Neurological Sciences (2024) 45:2783–2789
https://doi.org/10.1007/s10072-023-07286-7

ORIGINAL ARTICLE

Influence of cognition on the correlation between objective and subjective upper limb measures in people with multiple sclerosis

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Received: 24 April 2023 / Accepted: 20 December 2023 / Published online: 4 January 2024

Abstract

Background A comprehensive assessment of upper limb (UL) function is mandatory in people with multiple sclerosis (PwMS), and the use of multiple objective and subjective measures is advisable. Findings on the role of cognitive impairment on the assessment of UL function are scant and inconclusive. The present study investigated the influence of cognitive function on the distribution of objective and subjective UL measures and on their association.

Methods In the cross-sectional study, subjects with a diagnosis of MS, age ≥ 18 years, right-hand dominance, no presence of orthopedic UL impairment, or other neurological diseases were recruited. The assessment protocol included the Nine-Hole Peg Test (9-HPT), Box and Block Test (BBT), and hand grip strength (HGS), a validated PROM (MAM-36), and the Symbol Digit Modalities Test (SDMT).

Results Two hundred forty-six PwMS were recruited (158 females, mean age = 51.65 ± 13.45 years; mean EDSS = 5.10 ± 1.88) Subject with mild-to-moderate cognitive impairment (SDMT ≤ −2 SD of normative values) scored lower on the 9-HPT and higher on the BBT and MAM-36 when compared with subject with no cognitive impairment. Cognitive impairment showed a small but significant effect on the association between 9-HPT scores and the MAM-36.

Discussion Findings suggest that cognitive impairment is associated with subjects' performance on 9-HPT, BBT, and MAM-36 (but not HGS), resulting in scores indicating a poorer UL function. Interestingly, cognitive impairment slightly affected the congruence between subjective and objective UL measures, although only minor differences in the correlation pattern across groups reporting different cognitive performances emerged.

Keywords Multiple sclerosis · Upper limb · Cognition · Patient-reported outcome measures

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system leading to a wide range of symptoms [1]. Over the course of the disease, deficits affecting several functional systems may occur, leading to different levels of disability [2]. Usually, disability in people with MS (PwMS) is thought to be mainly related to ambulation; however, upper limb (UL) function is one of the most affected domains; about 50% of PwMS report self-perceived upper limb dysfunction [3] leading to loss of independence in activities of daily living and community participation [4, 5].

The gold standard to assess UL function in MS is the Nine-Hole Peg Test (9-HPT) [6]. Among other existing objective UL measures are the Box and Block Test (BBT)

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[7], a measure of gross manual dexterity, and the hand grip strength (HGS) test [8]. Findings indicate that these three measures showed only low-to-moderate correlations, suggesting that they assess different UL domains [9].

Still, Lamers and colleagues highlighted that no single measure is able to cover the entire range of UL functionality applicable across different UL disability levels in MS [10, 11]. By design, objective measures cannot provide a thorough assessment of subjects' ability in performing manual activities of daily living (ADL) with their arms, which in turn remains the ultimate outcome of UL treatment [12]. To overcome this issue, over the course of the last 10–15 years, patient-reported outcome measures (PROMs) have been developed to support clinical research [13], as well as clinical practice. Recent findings support the need of considering the use of both objective and subjective measures when a comprehensive assessment of UL is of interest [14].

Of note, PROM requires different cognitive skills to be completed, as adequate processing speed, sustained attention, working memory, episodic memory, and executive functions [15].

Cognitive impairment is a common consequence of MS, with a prevalence ranging from 34 to 65% [16]. It occurs early in the disease course and typically worsens over time [17, 18] impairing domains as processing speed, working and episodic memory, attention, executive function, verbal fluency, and visuospatial perception [19]. Among these domains, processing speed is commonly used to monitor cognitive dysfunctions in MS because it is early affected in the disease course, it is associated with impairment in other cognitive domains, and it predicts worse overall cognitive outcomes [19–21].

