headphones using Audacity. An interstimulus interval of 1.5 to 2.0 s was randomly delivered to avoid the stimuli becoming a metronome for walking. *Auditory-Stroop* accuracy and response time of incongruent stimuli were analyzed.

2.4. Procedures for assessment

First, the single-task assessments of *walking* and thereafter *standing* were performed. Before the recorded assessments the subject performed one or two practice trials of each motor task. Thereafter *auditory-Stroop* was presented. Two practice trials were performed in seated position. Then, one or two practice trials with *auditory-Stroop* dual-task conditions of each motor task were performed. Assessments of the single-task *auditory-Stroop* and the dual-task *standing* and *walking* while performing the *auditory-Stroop*, were then conducted in a randomized order created by a computerized random sequence generator (http://www.randomization.com). During dual-task assessments the subject was instructed to pay equal attention to both the motor and the cognitive tasks.

2.4.1. Data processing and statistical analysis

Summarized motor task data was exported from the Mobility Lab software to Excel (Microsoft), where data processing was performed. Mean values of three *standing* trials were calculated for each measure (sway area and RMS-sway). Likewise, mean values of left and right legs in *walking* were calculated for each measure (speed, stride length, and step time). The calculated values were used in the statistical analyses.

Recorded *auditory-Stroop* responses were analyzed using MATLAB version R2017b (MathWorks Inc., 2017). Response time was measured from the beginning of a stimulus to the beginning of the corresponding response. The *auditory-Stroop* audio files consisted of both congruent and incongruent stimuli, equally represented but presented in a randomized order. Unique audio files were consistently used in a standardized way in each trial. Response time was calculated as the mean of responses to all incongruent stimuli, irrespective of whether they were correct or incorrect. The first *auditory-Stroop* stimulus in each trial was excluded from the analysis to eliminate any bias of being surprised at the beginning of a trial. Mean standard deviation (SD) of response time was used as a measure of intraindividual variability. Accuracy was calculated as the percentage of correct responses of the total number of stimuli, where missing responses were counted as incorrect responses.

For each task, the dual-task effect (DTE) was calculated as described by Kelly and Janke (2010). For outcomes where a higher value indicated improved performance the following equation was used:

$$DTE(\%) = \frac{(Dual\ task - Single\ task)}{Single\ task}*100$$

For outcomes where a lower value indicated improved performance, a negative sign was inserted in the equation, thereby the presence of dual-task cost or benefit is indicated by either a negative or a positive DTE-value, respectively.

$$DTE(\%) = \frac{-\ (Dual\ task - Single\ task)}{Single\ task}*100$$

Table 1
Demographic characteristics with descriptions of statistically significant differences ($p < .05$) between groups.

Characteristics	Mild MS ($n = 28$)	Moderate MS ($n = 27$)	Healthy controls ($n = 30$)
Sex, no. (%)			
- Woman	19 (68)	20 (74)	22 (73)
- Men	9 (32)	7 (26)	8 (27)
Age, years, mean (SD)[a, b]	45.5 (9.4)	54.3 (8.1)	49.1 (10.9)
Height, m, mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight, kg, mean (SD)	72.4 (12.7)	77.2 (16.3)	74.3 (11.7)
Body mass index, kg/m2, mean (SD)	24.6 (3.6)	26.2 (5.5)	25.1 (3.6)
Education, years, mean (SD)	15.2 (2.2)	14.1 (2.4)	14.8 (1.7)
Use of walking aid, no. (%)[a, b, c]			
- No	22 (79)	11 (41)	30 (100)
- Yes, outdoors	6 (21)	10 (37)	0 (0)
- Yes, in- and outdoors	0 (0)	6 (22)	0 (0)
Have fallen last six months, no. (%)[b, c]			
- No	19 (68)	14 (52)	30 (100)
- Yes	9 (32)	13 (48)	0 (0)
Mini-BESTest[d], mean (SD)[a, b, c]	22.5 (3.1)	17.7 (3.7)	25.9 (1.3)
Cognitive function, MoCA[e], mean (SD)[b, c]	26.9 (1.8)	26.3 (2.0)	28.1 (1.4)
Mild Cognitive Impairment according to MoCA[e] (<26), no. (%)[b, c]			
- No	22 (79)	18 (67)	30 (100)
- Yes	6 (21)	9 (33)	0 (0)
Overall MS disability, EDSS[f], mean (SD)[a]	3.0 (0.5)	4.5 (0.5)	-
Course, no (%)[a]			
- Relapsing remitting	26 (93)	16 (59)	-
- Progressive	2 (7)	11 (41)	-
Years since diagnosis, mean (SD)	11.5 (8.1)	12.9 (9.2)	-

