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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Test-retest reliability of the 6-Minute Seated Interlimb Coordination Test in people with Multiple Sclerosis

Robbe Jonckers

Toon Slegers

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

PROMOTOR :

Prof. dr. Peter FEYS

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Abstract

Background: Previous research has used the 6 Minute Seated Coordination Task (6MSCT) in people with multiple sclerosis (pwMS), to map interlimb coordination (ILC). However, no study has been done that assesses the reliability of the 6MSCT for pwMS or healthy subjects.

Objectives: The aim of this study was to assess the intra- and intersession reliability of the 6MSCT in pwMS.

Methods: 21 Healthy controls (HC) and 42 pwMS participated in this study. For pwMS, Expanded Disability Status Scale (EDSS) scores ranged from 2.5 to 6.5. Participants were tested twice per session, with five to seven days between sessions. Amplitude (A), Frequency (F), Rotations Per Minute (RPM), Relative Phase (ϕ) and Standard Deviation of the Relative Phase (STD ϕ) were measured minute-by-minute during the 6MSCT. The reliability of these parameters was calculated using the Intra-Class Correlation Coefficient and Bland-Altman plots.

Results: Good to excellent intra- intersession reliability was observed for A and RPM for both groups. Good to excellent reliability was observed for F in the HC group in both intra- and intersession reliability. ϕ, and STD ϕ were moderate to well reliable when measurements were taken on the same day.

Conclusion: The highest reliability was observed for A and RPM. F was the least reliable within the MS group, though good to excellent reliability was observed for the HC group. The 6MSCT can reliably map lower limb performance in pwMS and HCs.

Keywords: 6MSCT, Multiple Sclerosis, Walking Fatigability, Reliability, Interlimb Coordination.

Introduction

Multiple Sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system affecting approximately 2.3 million people worldwide. It causes symptoms through a very heterogeneous spectrum because of the involvement of motor, sensory, visual, and autonomous systems (Doshi & Chataway, 2016). People with MS (pwMS) often have cognitive and motor impairments, which considerably impact their daily activities and quality of life (QOL) (Gil-González et al., 2020).

The most common symptom pwMS experience is fatigue (Krupp, 2006), affecting more than 80% of people diagnosed with MS (Minden et al., 2006). About 50% to 60% of pwMS consider fatigue the most distressing symptom affecting their QOL since it limits their ability to perform physical and mental activity (Amato et al., 2001; Rosenberg & Shafor, 2005). Fatigue, as stated by the Multiple Sclerosis Council for clinical practice guidelines (MS Council), is defined as "a subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual or desired activity". Instantaneous measures such as the BORG Rating of Perceived Exertion (BORG RPE) can be used to measure the perception of fatigability. However, fatigue should be distinct from fatigability, which refers to decreased performance over time during a given task. Walking fatigability (WF) is defined as a decline in walking speed over time, normally measured with the six-minute walking test (6MWT) and is present in more than one-third of pwMS. WF is more common in those with the progressive MS phenotype (up to 50%) and the more disabled persons, affecting 48.3% of pwMS with Expanded Disability Status Scale (EDSS) scores between 4.5-5.5, 46.3% with EDSS score of 6, and 51.5% for EDDS 6.5.(Leone et al., 2016). A decline of 10% or more is considered WF (Van Geel et al., 2020), where decreased muscle strength and balance (Van Geel et al., 2021) and exacerbation of MS-related symptoms can help to explain this decrease in distance walked. In addition, it has also been stated that pwMS perform an uncoordinated and asymmetrical (Plotnik et al., 2020) and unbalanced walking towards the end of the 6MWT (Arpan et al., 2020), which may be a limiting factor for those pwMS with higher levels of disability (Leone et al., 2016). As walking involves substantial proprioceptive and balance input, potentially leading to fatigue and tripping, which requires significant central integration (Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021), motor tasks that require limited proprioceptive and balance input but mimic lower limb coordination during walking could be useful to understand fatigability in more disabled pwMS better. One way to map lower limb coordination with minimal central integration is with the 6MSCT.

In the 6MSCT, movements are simple and require limited sensorimotor adaptation and strength. Two studies have been published that use a chair to examine lower body interlimb coordination (ILC) in pwMS (Goetschalckx, Van Geel, Meesen, Moumdjian, et al., 2021; Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021). In the study by Goetschalckx et al. (2021), an increase in variability was observed in pwMS in the generation of antiphase left-right movements towards the end of 6MSCT. This increase in variability was greatest in the WF group. In healthy subjects, this antiphase coordination occurs through an accurate and consistent ILC pattern (Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021). Similarly, a study by Swinnen et al. (1997) used a similar chair to measure ILC in both arms and legs in individuals with Parkinson's disease. Using the chair allows investigation into whether the brain can direct simple movements for an extended duration. This could indicate issues with signal transmission or generation, attention, cortical activation capacity, or timely integration of sensory input for walking. Individuals with disabilities may benefit from mapping their coordination and walking fatigability, as it can aid in constructing more targeted rehabilitation programs. Although there is promising evidence for the use of the 6MSCT to identify fatigability in those with MS, no study has yet investigated the test-retest reliability of this new measure.

This study aims to determine the intra- and intersession test-retest reliability of the 6MSCT in pwMS and healthy controls (HCs) for both the six-minute average and the minute-by-minute value. An instrument needs good test-retest reliability and information on the e measurement error before applying it in clinical research. All measurements are affected by an error component, meaning values obtained by a test will defer from their true value. Therefore, the actual value of the measurement should be adjusted to the measurement error (Bialocerkowski & Bragge, 2008). In intervention trials, the results are interpreted based on the measurement error. We hypothesise that the 6MSCT will have good intrasession reliability. Still, due to the day-to-day variability pwMS experience (Albrecht et al., 2001), we hypothesise that the intersession reliability will be less reliable.

Methods

Experimental procedure

This study is part of a large project aimed at identifying the psychometric properties of cognitive and coordination fatigability assessment and proof-of-concept of rehabilitation intervention. This study is funded by the MS Liga Vlaanderen (Steunfonds) and the Claire Fouconnier Foundation.

The sequence of clinical tests used in this study is shown in Figure 1. Before the beginning of the first session, each participant was informed about the study objectives and signed an informed consent allowing their participation. The study was approved by the Committee of Medical Ethics at the University of Hasselt. The study consisted of two test sessions separated by five to seven days. The same researcher conducted both sessions.

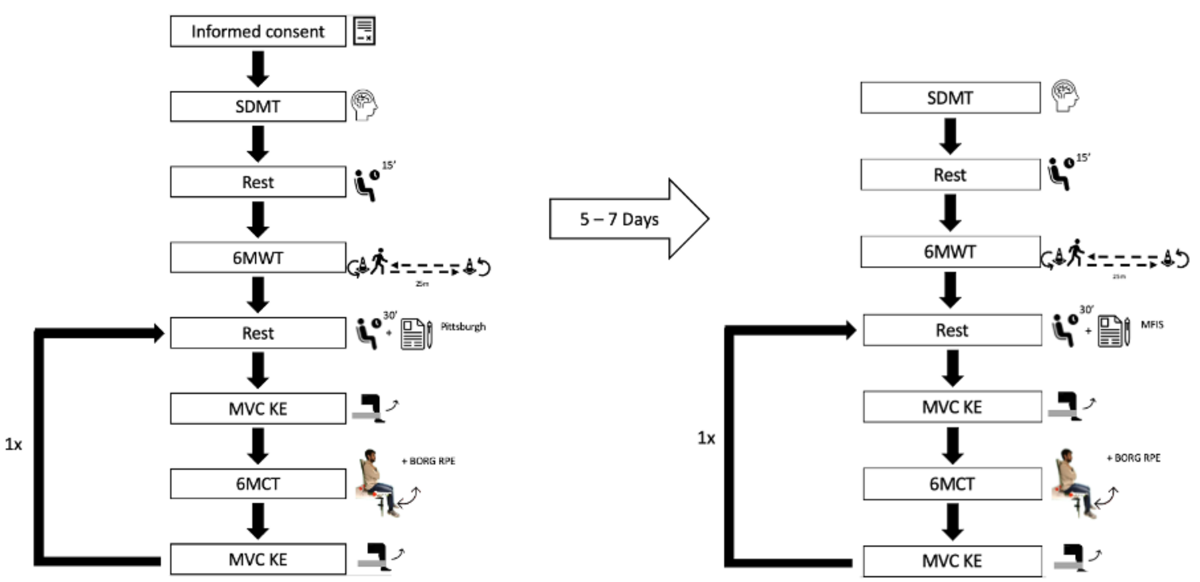
During the first session, the Symbol Digit Modalities Test (SDMT) was administered to assess cognitive function (Parmenter et al., 2007). After completing the SDMT, a 15-minute rest period was provided. To measure WF, the 6MWT was performed (Leone et al., 2016). Participants were asked to walk as fast as possible. After every minute, the BORG Rate of Perceived Exertion (RPE) scale, ranging from 1 to 10, was shown, and participants had to indicate their level of effort (Cleland et al., 2016). The BORG RPE scale was used to represent perceived fatigability.