The Symbol Digit Modalities Test (SDMT) is considered the gold standard to assess cognitive processing speed in MS; it also assesses attention and spatial working memory [22]. Van Schependom et al. [23] demonstrated that SDMT is the best predictor of general cognitive impairment because it outperformed other neuropsychological tests in predicting the outcome of a complete neuropsychological test battery. Indeed, SDMT has been suggested as a screening tool for cognitive impairments (CI) in MS [24] due to its high sensitivity (0.91) and specificity (0.60) [23] and its easy administration procedure that does not cause a significant amount of stress amongst subjects [25] and does not have to be administered by a trained neuropsychologist.

Several studies have evaluated the correlation between cognitive function, assessed through SDMT, and UL function, evaluated through the 9-HPT, reporting heterogeneous results among studies with an overall moderate-to-large effect size [25–31].

In literature, we could only find one study [32] evaluating the role of cognitive impairment on the validity and reliability of self-report health measures in MS, including a single-item for the assessment of self-perceived UL function. The study was performed on a sample of 187 PwMS, of which 80 subjects with cognitive impairment. Overall, the authors concluded that cognitive impairment did not affect the reliability and validity of the administered PROM. However, their results also showed that the correlation between an objective UL measure, the 9-HPT, and the single-item for UL function differed in size when comparing cognitive impaired subjects with patients showing no cognitive impairment [32]. To the best of our knowledge, no studies have examined the impact of cognitive impairment on the association between PROMs of UL function and the BBT and HGS measures.

Driven by the lack of conclusive findings, in the present study, we aim to investigate the influence of cognitive impairment, as assessed using the SMDT, on the distribution of, and correlations between objective UL measures, namely, the 9-HPT, BBT, and HGS measures, and a validated PROM assessing UL function in ADL, the Manual Ability Measure-36 (MAM-36).

Materials and methods

Study design

The present cross-sectional study was conducted between January 2016 and August 2019 in five Italian centers specialized in MS, the Department of Rehabilitation of CRRF "Mons. Luigi Novarese" in Moncrivello, "Department of Neurology, University of Catania", "Don Gnocchi Foundation" of Milano, "Rehabilitation Service of Liguria of the Italian Multiple Sclerosis Society (AISM)" of Genova, and "Sant'Andrea Hospital" of Rome.

Recruited subjects had a confirmed diagnosis of MS according to revised McDonald criteria [ref], age ≥ 18 years, right-hand dominance according to the Edinburgh Handedness Inventory, 5/6 aided or unaided vision, ability to understand study procedures, and provide informed consent. Subjects with orthopedic or other neurological diseases interfering with the use of UL and relapses or relapse-related treatments in the 3 months before the study entry were excluded. Subjects were administered an assessment protocol including demographic and clinical characteristics, EDSS, and the following measures: 9-HPT, BBT, HGS, SDMT, and MAM-36.

The study was carried out following the Declaration of Helsinki and approved by the local Ethics Committee of Genoa (P.R.196REG2015); and subjects gave their informed written consent before the beginning of the assessments.

Measures

Objective upper limb measures

The 9-HPT [33] assesses fine manual dexterity. It consists in taking nine small pegs from a container, one by one, and placing them into holes on a board, as quickly as possible, then removing each peg from the holes, and placing them back into the container. For the purpose of the present study, the time in seconds needed to complete each trial was recorded with a maximum time of 180 s. All subjects were evaluated on both arms: for each arm, the score consisted of the mean of the time of two trials in seconds.

The BBT [7] is a measure of gross manual dexterity. It consists of a box (53.7 × 9 × 25.4 cm) divided into two spaces by a panel (15.2-cm high), filled with 150 blocks. The task consists in moving as many blocks as possible from one compartment to the other, one at a time. Subjects are allowed 60 s to complete the task. For each arm, the score is represented by the number of displaced blocks in the given time.