[a] Statistical significant difference between the Mild and the Moderate MS groups;
[b] Statistical significant difference between the Moderate MS group and Healthy controls;
[c] Statistical significant difference between the Mild MS group and Healthy controls;
[d] The Mini-BESTest score ranges from 0 to 28;
[e] MoCA = Montreal Cognitive Assessment, the MoCA score ranges from 0 to 30;
[f] The EDSS score ranges from 0 to 10.

Descriptive statistics were used to summarize the data. Normality was assessed using the Shapiro-Wilk test, and by visual inspection of figures. Normally distributed data are presented with mean and SD. Non-normally distributed data are presented with median and interquartile range (IQR). Differences in characteristics between the groups were assessed using the independent t-test and a chi-square test.

For within group analyses between single-task and dual-task performances a repeated measures analysis of variance was used for normally distributed data and the Wilcoxon signed rank test for non-normally distributed data. For between groups analyses in dual-task performance an analysis of variance was used for normally distributed data and the independent samples sign test for non-normally distributed data.

To explore possible impact of cognitive function on the results, an exploratory analysis was performed after the main analysis was completed, on alternative groups of PwMS created based on the presence of mild cognitive impairment (MoCA score < 26) or normal cognitive function (MoCA score ≥ 26) (Nasreddine et al., 2005).

A p-value <.05 was considered statistically significant. Within group and between groups analyses were adjusted by the Bonferroni correction for multiple tests. IBM® SPSS® Statistics version 28 was used in the statistical analyses.

Table 2

Performance in single-task and dual-task conditions, differences, and dual-task effect on motor (*standing with eyes closed* and *walking*) and cognitive (*auditory-Stroop*) tasks, in people with mild (n = 28) and moderate (n = 27) multiple sclerosis and in healthy controls (n = 30). Negative dual-task effect values indicate a dual-task cost, and positive dual-task effect values indicate a dual-task benefit.

Task	Measure	Group	Single-task condition	Dual-task condition	*P* value[d]	Dual-task effect %
			Standing	*Standing+Cognitive*		*Motor measures(Standing)*
Motor *(Standing with eyes closed)*	Sway area (°²)[b]	Mild MS	4.80 (6.59)	3.92 (5.72)	.600	18.3 (-13.2)
		Moderate MS	9.24 (9.52)	6.46 (6.68)	1.00	30.1 (-29.8)
		Healthy controls	2.13 (1.97)	1.85 (1.49)	.756	13.0 (-24.2)
	RMS Sway[b]	Mild MS	.73 (.46)	.67 (.43)	.780	8.6 (-7.5)
		Moderate MS	1.12 (.82)	.99 (.73)	1.00	11.8 (-10.8)
		Healthy controls	.51 (.24)	.51 (.20)	.768	.1 (-17.1)
			Walking	*Walking+Cognitive*		*Motor measures(Walking)*
Motor *(Walking)*	Speed (m/s)[c]	Mild MS	1.35 (.17)	1.32 (.18)	.033	-2.3 (7.0)
		Moderate MS	1.19 (.21)	1.13 (.22)	<.001	-5.3 (4.7)
		Healthy controls	1.48 (.15)	1.44 (.17)	.006	-2.6 (12.3)
	Stride length (m)[c]	Mild MS	1.37 (.13)	1.35 (.14)	.002	-1.9 (6.5)
		Moderate MS	1.26 (.15)	1.21 (.16)	<.001	-3.8 (7.3)
		Healthy controls	1.47 (.11)	1.43 (.11)	<.001	-2.3 (5.2)
	Step time (s)[c]	Mild MS	.51 (.03)	.51 (.04)	.426	-.5 (5.8)
		Moderate MS	.53 (.05)	.54 (.06)	.041	-2.0 (6.5)
		Healthy controls	.50 (.04)	.50 (.04)	.326	-.6 (8.7)
			Cognitive	*A. Cognitive+Standing*		*Cognitive measures*
				B. Cognitive+Walking		
Cognitive *(auditory-Stroop [a])*	Accuracy (%)[b]	Mild MS	100 (.0)	*A.* 100 (.0)	1.00	.0 (.0)
				B. 100 (.0)	1.00	.0 (.0)
		Moderate MS	100 (5.0)	*A.* 100 (5.9)	.552	.0 (17.6)
				B. 100 (11.5)	1.00	.0 (130.8)
		Healthy controls	100 (.0)	*A.* 100 (.0)	1.00	.0 (.0)
				B. 100 (.0)	1.00	.0 (.0)
	Response time (s)[c]	Mild MS	.86 (.17)	*A.* .86 (.16)	.978	-.1 (-4.9)
				B. .92 (.17)	.003	-7.5 (2.5)
		Moderate MS	1.05 (.20)	*A.* 1.00 (.17)	.080	4.6 (-14.9)
				B. 1.08 (.33)	.454	-3.1 70.3)
		Healthy controls	.85 (.13)	*A.* .82 (.14)	.163	2.7 (6.2)
				B. .85 (.14)	.967	.1 (6.3)