After the 6MWT, a rest period of 30 minutes was provided. The Pittsburgh fatigability and sleep quality questionnaires were administered during this rest period (Carlozzi et al., 2021). Before and after the 6MSCT, the MVC of the knee extensors was measured for 5 seconds with a custom load cell (Bever et al., 1995). Each leg was alternately tested two times before and after the 6-minute seated interlimb coordination test. Lastly, the participants performed the 6MSCT (Goetschalckx et al., 2021) twice with 30 minutes of rest between.

The second session was constructed in the same way as the first session, except that during the rest period following the 6MWT, the Modified Fatigue Impact Scale (MFIS) was administered instead of the Pittsburgh questionnaires, which is a validated multidimensional scale to assess the perception of fatigue in pwMS (Fisk et al., 1994). The part after the rest period following the 6MWT corresponds to that of the first session.

Figure 1

Experimental procedure



Note. This figure visualises the sequence of the clinical tests used in this study in sessions 1 (left) and 2 (right), separated by five to seven days. SDMT = Symbol Digit Modalities Test; 6MWT = 6-Minute Walking Test; MVC KE = Maximal Voluntary Contraction Knee extensors; 6MSCT = 6-Minute Seated Coordination Test; BORG RPE = BORG Rating of Perceived Exertion; MFIS = Modified Fatigue Impact Scale

Participants

Fifty-one people with MS and twenty-two HCs were recruited in this study. The subjects were tested at the REVAL Rehabilitation Research Center of Hasselt University, the MS Rehabilitation Center in Noorderhart Overpelt, and the MS Centre in Melsbroek. PwMS and healthy people groups were matched by age, height, body mass and gender. Participants were included if presented age between 30 and 70 years old for both groups. Specifically for MS, individuals with moderate to severe disability (who required assistive devices to navigate their environment) disability were included based on an EDSS score between 2.5 and 6.5. Persons who experienced a relapse in the last month or could no longer walk for six minutes were not included (Table 1). Common exclusion criteria included pregnancy, other neurological diseases or musculoskeletal non-MS-related and cognitive impairment that impedes understanding the assignments. Due to dropouts and technical problems resulting in missing data, the included participants were reduced to 42 for intrasession reliability testing and 40 for intersession reliability testing in the MS group. For the HC group, participants were reduced to 20 in intrasession and 21 in intersession testing due to technical problems.

Table 1

Participant characteristics

		MS (n=51)	HC (n=23)
Gender (male/female;N%)		(17/34; 33,3/66,6)	(4/19; 17,4/8,6)
Age (years)		54,6 (9,4)	50,6 (6,2)
Body Mass (kg)		75,4 (18,8)	73,2 (17)
Height (m)		1,69 (0,34)	1,69 (0,07)
BMI (kg/(m*m))		26,2 (6,2)	25,5 (5,3)
EDSS Classification*	EDSS [3-3,9]	9	NA
	EDSS [4-4,9]	15	
	EDSS [5-5,9]	3	
	EDSS [6-6,5]	19	
Disease duration		17,8	NA
MS Phenotype *	RR	34	NA
	SP	9	
	PP	3	

Note. The participant characteristics are described as the mean (Standard Deviation). MS = Multiple Sclerosis; HC = Healthy Control; EDSS = Expanded Disability Status Scale; RR = Relapse Remitting; SP = Secondary Progressive; PP = Primary Progressive; NA = Not Applicable.

Clinical tests

The SDMT, MFIS, Pittsburgh fatigability and sleep questionnaires were taken to assess the participants' cognitive functioning and level of fatigue respectively (Carlozzi et al., 2021; Fisk et al., 1994; Parmenter et al., 2007). The Cognitive Fatigue Index (CFI) was calculated for the SDMT to assess cognitive fatigability for sustained attention and information processing speed. Here, the first 30 seconds were compared with the last 30 seconds. The MFIS is the most used and validated for pwMS multidimensional scale (Kos et al., 2005).

The maximal voluntary contraction was measured using the TAS606 Load Cell (maximal capacity: 50kg, data frequency: 10Hz). The participants were sat on a table with hips and knees in 90° flexion and were asked to perform a maximal isometric knee extension against resistance provided at the ankle. A tensioning strap was connected to the load cell attached to the other side of the table and positioned at the same height as the ankle. The other end of the tensioning strap was connected to an ankle strap attached to the participant's ankle and had a velcro strip that ensured the strap was secure around the ankle. Before each measurement, it was verified that the tension strap was horizontal when under tension and in line with the leg that was being tested. All participants were allowed to grab the side of the table and verbally encouraged to perform their best.

To measure WF, the 6MWT was administered. Participants were instructed to cover as much distance as possible while walking in six minutes on a 25-30m walkway with turns at both ends. During the test, the distance walked each minute was noted to calculate the Distance Walked Index (DWI) where DWI = ((Distance walked at minute 6 - Distance walked at minute 1)/Distance walked at minute 1) x100 (Leone et al., 2016).

Seated interlimb coordination test

To assess lower limb coordination and performance, participants performed the 6MSCT (Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021). The participants were sitting in a custom-made portable chair with foam-covered steel with two levers attached for the coordination test, where the lower legs were secured to two levers which allowed motion in all three planes. A belt at the back of the chair ensured a stable, supported posture (Figure 2). The portable chair was attached to a conventional table using 4 glue clamps. The participant was instructed to swing their legs up and down as high and as fast as possible for 6 minutes, mimicking the walking pattern. The verbal cue "swing your legs, as fast as possible, as you would while walking" was used. The knee’s lateral joint line during knee extension was aligned with the lever’s axis of rotation. Two incremental shaft encoders (Hengstler®, 1,000 bits per revolution, accuracy = 0.36°, sampling frequency = 100 Hz; Romsey, United Kingdom) were used to register joint angles. The data were processed using The MathWorks Inc. (2022).

MATLAB version: 9.13.0 (R2022b). Before the test and after each minute, the BORG RPE was taken.

Figure 2

Chair of the 6MSCT

The chair used for the 6 Minute Seated Coordination Task (6MSCT). The participant is seated in a custom-made portable chair with two levers attached. The knee’s lateral joint line is aligned with the lever's axis of rotation. The lower leg is secured to the lever using a Velcro strip, allowing movement in all three planes. A belt at the back of the chair ensures a stable and supported posture. During the test, the participant had to swing his/her legs up and down as high and fast as possible for six minutes and was instructed to cross their arms in front of their chest (not as shown in this picture).

During the 6MSCT, five parameters were measured:

1. Movement amplitude (A): signifies the spatial parameter and was measured as the peak-to-peak amplitude for each individual cycle (Serrien et al., 2000).
2. Movement frequency (F): signifies the temporal parameter and was measured as the number of movement cycles in one minute. One movement cycle was seen as the distance between two successive peak extension positions (Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021).