Hand grip strength [8], quantifying the maximum isometric strength of each hand, was evaluated with a dynamometer and scored in kilograms, with the final score being the mean of three HGS trials.

For all measures, three scores were computed: best and worst performance scores and overall mean score.

Subjective upper limb measure

The MAM-36 consists of 36 items investigating subjects' perceived ability in performing common tasks (e.g., eating, dressing, buttoning clothes), excluding the use of adaptive equipment. Each item is rated on a 4-point scale ranging from 1 (cannot do it) to 4 (easy). Tasks that are almost never performed are scored 0. For the purpose of the present study, the MAM-36 was scored by summing item responses [ref]. The score showed excellent reliability based on Cronbach's alpha (α = 0.96).

Cognitive assessment

The SDMT evaluates both rapid information processing and visual scanning and, to a lesser extent, working memory [34]. It consists of a sheet of paper with, at the top, a sequence of nine symbols and nine corresponding numbers (1–9) (key) [35]. The rest of the paper presents a pseudo-randomized sequence of symbols. Participants must assign (by voicing) the number to the corresponding symbol, as fast as possible. The result is given by the total number of correct associations performed in 90 s.

Assessor training to standardize the administration procedures of the various scales was required for study personnel in the five study centers. Expert neurologists (one for each center) trained for the Neurostatus-EDSS performed the EDSS, while occupational or physical therapists performed the objective and subjective upper limb assessments. A cut-off value of 34 over the raw SDMT score to detect subjects with probable cognitive impairment (i.e., SDTM equal or below 2 standard deviation under the normative value as reported by Goretti and colleagues) [34].

Data analysis

As a preliminary analytical step, Shapiro–Wilk tests were performed to check all continuous study measures for compliance with normality. All measures significantly ($p < 0.05$) deviated from normality, except for worst arm BBT scores ($p = 0.542$) and overall mean ($p = 0.190$).

Then, we looked at differences in the mean values of both objective and subjective measures of upper limb functions across groups with different levels of cognitive impairment according to the SDMT measure. Because of the non-normality of many measures, we used non-parametric Mann–Whitney U tests to determine differences in the distribution of both objective and subjective UL measures according to patients' cognitive impairment (impaired = SDMT ≤ 34; not impaired = else [34]). As a supplementary analytical step, we also ran non-parametric Spearman rank correlations between the SDMT score and all UL measures, both a zero-order correlations, and controlling for age, disease duration, disability level according to EDSS, and disease course (PMS = 1, RRMS = 0).

Finally, we look at the association between subjective (i.e., MAM-36) and objective UL measures (i.e., 9-HPT BBT, HGS, scores for both arms and the overall mean); associations are examined both in the whole sample and in subgroups of patients with different cognitive impairment. Again, because of the non-normality of most of UL measures, associations were examined using the non-parametric Spearman correlation coefficient. Finally, differences in correlation size across the subgroups were tested using the Fisher Z transformation procedure. As supplementary analytical step, we ran non-parametric Spearman correlation again controlling for age, disease duration, disability level according to EDSS, and disease course (PMS = 1, RRMS = 0), and ran the Fisher Z transformation procedure on the obtained partial correlations.

Results

Recruited sample consisted of 246 PwMS, of which 158 females, with a mean age of 51.65 ± 13.45 years (range18–85), mean disease duration of 14.50 ± 10.80 years (range 0–53), and mean EDSS of 5.10 ± 1.88 (range 0–8.5);

121 had a relapsing remitting form, 51 primary progressive, and 74 secondary progressive.

Next, we look at differences in the distribution of UL measures in the groups characterized by different cognitive impairment. Table 1 reports descriptive statistics (mean, standard deviation) for subjective and objective UL measures in the whole sample, as well as by cognitive impairment (no impairment vs. impairment). Among the examined measures, the MAM-36 score and all 9-HPT and BBT measures showed significantly different distributions depending on the patients' level of cognitive impairment. More in detail, when compared with patients with cognitive impairment, patients with no cognitive impairment reported lower 9-HPT scores (in seconds) and higher BBT and MAM-36 scores. There were no difference across groups on HGS measures.