[a] Incongruent stimulus in *auditory-Stroop*.
[b] Values presented in median and interquartile range.
[c] Values presented in mean and standard deviation.
[d] Bonferroni adjustment for multiple comparisons. RMS = root mean square.

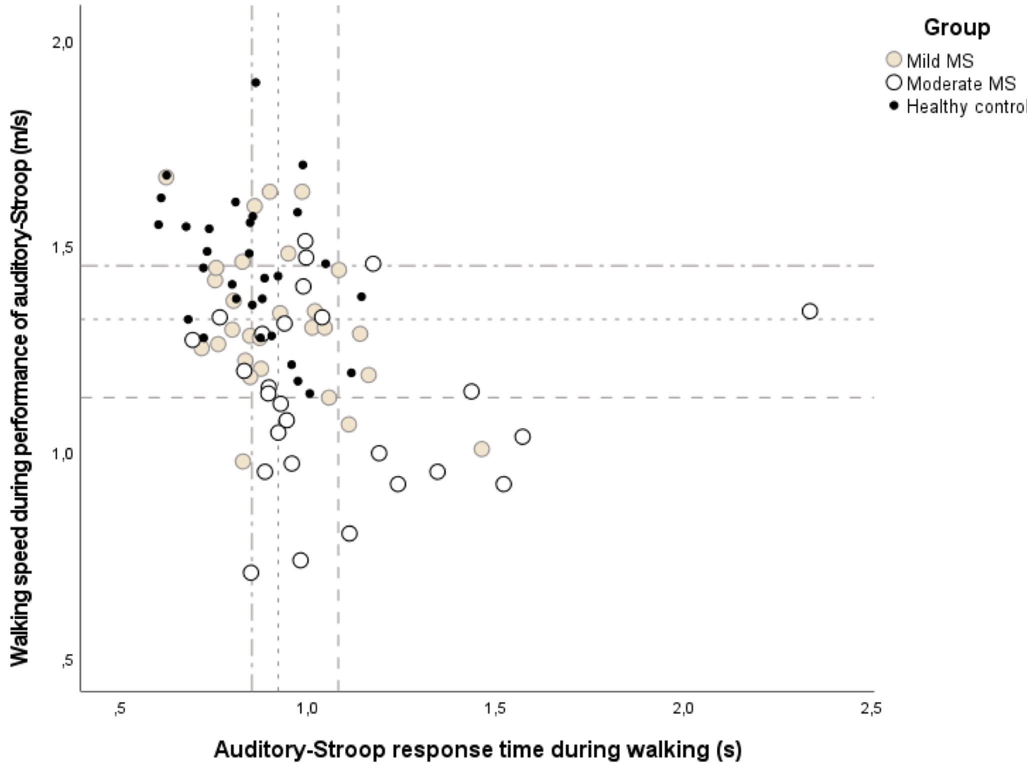

Fig. 1. Scatter plot on performance of dual-task *walking* speed and *auditory-Stroop* response time in people with mild ($n = 28$, gray circles) and moderate ($n = 27$, white circles) multiple sclerosis and in healthy controls ($n = 30$, black circles). Mean values on speed and response time are marked for mild MS with dotted lines, for moderate MS with dashed lines, and for healthy controls with dash-dotted lines.