3. Rotations per minute (RPM): indicates the movement speed, measured as amplitude over time.
4. Relative phase (ϕ): expresses the relative timing between the contralateral peaks [360*(next peak time/cycle time)] ((Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021).
5. Standard deviation of the relative phase (STD ϕ): shows the consistency in generating the antiphase movement pattern (Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021).

For A, F, and RPM, the results were obtained for each leg separately. The results were measured for six minutes so the evolution of the parameters could be observed.

Statistical analysis

Data analysis was performed using the SAS JMP PRO 16.2.0. To express each parameter, the mean value of the six minutes and each minute separately were used to represent the parameter. To explore for outliers the quantile range outliers test was performed using a tail quantile of 0.05 resulting in a confidence interval of 95%. After inspection of identified outliers, these were labelled as mistrials and excluded from the analysis. A mixed model was used to calculate the intraclass correlation (ICC) for intra- and intersession reliability in each parameter. ICC values less than 0.5 were considered poor, values between 0.5 and 0.75 moderate, values between 0.75 and 0.9 good, and values greater than 0.9 excellent based on a 95% confidence interval (Portney, 2020). To visualize this data a heat map and the Bland Altman plot were constructed.

Correlations between the variables with a normal distribution were examined using the Pearson correlation. Spearman Rho coefficient was used when there was no normal distribution of the variables. For pwMS, the normality of the data was assumed based on sample size (n>30) , while the normal distribution of HCs was examined using the Shapiro-Wilk's test (n<30).

The Shapiro-Wilk's test was used to assess for normal distribution of the variables of the HC group. The only variable that was not normally distributed in the HC group, was the STD ϕ and the BORG Pre (BORG RPE score before the 6MSCT), BORG Post (BORG RPE after the 6MSCT) and BORG Post-Pre (difference in BORG RPE score from after and before the 6MSCT).

A mixed model was used to calculate the intraclass correlation (ICC) for intra- and intersession reliability in each parameter. The data from the two 6MSCT within the same session were used to calculate intrasession reliability. The data from the first trial on each day was used to calculate intersession reliability. In both statistical analyses, a 95% confidence interval was used. To test the correlation between the outcomes of the parameters of the 6MSCT and other outcomes, like the maximal isometric force and the BORG scale, the Pearson correlation coefficient was used for normally distributed data, and the Spearman's rho coefficient was used for non-normally distributed data.

Our analysis did not include the clinical tests cited in the experimental procedure. These mainly serve better to understand the two groups' functioning levels (Table 2).

Results

The results of the cognitive outcomes and questionnaires are shown in Table 2. ICC-values for Intra- and inter-session reliability are shown in Tables 3-4, presented in the form of a heatmap**.** Bland-Altman analyses are represented in Tables 5-6 and Figure 1. PwMS were classified as WF or NWF (non-walking fatigability) using the 6MWT. When there was a decline of 10% or more in the distance walked in the last minute compared to the first minute, this was considered WF (Van Geel et al., 2020). This divided the group into 23 WF and 28 NWF.

Table 2

Cognitive outcomes and questionnaires

		MS (n=42)	HC (n=21)
SDMT	Total	50,69 (11,65)	58,04 (15,63)
	CFI (%)	-12,06 (19,84)	-8,27 (11,91)
PFS	Physical	31,88 (8,49)	16,52 (8,17)
	Mental	23,31 (10,62)	10,65 (6,11)
PSQI		8,46 (5,39)	8 (4,62)
MFIS	Physical	21,26 (5,01)	9,20 (7,13)
	Cognitive	17,09 (7,79)	10,90 (6,30)
	Psychosocial	4,11 (1,90)	1,50 (1,43)
	Total (0-84)	38,29 (17,10)	21,6 (14,01)

This table shows the results of descriptive questionnaires and tests. The first number is the mean for each group followed by the standard deviation in brackets. SDMT = Symbol Digit Modalities Test; PFS = Pittsburgh Fatigability Scale; PSQI = Pittsburgh Sleep Quality Index; MFIS = Modified Fatigue Impact Scale

Intrasession reliability:

The within session test-retest reliability (Table 3) showed excellent ICC values, in both HC and pwMS, for A (ICC 0.91 - 0.93, mean ICC 0.92) and for RPM (ICC 0.92 - 0.94, mean ICC 0.93). The mean values of F showed poor to good reliability (ICC 0.41 - 0.88, mean ICC 0.68). The ϕ mean values showed moderate to good intrasession reliability (ICC 0.50 - 0.76, mean ICC 0.63). The mean STD ϕ showed moderate to excellent reliability (ICC 0.73 - 0.97, mean ICC 0.85).

In the MS group, the ICC of the mean F parameter was considerably lower when compared to the HC group. Where the MS group showed poor to moderate reliability (ICC 0.41 - 0.54, mean ICC 0.48), the HC group showed good reliability (ICC 0.88). The reliability of the STD ϕ was also lower in the MS group than in the HC group. Whereas moderate reliability was found in the MS group (ICC 0.73), while excellent reliability prevailed for the HC group (ICC 0.97). The mean ϕ had good reliability for the MS group (ICC 0.76) while only moderate reliability was found in the HC group (ICC 0.50).

The minute-by-minute reliability measurements (Table 3) of both groups showed good to excellent ICC values for A (ICC 0.88 - 0.93, mean ICC 0.91 and STD 0.01) and excellent reliability for RPM (ICC 0.90 - 0.94, mean ICC of 0.92 and STD 0.01). F reliability was poor to excellent (ICC 0.15 - 0.92, mean ICC 0.66 and STD 0.24). ϕ and STD ϕ both showed poor to good reliability, with values of (ICC 0.15 - 0.79, mean ICC 0.55 and STD 0.18) for ϕ, and (ICC 0.47 - 0.88, mean 0.65 and STD 0.16) for STD ϕ.

In the MS group, the minute-by-minute ICC of F were considerably less reliable when compared with the HC group. With overall good to excellent reliability in the HC group (ICC 0.84 - 0.92, mean ICC 0.87 and STD 0.03), and poor to moderate reliability in the MS group (ICC 0.15 - 0.59, mean ICC 0.45, STD 0.15). The reliability of the ϕ ranged from moderate to good within the MS group (ICC 0.60 - 0.79, mean ICC 0.67 and STD 0.07) and poor to moderate in the HC group (ICC 0.15 - 0.63, mean ICC 0.43 and STD 0.17). The STD ϕ reliability of the MS group ranged from moderate to good (ICC: 0.54 - 0.88, mean ICC 0.74 and STD 0.13) and varied from poor to good in the HC group (ICC 0.47 - 0.76, mean 0.55 and STD 0.12). For A and RPM, these values were similar with good to excellent reliability for A, and excellent reliability for RPM in both groups.

Table 3

ICC Heatmap for intrasession reliability

	A		F		RPM		ϕ	STD ϕ
	R	L	R	L	R	L		
				HC				
Mean	0,91	0,92	0,88	0,88	0,92	0,92	0,50	0,97
Min 1	0,91	0,92	0,91	0,92	0,90	0,90	0,15	0,47
Min 2	0,91	0,93	0,90	0,90	0,92	0,92	0,37	0,49
Min 3	0,91	0,91	0,86	0,86	0,92	0,92	0,39	0,62
Min 4	0,91	0,91	0,86	0,86	0,93	0,93	0,47	0,76
Min 5	0,89	0,90	0,84	0,84	0,91	0,91	0,63	0,48
Min 6	0,88	0,91	0,84	0,85	0,91	0,91	0,56	0,49
				MS				
Mean	0,93	0,92	0,41	0,54	0,94	0,94	0,76	0,73
Min 1	0,92	0,87	0,40	0,56	0,93	0,93	0,60	0,54
Min 2	0,91	0,90	0,15	0,59	0,93	0,93	0,65	0,61
Min 3	0,92	0,89	0,39	0,40	0,93	0,93	0,68	0,80
Min 4	0,91	0,92	0,58	0,39	0,92	0,92	0,62	0,84
Min 5	0,91	0,93	0,53	0,66	0,94	0,94	0,79	0,79
Min 6	0,91	0,91	0,27	0,45	0,94	0,94	0,68	0,88

This table shows the intrasession reliability through the ICC. Values are coloured according to the reliability, where red indicates poor reliability, yellow moderate reliability, light green good reliability, and darker green excellent reliability. ICC = Intraclass correlation coefficient; A = Amplitude; F = Frequency; RPM = Rotations per minute; ϕ = Relative phase; STD ϕ = Standard deviation of the relative phase; R = Right leg; L = Left leg.