3. Results

3.1. Description of sample

Of 90 PwMS interested in participation in the study, a total of 55 PwMS were included, 28 with mild and 27 with moderate MS. For comparison, a total of 30 sex-and-age-matched HC were included. Demographic characteristics of the groups are presented in Table 1.

3.2. Performance during single-task and dual-task conditions

During *standing* within each group (mild MS, moderate MS, and HC), no significant differences between the performance in single-task and dual-task conditions were shown in sway area and RMS-sway (Table 2). However, all groups tended to decrease in sway area and RMS-sway during the dual-task condition, compared with the single-task condition.

During *walking*, there were significant differences between single-task and dual-task performance in speed and stride length across all groups (Table 2). For moderate MS also step time was significantly prolonged. All groups showed a significant dual-task cost in speed and stride length; the effect size for both measures were about twice as large in moderate MS as compared to mild MS and HC.

The median *auditory-Stroop* accuracy was 100% in both single-task and dual-task conditions of both motor tasks across the three groups (Table 2). However, although median accuracy in single-task was also 100% in moderate MS, the variance showed that some had difficulties with the task. The mean *auditory-Stroop* response time during single-task conditions in mild MS and HC were similar, while it was higher in moderate MS. In mild MS, response time during *standing* remained unchanged, while moderate MS and HC tended to have a dual-task benefit. Mild MS showed a significant difference in response time between single-task and dual-task *walking,* the dual-task cost was 7.5%.

The dual-task performance of *walking* speed and *auditory-Stroop* response time showed an increased variance with increased disability (see Table 2). In Fig. 1, the mean differences, and the scattered, linear distribution in the dual-task performance of these measures are shown for the three groups.

3.3. Comparisons of dual-task performance between groups

During dual-task *standing*, mild and moderate MS had significantly larger sway area compared to HC, but there was no significant sway area difference between mild and moderate MS (Table 3). Regarding dual-task RMS-sway there were significant differences between all groups, (i.e., moderate MS > mild MS > HC).

During dual-task *walking*, moderate MS walked significantly slower, with shorter stride length and longer step time compared to mild MS and HC, but there were no significant differences in walking between mild MS and HC (Table 3). Moderate MS had a larger dual-task cost in stride length than mild MS.

The between group comparisons of *auditory-Stroop* accuracy could not be computed since all values across the groups were less than, or equal to, the median (Table 3). However, there was significantly longer response time in moderate MS compared to the other two groups during *standing* and during *walking.*

3.4. Comparison of performance of the cognitive task during standing and walking

Mild MS increased by 7.5% in *auditory-Stroop* response time from dual-task *standing* to dual-task *walking* (Table 4). Moderate MS and HC also increased in response time from *standing* to *walking*, albeit not significantly. In Fig. 2, the differences, and the linear distribution in dual-task response time during *standing* and during *walking* for the three groups, implying increased response time and variance with increased disability.

Table 3
Between group comparison of dual-task performance and dual-task effect, in dual-task conditions of motor (*standing with eyes closed* and *walking*) and cognitive (*auditory-Stroop*) tasks, in people with mild ($n = 28$) and moderate ($n = 27$) multiple sclerosis and in healthy controls ($n = 30$).

Task	Measure	Dual-task	Group comparison	Dual-task performance		Dual-task effect %	
				Mean-/Median difference	*P* value[e]	Mean-/Median difference	*P* value[e]
Motor *(Standing with eyes closed)*	Sway area (°²)[b]	*auditory-Stroop*	Moderate MS–Mild MS	2.54	.130	f	-
			Moderate MS–Healthy controls	4.61	.000	f	-
			Mild MS–Healthy controls	2.07	.001	f	-
	RMS sway[b]	*auditory-Stroop*	Moderate MS–Mild MS	.26	.031	f	-
			Moderate MS–Healthy controls	.48	.000	f	-
			Mild MS–Healthy controls	.16	.001	f	-
Motor*(Walking)*	Speed (m/s)[c]	*auditory-Stroop*	Moderate MS–Mild MS	-.19	.001	-3.2	.126
			Moderate MS–Healthy controls	-.31	<.001	-2.8	.217
			Mild MS–Healthy controls	-.12	.058	.4	1.00
	Stride length (m)[c]	*auditory-Stroop*	Moderate MS–Mild MS	-.14	.001	-2.0	.047
			Moderate MS–Healthy controls	-.23	<.001	-1.6	.163
			Mild MS–Healthy controls	-.09	.065	.5	1.00
	Step time (s)[c]	*auditory-Stroop*	Moderate MS–Mild MS	.03	.035	1.5	.412
			Moderate MS–Healthy controls	.04	.001	1.5	.439
			Mild MS–Healthy controls	.01	.899	-.1	1.00
Cognitive *(auditory-Stroop[a])*	Accuracy (%)[b]	*Standing*	Moderate MS–Mild MS	d	-	f	-
			Moderate MS–Healthy controls	d	-	f	-
			Mild MS–Healthy controls	d	-	f	-
		Walking	Moderate MS–Mild MS	d	-	f	-
			Moderate MS–Healthy controls	d	-	f	-
			Mild MS–Healthy controls	d	-	f	-
	Response time (s)[c]	*Standing*	Moderate MS–Mild MS	.15	.002	-4.2	.419
			Moderate MS–Healthy controls	.18	<.001	-1.0	1.00
			Mild MS–Healthy controls	.03	1.00	3.2	.729
		Walking	Moderate MS–Mild MS	.16	.031	-6.3	.301
			Moderate MS–Healthy controls	.24	<.001	2.0	1.00
			Mild MS–Healthy controls	.07	.650	8.3	.080

[a] Incongruent stimulus in *auditory-Stroop*.
[b] Median values used.
[c] Mean values used.
[d] Unable to compute: All test field values were less than or equal to the median.
[e] Significance values were adjusted by the Bonferroni correction for multiple tests.
[f] Multiple comparisons were not performed because the overall test did not show significant differences across samples. RMS = root mean square.

Table 4
Descriptive results of performance in dual-task condition, differences, and change in *auditory-Stroop* response time during *standing with eyes closed* and during *walking* in people with mild ($n = 28$) and moderate ($n = 27$) multiple sclerosis and in healthy controls ($n = 30$).

Task	Measure	Group	Performance in dual-task conditions		P value	Percentage change between A and B
			A. Cognitive+Standing	*B. Cognitive+Walking*		
Cognitive *(auditory-Stroop[a])*	Response time (s)[b]	Mild MS	.86 (.16)	.92 (.17)	<.001	7.5 (7.8)
		Moderate MS	1.00 (.17)	1.08 (.33)	.172	8.0 (100.1)
		Healthy controls	.82 (.14)	.85 (.14)	.222	2.7 (.1)

[a] Incongruent stimulus in *auditory-Stroop*.
[b] Values presented in mean and standard deviation.

3.5. *Exploratory analysis of the influence of cognitive function on dual-task performance in PwMS*

The group with mild cognitive impairment performed significantly worse in *auditory-Stroop* response time both during *standing* and during *walking* compared with the group with normal cognitive function (Table 5). There were no other significant differences in dual-task performance between the groups. However, the group with mild cognitive impairment had a larger dual-task cost in *walking* step time.

4. Discussion

This study explored dual-task effects on two motor tasks (*standing* and *walking*) and a cognitive task (*auditory-Stroop*) in groups of people with mild and moderate MS, and HC. In motor measures, *walking* deteriorated during dual-task in all groups when performing the *auditory-Stroop* simultaneously, but no dual-task effects were found in *standing*. Furthermore, only mild MS showed dual-task cost in response time during *walking*. During *standing* no cognitive or motor dual-task effects were