Bland-Altman analyses were performed for the 6-minute mean value of each parameter. Results are shown in Tables 5 and 6 and Figure 1. All parameters showed low mean differences with high p-values for both pwMS and HCs, suggesting insignificant differences and good agreement. In pwMS, A and RPM showed relatively narrow limits of agreement (LoA), indicating good agreement, while the LoA were wide for F, ϕ and STD ϕ, indicating more variability between the two measurements. HCs had similar results, the only difference being smaller LoA for F, ϕ and STD ϕ. Heteroscedasticity was visually checked for the parameters. Only for STD ϕ in the MS group heteroscedasticity was reported, meaning there is a systematic change in the variance of the differences across the range of measurements. This could mean that the variability of the differences may increase as the mean value increases in pwMS.

Table 5

Bland-Altman analyses results for pwMS

	Mean difference	p-value	LoA	
			Lower	Upper
		Intrasession		
A	0,92	0,5665	-18,53	20,37
F	-1,97	0,4741	-17,75	13,80
RPM	0,50	0,9031	-52,76	53,75
ϕ	1,52	0,5665	-27,93	30,97
STD ϕ	1,13	0,6717	-31,99	34,25
		Intersession		
A	-2,44	0,1720	-24,94	20,05
F	0,19	0,3137	-19,41	19,79
RPM	-8,29	0,1692	-82,40	65,81
ϕ	-1,50	0,5729	-34,17	31,18
STD ϕ	3,78	0,0979	-23,47	31,02

Note. A = Amplitude; F = Frequency; RPM = Rotations Per Minute; ϕ = Relative phase; STD ϕ = Standard deviation of the relative phase; LoA = Limits of agreement.

Table 6

Bland-Altman analyses results for HCs

	Mean difference	p-value	LoA	
			Lower	Upper
		Intrasession		
A	-1,80	0,5169	-25,78	22,18
F	-1,24	0,1327	-8,1551	5,68
RPM	-12,13	0,2726	-106,32	82,06
ϕ	-0,27	0,9119	-21,70	21,15
STD ϕ	0,78	0,0787	-2,91	4,47
		Intersession		
A	0,26	0,9542	-40,02	40,55
F	-1,09	0,1796	-7,9361	5,7592
RPM	-5,09	0,8695	-99,48	89,31
ϕ	0,55	0,8100	-19,64	20,74
STD ϕ	0,20	0,3471	-3,60	3,99

Note. A = Amplitude; F = Frequency; RPM = Rotations Per Minute; ϕ = Relative phase; STD ϕ = Standard deviation of the relative phase; LoA = Limits of agreement

Intersession reliability:

The reliability measures of the mean values (Table 4) of both groups showed good ICC values for A (ICC 0.86 - 0.89, mean ICC 0.87) and for RPM (ICC 0.88 - 0.89, mean ICC 0.89). The mean values of F showed moderate to good reliability (ICC 0.55 - 0.87, mean ICC 0.76). ϕ mean values showed moderate intersession reliability (ICC 0.57 - 0.64, mean ICC 0.60). The mean STD ϕ showed poor reliability (ICC 0.13 - 0.45, mean ICC 0.29). The reliability of the mean F was significantly lower in the MS group compared to the HC group. Where the mean F values within the MS group had moderate reliability (ICC 0.65) and good reliability within the HC group (ICC 0.87). The other mean values were comparable in reliability. For instance, there was good reliability for mean A (MS ICC 0.86; HC ICC 0.89) and mean RPM (MS ICC 0.88; HC ICC 0.89), moderate reliability for mean ϕ (MS ICC 0.64; HC ICC 0.57) and poor reliability for mean STD ϕ (MS ICC 0.45; HC ICC 0.13).

The minute-by-minute reliability measurements (Table 4) for both groups showed good ICC values for A (ICC 0.78 - 0.89, mean ICC 0.86 and STD 0.02) and good to excellent reliability for RPM (ICC 0.81 - 0.92, mean ICC of 0.87 and STD 0.03). Reliability for F was poor to good (ICC

0.45 - 0.88, mean ICC 0.72 and STD 0.16). ϕ and STD ϕ both showed poor to moderate reliability, with for ϕ, values of (ICC 0.18 - 0.68, mean ICC 0.48 and STD 0.16), and for STD ϕ (ICC 0.01 - 0.65, mean ICC 0.34 and STD 0.23).

F reliability was noticeably lower in the MS group compared to the HC group. Whereas the F values within the MS group ranged from poor to moderate (ICC 0.45 - 0.74, mean 0.58, STD 0.1) and good reliability within the HC group (ICC 0.83 - 0.88, mean 0.86 and STD 0.02). In the MS group, good reliability was found for RPM (ICC 0.85 - 0.88, mean ICC 0.86 and STD 0.01) while in the HC group good to excellent reliability was observed (ICC 0.81 - 0.92, mean ICC 0.88 and STD 0.04). The other values were similar in reliability. For instance, in both groups there was good reliability for A (MS ICC 0.85 - 0.89; HC ICC 0.78 - 0.88), and poor to moderate reliability for both ϕ (MS ICC 0.48 - 0.68; HC ICC 0.18 - 0.62) and STD ϕ (MS ICC 0.23 - 0.55; HC ICC 0.01 - 0.65).

Table 4

ICC heatmap for Intersession Reliability for HC and pwMS, for 5 parameters

	A		F		RPM		ϕ	STD ϕ
	R	L	R	L	R	L		
				HC				
Mean	0,86	0,86	0,87	0,87	0,89	0,89	0,57	0,13
Min 1	0,88	0,84	0,88	0,88	0,92	0,92	0,34	0,65
Min 2	0,88	0,84	0,87	0,87	0,92	0,92	0,46	0,59
Min 3	0,87	0,87	0,87	0,87	0,90	0,90	0,62	0,60
Min 4	0,85	0,84	0,86	0,87	0,88	0,88	0,56	0,01
Min 5	0,81	0,85	0,84	0,84	0,84	0,84	0,22	0,02
Min 6	0,78	0,83	0,83	0,83	0,81	0,81	0,18	0,08
				MS				
Mean	0,88	0,89	0,74	0,55	0,88	0,88	0,64	0,45
Min 1	0,86	0,86	0,52	0,50	0,85	0,85	0,48	0,47
Min 2	0,87	0,87	0,54	0,46	0,87	0,87	0,51	0,55
Min 3	0,88	0,87	0,74	0,52	0,88	0,88	0,58	0,23
Min 4	0,85	0,89	0,68	0,45	0,87	0,87	0,52	0,34
Min 5	0,86	0,88	0,72	0,59	0,86	0,86	0,68	0,23
Min 6	0,85	0,88	0,60	0,60	0,85	0,85	0,65	0,33

Values are coloured according to reliability where red indicates poor reliability, yellow moderate reliability, light green good reliability, and darker green excellent reliability. ICC = Intraclass correlation coefficient; A = Amplitude; F = Frequency; RPM = Rotations per minute; ϕ = Relative phase; STD ϕ = Standard deviation of the relative phase; R = Right leg; L = Left leg.

Bland-Altman analyses for intersession reliability showed similar results, see Tables 5 and 6, and Figure 1, to the analyses from the intrasession reliability with low and insignificant mean differences and wide LoA only for F, ϕ and STD ϕ in the MS group and for A in the HC group. Heteroscedasticity was only reported for STD ϕ in the MS group as well.