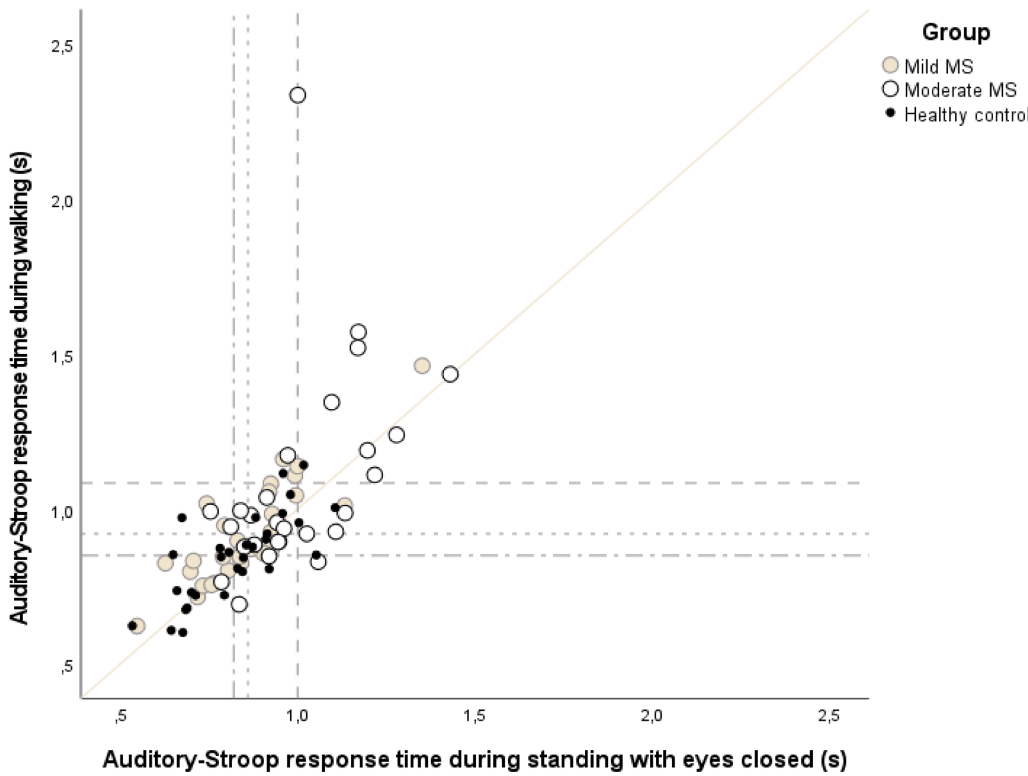

Fig. 2. Scatter plot on dual-task performance of *auditory-Stroop* response time during *standing with eyes closed* and during *walking* in people with mild ($n = 28$, gray circles) and moderate ($n = 27$, white circles) multiple sclerosis and in healthy controls ($n = 30$, black circles). Mean values on response times are marked for mild MS with dotted lines, for moderate MS with dashed lines, and for healthy controls with dash-dotted lines.

Table 5
Exploratory analysis of the influence of cognitive function on dual-task performance. Between group comparison of dual-task performance and dual-task effect, in dual-task conditions of motor (*standing with eyes closed* and *walking*) and cognitive (*auditory Stroop*) tasks, in people with MS with mild cognitive impairment[a] ($n = 15$) and people with MS with normal cognitive function[a] ($n = 40$). Negative dual-task effect values indicate a dual-task cost, and positive dual-task effect values indicate a dual-task benefit.

Task	Measure	Dual-task	Dual-task performance			Dual-task effect %		
			Mild cognitive impairment[a] ($n = 15$) Mean-/Median	Normal cognitive function[a] ($n = 40$) Mean-/Median	*P* value	Mild cognitive impairment[a] ($n = 15$) Mean-/Median	Normal cognitive function[a] ($n = 40$) Mean-/Median	*P* value
Motor *(Standing with eyes closed)*	Sway area (°2)[c]	auditory-Stroop	5.24	6.02	.601[g]	16.2	13.4	.491[g]
	RMS sway[c]	auditory-Stroop	.75	.85	.934[g]	10.9	5.9	.491[g]
Motor *(Walking)*	Speed (m/s)[d]	auditory-Stroop	1.17	1.25	.242[f]	-6.3	-2.8	.064[f]
	Stride length (m)[d]	auditory-Stroop	1.26	1.29	.589[f]	-3.7	-2.6	.268[f]
	Step time (s)[d]	auditory-Stroop	.54	.52	.166[f]	-3.1	-.6	.041[f]
Cognitive *(auditory-Stroop[b])*	Accuracy (%)[c]	Standing	100	100	[e]	.0	.0	.258[g]
		Walking	100	100	[e]	.0	.0	.256[g]
	Response time (s)[d]	Standing	1.01	.90	.029[f]	.4	1.7	.687[f]
		Walking	1.14	.95	.016[f]	-8.8	-4.3	.345[f]