ICC values were calculated for BORG Pre, BORG Post and BORG Post-Pre and were shown in table 8. For HCs, ICC values were moderate to excellent (ICC 0.73-0.79, mean 0.82 and STD 0,08). For PwMS, ICC values were moderate to good (ICC 0.55-0.86, mean 0.72 and STD 0.13)

Table 7

ICC values for BORG RPE

	BORG PRE	BORG POST	BORG POST-PRE
		Intrasession	
HC	0,83	0,97	0,73
MS	0,86	0,84	0,75
		Intersession	
HC	0,78	0,82	0,80
MS	0,55	0,70	0,60

Note. BORG Pre = BORG RPE score before the 6MSCT; BORG Post = BORG RPE after the 6MSCT; BORG Post-Pre = difference in BORG RPE score from after and before the 6MSCT

Correlation analyses

The results of correlation analyses were reported in Table 7. In the HC group, Pearson correlation coefficient showed only a significant correlation between the MVC Pre and ϕ (r= -0.44, p-value= 0.0391). In the MS group, significant correlations were found between A (R) and MVC Pre (r=0.39, p-value= 0.0082), A (L) and MVC Pre (r=0.53, p-value= 0.0002), RPM and MVC Pre (r=0.45, p-value= 0.0020). MVC Post correlated with A (R) (r=0.30, p-value= 0,048), A (L) (r=0,49, p-value=0,0006), with F (L) (r=0.33, p-value=0.026), and with RPM (R+L) (r=0.37, p-value 0.0127).

Table 8

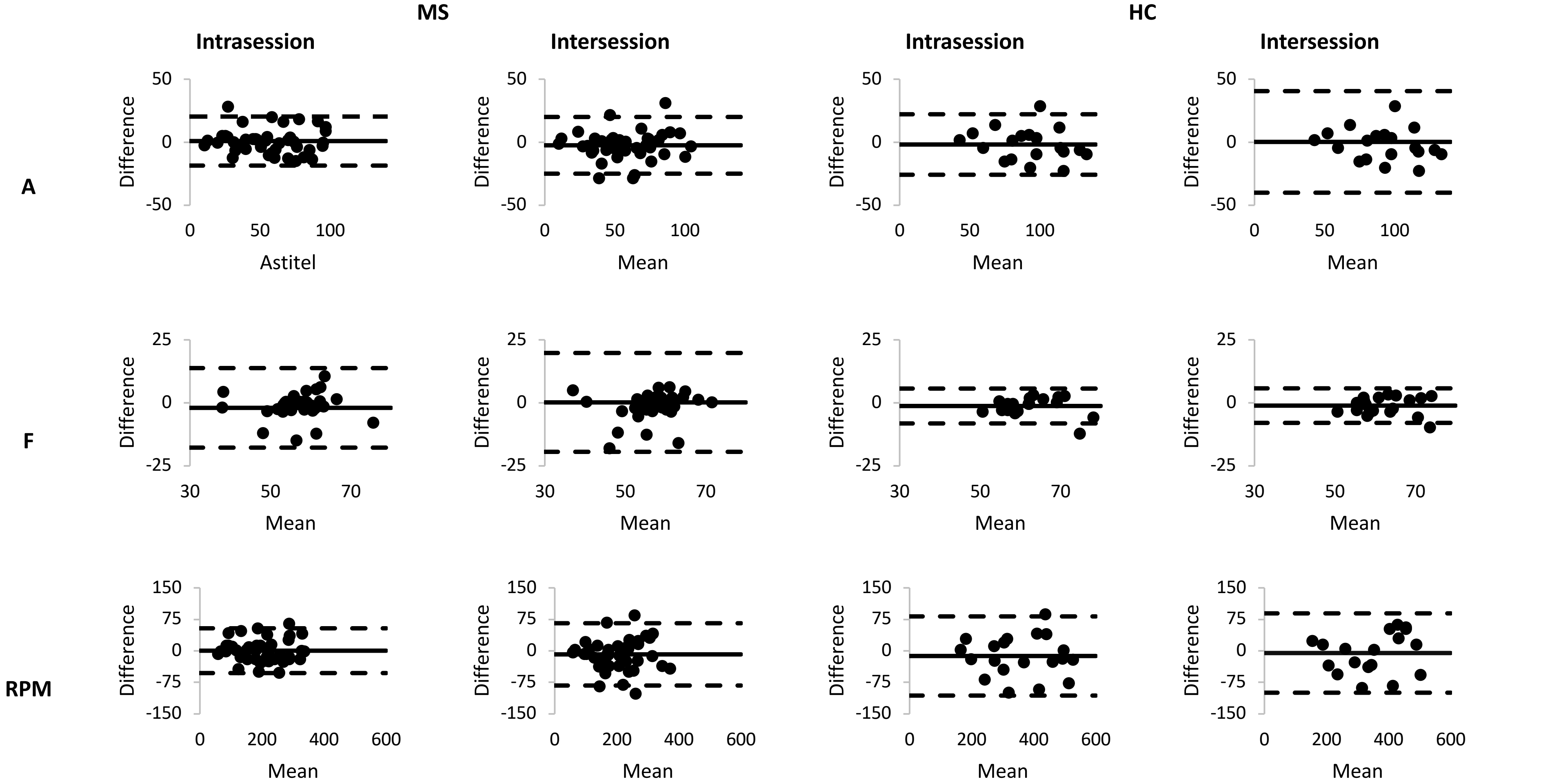
Correlation analyses

		A		F		RPM		ϕ	STD ϕ
		R	L	R	L	R	L		
HC									
MVC Pre	r	0,04	0,18	0,15	0,15	0,32	0,32	-0,44	-0,30
	p	0,1673	0,4335	0,493	0,4937	0,1485	0,1485	0,0391*	*0,1718*
MVC Post	r	0,27	0,16	0,22	0,22	0,28	0,28	-0,42	-0,41
	p	0,2225	0,4853	0,3229	0,3325	0,2014	0,2014	0,0509	*0,0600*
MVC Pre-Post	r	-0,03	-0,02	-0,20	-0,20	-0,03	-0,03	0,10	0,24
	p	0,9073	0,9407	0,3771	0,3752	0,9001	0,9001	0,6574	*0,2824*
BORG Pre	r	0,27	0,13	0,35	0,35	0,27	0,27	0,08	*-0,23*
	p	0,3169	0,6371	0,1857	0,1857	0,3097	0,3097	0,7646	*0,3864*
BORG Post	r	0,34	0,51	0,43	0,43	0,42	0,42	-0,14	*-0,32*
	p	0,1925	0,0457	0,0971	0,0971	0,0997	0,0997	0,6062	*0,2321*
BORG Post-Pre	r	0,27	0,32	0,37	0,37	0,37	0,37	-0,17	-0,30
	p	*0,3207*	*0,0586*	*0,1622*	*0,1622*	*0,1585*	*0,1585*	*0,5185*	*0,2638*
MS									
MVC Pre	r	0,39	0,53	0,22	0,28	0,45	0,45	0,00	-0,29
	p	0,0082*	0,0002*	0,1521	0,0621	0,0020*	0,0020*	0,9793	0,056
MVC Post	r	0,30	0,49	0,28	0,33	0,37	0,37	0,05	-0,24
	p	0,0481*	0,0006*	0,0606	0,026*	0,0127*	0,0127*	0,7399	0,1052
MVC Pre-Post	r	0,11	-0,09	-0,24	-0,23	0,05	0,05	-0,14	-0,01
	p	0,4905	0,579	0,1095	0,1307	0,7442	0,7442	0,3594	0,9476
BORG Pre	r	0,22	-0,10	-0,22	-0,03	0,16	0,16	0,11	-0,15
	p	0,1347	0,5055	0,1354	0,8326	0,2925	0,2925	0,4721	0,3200
BORG Post	r	0,26	0,05	-0,17	-0,05	0,23	0,23	0,05	-0,12
	p	0,0778	0,7575	0,2506	0,7410	0,1324	0,1324	0,7591	0,4360
BORG Post-Pre	r	0,10	0,16	0,01	-0,03	0,12	0,12	-0,45	0,01
	p	0,4936	0,2909	0,9648	0,8421	0,4209	0,4209	0,7434	0,9876

Note. Correlation analyses for the numbers in white were performed with the Pearson correlation coefficient and the Spearman's Rho was used for the numbers in grey. A = Amplitude; F = Frequency; RPM = Rotations Per Minute; ϕ = Relative phase; STD ϕ = Standard deviation of the relative phase; MVC Pre = Maximal Voluntary Contraction before the 6 Minute seated coordination task (6MSCT); MVC Post = Maximal Voluntary Contraction after the 6MSCT; MVC Pre-Post= Difference between MVC before and after the 6MSCT; BORG Pre = BORG Rate of Perceived Exertion scale before the 6MSCT; BORG Post = BORG Rate of Perceived Exertion scale before the 6MSCT after the 6MSCT; BORG Post-Pre = Difference in BORG score after and before the 6MSCT; p = p-value based on 95% confidence interval; r = correlation coefficient

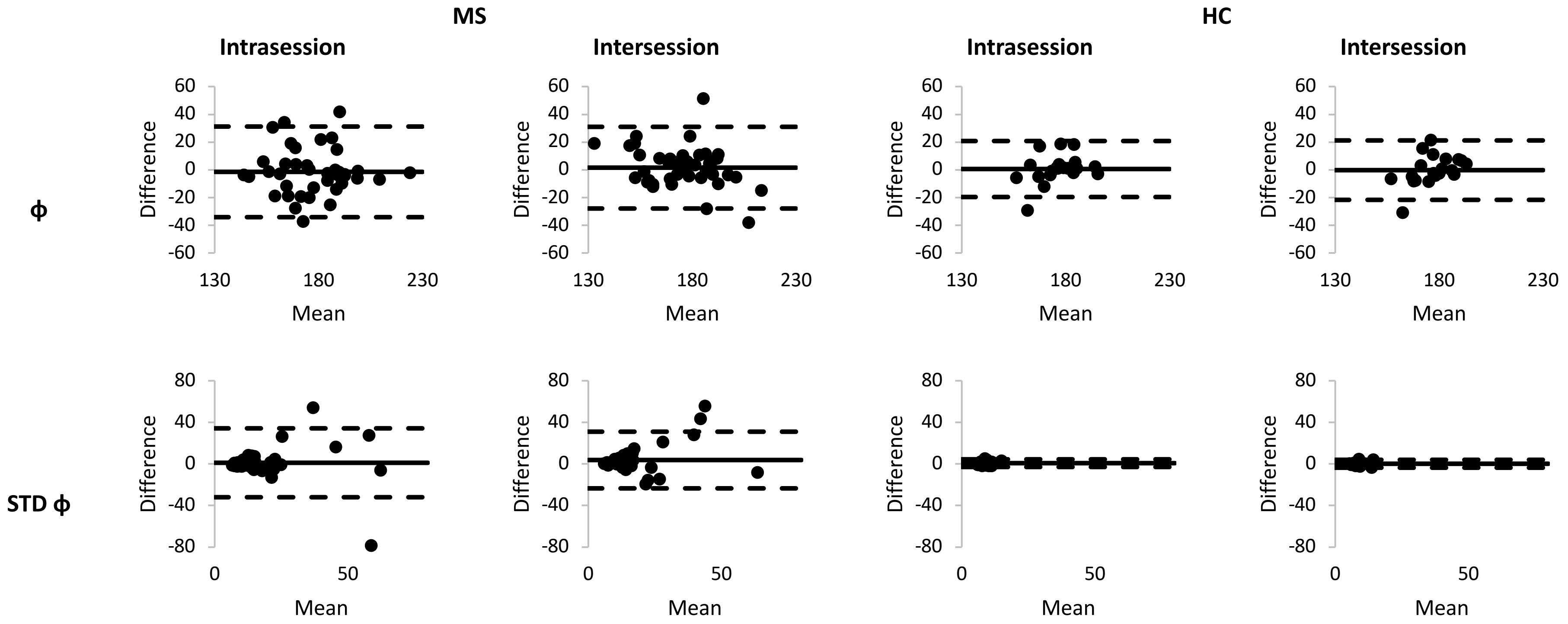
Figure 3

Bland-Altman table plots for intra-and-intersession reliability in MS (left) and HC (right)



Continued.

Continued.



Note. The X-axes represent the mean value of both trials for each participant and the Y-axes represent the difference between values for each participant. For the MS group, n = 42 in intrasession analyses and n = 40 in intersession analyses. For the HC group, n = 20 in intrasession analyses and n = 21 in intersession analyses. Means, p-values and limits of agreement are reported in table 3 and table 4. A = Amplitude; F = Frequency; RPM = Rotations Per Minute; ϕ = Relative phase; STD ϕ = Standard deviation of the relative phase; LoA = Limits of agreement.

Discussion

This study investigated the intra-and-intersession reliability of the 6MSCT in HCs and pwMS.

Overall, the 6MSCT demonstrated good-to-excellent intra-and-intersession reliability for A and RPM. Good-to-excellent intrasession reliability for F was reported for the HC group, while poor-to-moderate reliability was reported for the MS group. The minute-by-minute ϕ and STD ϕ were less reliable in the HC group than in the MS group for intrasession reliability. Bland-Altman plots revealed good agreement with narrow LoA for A, F, and RPM. While wider LoA were observed for ϕ and STD ϕ, indicating more variability between measurements. Heteroscedasticity was reported for STD ϕ, indicating a systematic change in the variance of the differences across the range of measurements. Similar results were observed for intersession reliability, where the reliability of F was lower in the MS group than in the HC group. ϕ and STD ϕ showed overall poor-to-moderate reliability in both groups. Bland-Altman plots revealed similar intersession reliability results as intrasession reliability with an overall good agreement and small LoA for A, F, and RPM and wide LoA for ϕ and STD ϕ. Heteroscedasticity was reported for STD ϕ.

The good-to-excellent reliability for F in the HC group but poor-to-moderate reliability in the MS group can possibly be explained by fatigue towards the end of the task. This resulted in attempts to ensure A and RPM but led to an inconsistent F.

The 6MSCT is designed to minimise balance requirements or large muscle effort and theoretically emphasises the central neural mechanism (Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021). ϕ and STD ϕ are the key variables mapping interlimb coordination. The results of this study show good reliability for mean ϕ and moderate reliability for mean STD ϕ for same-day measurements at pwMS. The minute-by-minute analyses showed moderate to good reliability. The low to moderate reliability of ϕ and STD ϕ between two different sessions may be due to the large day-to-day variability known in pwMS (Albrecht et al., 2001). Another possible explanation for the low to moderate reliability of ϕ in pwMS is the degree of asymmetry that pwMS exhibit towards the end of the task (Plotnik et al., 2020). In addition, previous research has shown that bilateral lower limb coordination is linked to the white matter microstructural integrity of the dorsal premotor and primary motor bundles in pwMS, which is reduced in pwMS when compared with an HC group. Moreover, these structural constraints are correlated with reduced consistency and accuracy during gait in pwMS (Richmond et al., 2022). This may help to explain why poor-to-moderate reliability is observed for F in the MS group and good-to-excellent reliability in the HC group.

Because of the good intra- and intersession reliability of A and RPM, the 6MSCT could be used as a clinical application for pwMS to examine unloaded lower limb performance. Further research should explore the applicability of the 6MSCT for other neurological conditions that present fatigue and coordination deficits, like Parkinson (Siciliano et al., 2018) and stroke (Colle et al., 2006). However, for pwMS, some caution should be exercised to use the task for interlimb coordination parameters because day-to-day variability may make the test less reliable.