[a] According to the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005).
[b] Incongruent stimulus in auditory Stroop.
[c] Median values used.
[d] Mean values used.
[e] Unable to compute: All test field values were less than or equal to the median.
[f] Significance values were adjusted by the Bonferroni correction for multiple tests.
[g] Yates's Continuity Corrected Asymptotic Sig. RMS = root mean square.

found, although the dual-task *standing* performance deteriorated with the level of overall MS-disability (moderate MS > mild MS > HC), apart from a non-significant difference between mild and moderate MS in sway area. In all dual-task conditions, moderate MS performed worse compared to mild MS and HC. Mild MS also showed worsened performance in dual tasking compared with HC. The results imply that an increased level of overall MS-disability is associated with a greater deterioration of motor-cognitive dual-task capacity (Rooney et al., 2020).

Most previous studies addressing CMI in PwMS during *standing* have been conducted with eyes open and have consistently demonstrated a dual-task cost on postural sway (Etemadi, 2017; Prosperini et al., 2016; Castelli et al., 2016; Wajda et al., 2014). The advantage of assessing *standing* in eyes-closed condition in PwMS, as in our study, is that the frequently occurring impact of impaired somatosensory and vestibular functions on balance control (Gelfand, 2014) becomes central since the options for compensation by visual input are eliminated. Interestingly, we found a trend of a dual-task benefit in sway area and RMS-sway across all groups. This has also been shown in two other studies using eyes-closed condition (Negahban et al., 2011, 2018). Another study has suggested that mild stress induced by dual tasking might enhance attention (Shields et al., 2019). Transferred to our study, stress could be a likely explanation of the results, with a dual-task benefit of the balance performance during *standing* with eyes closed. No benefit was shown in eyes-open condition which might be because when standing with eyes open, it is less of a challenge to maintain balance. Thus, increased attention might not be needed when visual input is allowed. Hence, the difference in performance in *standing* with eyes closed between PwMS and HC regardless of variation in overall MS-disability might be explained by the impairment in somatosensory and vestibular functions commonly occurring in PwMS (Gelfand, 2014).

All groups showed dual-task costs on *walking* speed and stride length in line with a meta-analysis of CMI in people with mild MS and HC (Learmonth et al., 2017). This indicates a need for feasible methods to assess in the clinic the dual-task capacity in mild MS as well. Moderate MS differed from the other groups in dual-task *walking* performance, while mild MS and HC performed similarly. The differences shown may be linked to the group categorization based on the EDSS, where increased limitations in walking correspond to a higher EDSS score (Kurtzke, 1983). However, the EDSS is frequently used in MS research, which facilitates the transferability of results.

Most studies conducted in PwMS have investigated CMI during *walking* intermittently on a ten-meter distance (Etemadi, 2017; Postigo-Alonso et al., 2019; Veldkamp et al., 2021; Leone et al., 2020). Our study investigated CMI during a 2 min continuous *walking* trial corresponding to approximately 150 meters, which to our knowledge has been done only once previously (Argento et al., 2021). The advantage of using longer continuous *walking* trials is that the CMI phenomenon is studied in a setting more resembling real-life. The mobile sensor-based system (APDM Inc., 2017) used in this study is one of several newer systems available that enable this type of assessment.

The response time during *walking* increased in mild MS, implying that walking requires greater processing resources, thus limiting cognitive processing (Bayot et al., 2018) in mild MS, as well. For moderate MS, during *standing*, accuracy but not response time was significant. However, there was no dual-task effect, which might result from the non-normal distribution of data. In single-task *auditory-Stroop*, mild MS performed similarly to HC in both accuracy and response time and was faster than moderate MS. The results in our study indicate that the moderate MS population is associated with greater variation in CMI compared with the mild MS and the healthy populations, as illustrated by the increased variance as disability increases in Fig. 1. However, these difficulties are also present in mild MS (Learmonth et al., 2017; Downer et al., 2016), although this is often a hidden impairment that needs to be managed consciously.

For exploration of CMI, we used a cognitive task that challenges executive functions and involves conflicting stimuli, as suggested for increased methodological stringency when investigating CMI in PwMS (Prosperini et al., 2016). Furthermore, the conflicting stimuli were delivered with a larger difference in frequency between high and low pitches than previously described (Leone et al., 2020). Thereby, the risk of not perceiving the difference in frequency between pitches was reduced.