Post hoc analysis for intersession reliability of BORG Pre resulted in moderate reliability with an ICC value of 0.55 for pwMS, whereas good reliability (ICC 0.78) was observed for the HC group. This finding may explain the low intersession reliability for F, ϕ, and STD ϕ. High variability in perceived exertion, measured with the BORG RPE, will impact the performance of the 6MSCT. These findings on perceived exertion are consistent with the results of previous research where the reliability of the 6MWT was compared in healthy subjects and pwMS. Here, moderate reliability was also observed in the MS group, while the degree of exertion did have good reliability in the healthy group (Hadouiri et al., 2021). These findings are consistent with previous assumptions that the day-to-day variability experienced by pwMS should be considered since this impact task performance. However, correlation analyses showed a low correlation between BORG Pre and F, ϕ, and STD ϕ for pwMS. As a result, the low intersession reliability of these parameters cannot be fully attributed to day-to-day variability in fatigue and effort perceived during the 6MSCT.

This study reported good reliability for A and RPM in both pwMS and HCs. Post-hoc analyses showed that the correlations between MVC and A, and RPM were also significant in pwMS in all trials. This could explain the good to excellent reliability results in the MS group for intra- and intersession reliability and could indicate that these results aren’t affected by day-to-day variability. The good test-retest reliability of the MVC may explain these results (Van Geel et al., 2021).

Previous research investigating the difference in ILC of the lower limbs during a seated coordination test between HCs and pwMS (Goetschalckx, Van Geel, Meesen, Moumdjian, et al., 2021) observed a higher variability in ILC in pwMS when compared with an HC group. To map ILC, the Phase Coordination Index (PCI) was calculated. This parameter was used to map the accuracy and stability in generating antiphase movements of the lower limbs in sitting. Accuracy in generating antiphase movements can be related to ϕ, and stability to STD ϕ, used in this study. The intrasession reliability of mean ϕ and STD ϕ, examined in this current study showed that for HCs, the reliability of the mean value of ϕ was moderate (ICC=0.50), and excellent for STD ϕ (ICC=0.97). For pwMS, good reliability (ICC=0.76) was observed for mean ϕ and moderate reliability (ICC=0.73) for mean STD ϕ. This may imply that the results related to the PCI are reliable for HCs and pwMS. More research on the correlation between the parameters of this study and the PCI is needed to confirm this statement. Another study investigated how ILC antiphase pattern changes during a six-minute seated coordination task in pwMS with WF, NWF and HCs (Goetschalckx, Van Geel, Meesen, Triccas, et al., 2021). Data was measured minute-by-minute to observe a change in antiphase pattern. ILC was mapped using the PCI and spatiotemporal parameters (A and F) were also included. Increased ILC variability was observed over time in all groups but with the largest decrease in pwMS with WF and a decrease in A overtime in pwMS with WF was observed. For F, no significant change was observed over time in any group. The intrasession reliability of minute-by-minute results in HCs showed poor-to-moderate reliability (mean ICC 0.43 and STD 0.17) for ϕ and poor-to-good reliability (mean 0.55 and STD 0.12) for STD ϕ. The intrasession reliability was better for pwMS with a moderate-to-good reliability for ϕ (mean ICC 0.67 and STD 0.07) and STD ϕ (mean ICC 0.74 and STD 0.13). Based on these minute-by-minute results, precaution should be taken when interpreting these results from previous study regarding the ILC in HCs. Good to excellent intrasession reliability (mean ICC 0.91 and STD 0.01) is observed for minute-by-minute A in both groups, indicating there is a true decrease in A in pwMS with WF during the 6MSCT. There was no significant effect of time on F found in any group, but based on the results of this test-retest study this statement may not be accurate due to the poor to moderate reliability (mean ICC 0.45, STD 0.15) for F.

One main limitation of this study is the lack of participants. The HC group consisted of fewer than 30 participants. This leaves the representativeness of this study limited and statistical power low. The MS group consisted of a total of 51 participants, where 28 were classified as NWF and 23 with WF. To increase the statistical power, these two subgroups were combined. As a result of this short falling of participants, our statistical analysis did not distinguish between the two subgroups. In addition, all MS patients were recruited from the MS centres in Belgium, but no patients outside these centres were included in the study. This potentially increases the risk of selection bias and limits the findings' representativeness to the broader population of pwMS. This study aimed to assess the inter- and intrasession reliability of the 6MSCT. This study did not include other important psychometric properties of this measurement instrument. Further research should be conducted with larger sample sizes to investigate the differences between pwMS with WF and NWF. It should include multiple psychometric properties, such as the different validity measures, to identify the usability and clinical relevance of the 6MSCT.

Conclusion

The highest reliability was observed for A and RPM. F was the least reliable within the MS group, though good-to-excellent reliability was observed for the HC group. ϕ, and STD ϕ were moderate-to-good reliable for the MS group when measurements were taken on the same day, but only low-to-moderate reliable when measurements were taken on two separate days. The intrasession reliability was good-to-excellent for the mean values and minute-by-minute analysis of A, F, and RPM for the HC group. Within the MS group, similar results were observed except for F, which had low-to-moderate reliability. The intersession reliability of the 6MSCT had overall good mean and minute-by-minute reliability for A and F and even good-to-excellent reliability in the minute-by-minute analysis for RPM in the HC group. Within the MS group, F had moderate reliability for the mean values and low-to-moderate reliability for the minute-per-minute analysis. Both groups showed low-to-moderate reliability for ϕ and STD ϕ.

Reference list:

Albrecht, H., Wötzel, C., Erasmus, L. P., Kleinpeter, M., König, N., & Pöllmann, W. (2001). Day-to-day variability of maximum walking distance in MS patients can mislead to relevant changes in the Expanded Disability Status Scale (EDSS): average walking speed is a more constant parameter. *Mult Scler*, *7*(2), 105-109. https://doi.org/10.1177/135245850100700206

Amato, M. P., Ponziani, G., Rossi, F., Liedl, C. L., Stefanile, C., & Rossi, L. (2001). Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Multiple Sclerosis Journal*, *7*(5), 340-344. https://doi.org/10.1177/135245850100700511

Arpan, I., Fino, P. C., Fling, B. W., & Horak, F. (2020). Local dynamic stability during long-fatiguing walks in people with multiple sclerosis. *Gait Posture*, *76*, 122-127. https://doi.org/10.1016/j.gaitpost.2019.10.032

Bever, C. T., Anderson, P. A., Smith, G. V., Panitch, H. S., & Johnson, K. P. (1995). Isometric Measurement of Hamstrings and Quadriceps Strength in Multiple Sclerosis Patients: Sensitivity and Variability. *Journal of Neurologic Rehabilitation*, *9*(4), 221-227. https://doi.org/10.1177/154596839500900405

Bialocerkowski, A. E., & Bragge, P. (2008). Measurement error and reliability testing: Application to rehabilitation. *International Journal of Therapy and Rehabilitation*, *15*(10), 422-427. https://doi.org/10.12968/ijtr.2008.15.10.31210

Carlozzi, N. E., Boileau, N. R., Murphy, S. L., Braley, T. J., & Kratz, A. L. (2021). Validation of the Pittsburgh Fatigability Scale in a mixed sample of adults with and without chronic conditions. *J Health Psychol*, *26*(9), 1455-1467. https://doi.org/10.1177/1359105319877448

Cleland, B. T., Ingraham, B. A., Pitluck, M. C., Woo, D., & Ng, A. V. (2016). Reliability and Validity of Ratings of Perceived Exertion in Persons With Multiple Sclerosis. *Arch Phys Med Rehabil*, *97*(6), 974-982. https://doi.org/10.1016/j.apmr.2016.01.013

Colle, F., Bonan, I., Gellez Leman, M., Bradai, N., & Yelnik, A. (2006). Fatigue after stroke. *Annales de Réadaptation et de Médecine Physique*, *49*(6), 361-364. https://doi.org/10.1016/j.annrmp.2006.04.010

Doshi, A., & Chataway, J. (2016). Multiple sclerosis, a treatable disease. *Clin Med (Lond)*, *16*(Suppl 6), s53-s59. https://doi.org/10.7861/clinmedicine.16-6-s53

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., & Schlech, W. F. (1994). Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis*, *18 Suppl 1*, S79-83. https://doi.org/10.1093/clinids/18.supplement_1.s79

Gil-González, I., Martín-Rodríguez, A., Conrad, R., & Pérez-San-Gregorio, M. (2020). Quality of life in adults with multiple sclerosis: a systematic review. *BMJ Open*, *10*(11), e041249. https://doi.org/10.1136/bmjopen-2020-041249

Goetschalckx, M., Van Geel, F., Meesen, R., Moumdjian, L., Geraerts, M., & Feys, P. (2021). Rhythmic interlimb coordination of the lower limbs in multiple sclerosis during auditory pacing to three different frequencies. *Gait Posture*, *86*, 334-340. https://doi.org/10.1016/j.gaitpost.2021.04.001

Goetschalckx, M., Van Geel, F., Meesen, R., Triccas, L. T., Geraerts, M., Moumdjian, L., & Feys, P. (2021). Interlimb Coordination Performance in Seated Position in Persons With Multiple Sclerosis: Reduced Amplitude Over 6 min and Higher Coordination Variability in Persons With Walking Fatigability. *Front Hum Neurosci*, *15*, 765254. https://doi.org/10.3389/fnhum.2021.765254

Hadouiri, N., Monnet, E., Gouelle, A., Decavel, P., & Sagawa, Y. (2021). Evaluation of Prolonged Walking in Persons with Multiple Sclerosis: Reliability of the Spatio-Temporal Walking Variables during the 6-Minute Walk Test. *Sensors (Basel)*, *21*(9). https://doi.org/10.3390/s21093075

Kos, D., Kerckhofs, E., Carrea, I., Verza, R., Ramos, M., & Jansa, J. (2005). Evaluation of the Modified Fatigue Impact Scale in four different European countries. *Mult Scler*, *11*(1), 76-80. https://doi.org/10.1191/1352458505ms1117oa

Krupp, L. (2006). Editorial. *Multiple Sclerosis Journal*, *12*(4), 367-368. https://doi.org/10.1191/135248506ms1373ed

Kwak, S. K., & Kim, J. M. (2017). Central limit theorem: the cornerstone of modern statistics. *Korean Journal of Anesthesiology*, *70*(2), 144. https://doi.org/10.4097/kjae.2017.70.2.144

Leone, C., Severijns, D., Dolezalova, V., Baert, I., Dalgas, U., Romberg, A., Bethoux, F., Gebara, B., Santoyo Medina, C., Maamagi, H., Rasova, K., Maertens de Noordhout, B., Knuts, K., Skjerbaek, A., Jensen, E., Wagner, J. M., & Feys, P. (2016). Prevalence of Walking-Related Motor Fatigue in Persons With Multiple Sclerosis: Decline in

Walking Distance Induced by the 6-Minute Walk Test. *Neurorehabil Neural Repair*, *30*(4), 373-383. https://doi.org/10.1177/1545968315597070

Minden, S. L., Frankel, D., Hadden, L., Perloff, J., Srinath, K. P., & Hoaglin, D. C. (2006). The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. *Multiple Sclerosis Journal*, *12*(1), 24-38. https://doi.org/10.1191/135248506ms1262oa

Parmenter, B. A., Weinstock-Guttman, B., Garg, N., Munschauer, F., & Benedict, R. H. (2007). Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. *Multiple Sclerosis Journal*, *13*(1), 52-57. https://doi.org/10.1177/1352458506070750

Plotnik, M., Wagner, J. M., Adusumilli, G., Gottlieb, A., & Naismith, R. T. (2020). Gait asymmetry, and bilateral coordination of gait during a six-minute walk test in persons with multiple sclerosis. *Sci Rep*, *10*(1), 12382. https://doi.org/10.1038/s41598-020-68263-0

Portney, L.G. and Watkins, M.P. (2000) Foundations of clinical research: Applications to practice. 2nd Edition, Prentice Hall Health, Upper Saddle River.

Richmond, S. B., Peterson, D. S., & Fling, B. W. (2022). Bridging the callosal gap in gait: corpus callosum white matter integrity's role in lower limb coordination. *Brain Imaging Behav*, *16*(4), 1552-1562. https://doi.org/10.1007/s11682-021-00612-7

Rosenberg, J. H., & Shafor, R. (2005). Fatigue in multiple sclerosis: a rational approach to evaluation and treatment. *Curr Neurol Neurosci Rep*, *5*(2), 140-146. https://doi.org/10.1007/s11910-005-0012-5

Serrien, D. J., Swinnen, S. P., & Stelmach, G. E. (2000). Age-related deterioration of coordinated interlimb behavior. *J Gerontol B Psychol Sci Soc Sci*, *55*(5), P295-303. https://doi.org/10.1093/geronb/55.5.p295

Siciliano, M., Trojano, L., Santangelo, G., De Micco, R., Tedeschi, G., & Tessitore, A. (2018). Fatigue in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*, *33*(11), 1712-1723. https://doi.org/10.1002/mds.27461

Swinnen, S. P., Van Langendonk, L., Verschueren, S., Peeters, G., Dom, R., & De Weerdt, W. (1997). Interlimb coordination deficits in patients with Parkinson's disease during the production of two-joint oscillations in the sagittal plane. *Mov Disord*, *12*(6), 958-968. https://doi.org/10.1002/mds.870120619

The MathWorks Inc. (2022). MATLAB version: 9.13.0 (R2022b), Natick, Massachusetts: The MathWorks Inc. https://www.mathworks.com

Van Geel, F., Hvid, L. G., Van Noten, P., Eijnde, B. O., Dalgas, U., & Feys, P. (2021). Is maximal muscle strength and fatigability of three lower limb muscle groups associated with walking capacity and fatigability in multiple sclerosis? An exploratory study. *Mult Scler Relat Disord*, *50*, 102841. https://doi.org/10.1016/j.msard.2021.102841

Van Geel, F., Moumdjian, L., Lamers, I., Bielen, H., & Feys, P. (2020). Measuring walking-related performance fatigability in clinical practice: a systematic review. *Eur J Phys Rehabil Med*, *56*(1), 88-103. https://doi.org/10.23736/S1973-9087.19.05878-7

Appendix

Means and standard deviation for both groups on parameters

		HC		MS	
		mean	std	mean	std
A	R	93,76	27,55	58,21	23,15
	L	94,02	25,53	66,54	22,97
F	R	61,59	6,94	56,28	7,05
	L	61,59	6,94	56,83	7,09
RPM	R	352,76	119,05	202,58	73,64
	L	352,76	119,05	202,58	73,64
ϕ		176,87	12,5	177,98	19,81
STD ϕ		10,69	7,76	18,76	14,93
BORG Pre		1,35	0,7	2,58	1,78
BORG Post		3,71	2,39	5,29	2,25
BORG Post-Pre		2,35	2,29	2,71	1,81
MVC Pre		34,36	7,74	28,32	11,19
MVC Post		32,23	8,94	25,22	122,78
MVC Pre-Post		2,13	3,99	3,09	8,08

Note. A = Amplitude; F = Frequency; RPM = Rotations Per Minute; ϕ = Relative phase; STD ϕ = Standard deviation of the relative phase; BORG Pre = BORG Rate of Perceived Exertion scale before the 6MSCT; BORG Post = BORG Rate of Perceived Exertion scale before the 6MSCT after the 6MSCT; BORG Post-Pre = Difference in BORG score after and before the 6MSCT; MVC Pre = Maximal Voluntary Contraction before the 6 Minute seated coordination task (6MSCT); MVC Post = Maximal Voluntary Contraction after the 6MSCT; MVC Pre-Post= Difference between MVC before and after the 6MSCT; R = Right leg; L = left leg; std = standard deviation.