Mild MS had longer *auditory-Stroop* response time during *walking* than during *standing*. A similar trend was seen in moderate MS. Further, the effect differences on response time between the dual-task *standing* and dual-task *walking* among PwMS, were three times larger than among HC. This indicates that the cognitive task is negatively affected when performing the dual-task in *walking* in comparison to *standing* within PwMS but not within the healthy population. This might result from automaticity, i.e., that motor tasks can be performed automatically within a healthy population (Clark, 2015), but that they require greater processing resources in PwMS (Wajda et al., 2019; Rooney et al., 2020).

The exploratory analysis of groups of PwMS based on cognitive function according to MoCA (Nasreddine et al., 2005), paralleled the study's main analysis. Interestingly, no significant differences in dual-tasking were shown between the groups regarding the motor tasks, which may be an argument for using EDSS to categorize groups when exploring CMI, in order to also consider the aspect of impaired motor function. However, it should be noted that the sample was unevenly distributed between the groups and that the group with mild cognitive impairment was non-normally distributed. To control for impact of cognitive function a higher precision in its' classification should be accomplished by usage of a more extensive cognitive assessment battery.

Our findings substantiate the value of assessing dual-task performance as an estimate of disability in PwMS, in consistence with a recent systematic review (Rooney et al., 2020). For the individual, dual-task assessment might increase awareness of dual-task capacity, understanding of one's limitations, and possible related consequences. Higher dual-task cost during *standing* has been associated with worse health-related quality of life (Castelli et al., 2016), which implies that balance training that include dual-tasking can positively impact both functioning and health-related quality of life.

Strengths of this study contributing to justification of the results include the larger sample of PwMS and HC compared to other studies in the field, the similar demographics and sizes across the three groups, a sample distribution reflecting the prevalence of the underlying condition, advanced equipment enabling methodologically stringent test procedures, and that the results were presented for all tasks.

Limitations in the study were that cognitive function in the sample was briefly assessed that the difference in foot placement between subjects in the *standing* task (i.e., performed either with feet placed together or apart) was not controlled for in the analysis, and that the cognitive task could have been more challenging. The cognitive task *auditory-Stroop* could be further developed by the inclusion of additional types of conflicting stimuli requiring cognitive function (e.g., combining the stimuli with different names or numbers or adding memory challenging components), to increase the usefulness of accuracy as an outcome measure. The motor task *walking* could also be further developed by assessment at maximum speed. A further limitation was that the data collection had to be closed before completion due to the COVID pandemic.

Future CMI studies conducted with longer walking trials and during standing with eyes closed are needed. Furthermore, studies exploring brain activity during dual tasking are warranted to better understand the mechanisms of CMI. This could be performed with functional near-infrared spectroscopy, which enables the measurement of real-time brain activity during different motor tasks (Gramigna et al., 2017).

5. Conclusions

This study showed that CMI in PwMS is present also in the early phases of the disease, as shown during dual tasking with slower walking and the need of longer response time in the cognitive task compared to HC. Moderate MS performed worse in almost every aspect of motor and cognitive assessments in dual-task condition, compared to mild MS and HC. Furthermore, during *standing*, people with MS performed worse in *standing* measures compared to HC. Additionally, HC showed no cognitive interference during motor tasks.

The results implicate that assessment of dual-tasking in the clinic might increase the individual's knowledge of dual-task capacity and contribute to an understanding of possible related consequences. To accomplish this, feasible equipment for the assessment in the clinic needs to be developed. Further, development of specific training interventions for improved motor and cognitive dual-task ability among PwMS are needed.

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CRediT authorship contribution statement

Andreas Wallin: Conceptualization, Supervision, Visualization, Project administration, Data curation, Formal analysis, Writing – review & editing. **Erika Franzén:** Conceptualization, Supervision, Visualization, Writing – review & editing. **Lucian Bezuidenhout:** Conceptualization, Supervision, Visualization, Formal analysis, Writing – review & editing. **Urban Ekman:** Conceptualization, Supervision, Visualization, Writing – review & editing. **Fredrik Piehl:** Conceptualization, Supervision, Visualization, Writing – review & editing. **Sverker Johansson:** Conceptualization, Supervision, Visualization, Project administration, Writing – review & editing.

Declaration of Competing Interest

None.

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