Next, we looked at correlations between SDMT and UL measures. Small-to-moderate negative correlations emerged between the SDMT and all the 9-HPT measures (9-HPT_{best}, $\rho = -0.351, p < 0.01$; 9-HPT_{worst}, $\rho = -0.283$, $p < 0.001$; 9-HPT_{mean}, $\rho = -0.312$, $p < 0.001$), while small-to-moderate positive correlations emerged between the SMDT and the BBT measures (BBT_{best} $\rho = 0.297$, $p = 0.02$, BBT_{worst} $\rho = 0.324$, $p < 0.001$, BBT_{mean} $\rho = 0.325$, $p < 0.001$). A small positive correlation emerged between the SDMT and the MAM-36 ($\rho = 0.218$, $p = 0.001$), while no significant correlation emerged with the HGS measures. Note that correlations between SDMT and UL measures were also examined controlling for age, disease duration, disability level according to EDSS, and disease course. Partial (Spearman) correlations between SDMT and UL measures showed the same pattern of associations of zero-order correlations but were slightly reduced in size (See supplementary material, Table S1).

Finally, we studied the association between subjective and objective upper limb measures. More in details, we looked at the correlation between the MAM-36 and the objective UL measures in the whole sample and in the two subsamples of patients showing mild-to-moderate cognitive impairment (SDMT ≤ 34) and those showing no cognitive impairment (SDMT > 34). In the whole sample, objective upper limb measures showed small-to-moderate correlations with the MAM-36 (Table 2), while in both subgroups mild-to-moderate cognitive impairment, the MAM-36 showed significant correlations were significant except for the correlation between the worst performance of HGS score among patients showing mild-to-moderate cognitive

Table 1 Mean differences in upper limb measures by cognitive function level

	Whole sample (*N* = 246)		SDMT ≤ 34 (*N* = 100)		SDMT > 34 (*N* = 146)		
	M	SD	M	SD	M	SD	p
MAM-36	123.04	20.54	118.21	22.92	126.36	18.08	0.003
9-HPT (best, s)	31.91	22.55	37.47	27.27	28.11	17.78	< 0.001
9-HPT (worst, s)	50.56	44.93	63.51	52.80	41.69	36.23	< 0.001
9-HPT (mean, s)	41.24	31.29	50.49	36.44	34.90	25.47	< 0.001
HGS (best, kg)	22.07	9.22	21.91	9.56	22.17	9.01	0.750
HGS (worst, kg)	16.09	9.27	15.31	9.47	16.63	9.13	0.247
HGS (mean, kg)	19.08	8.74	18.61	8.91	19.40	8.63	0.350
BBT (best, blocks)	48.12	14.59	42.23	12.50	52.15	14.58	< 0.001
BBT (worst, blocks)	40.82	15.60	34.00	14.57	45.49	14.57	< 0.001
BBT (mean, blocks)	44.47	14.59	38.12	12.84	48.82	14.15	< 0.001

Table 2 Correlations between subjective (MAM-36) and objective (HGS, 9-HPT, BBT) upper limb measures by cognitive function level

Objective UL measures	Whole sample (N = 246)	SDMT ≤ 34 (*N* = 100)	SDMT > 34 (*N* = 146)	*p*
9-HPT (best, s)	−0.436, *p* < 0.001	−0.290, *p* = 0.003	−0.485, *p* < 0.001	0.040
9-HPT (worst, s)	−0.449, *p* < 0.001	−0.294, *p* = 0.003	−0.508, *p* < 0.001	0.025
9-HPT (mean, s)	−0.463, *p* < 0.001	−0.312, *p* = 0.002	−0.519, *p* < 0.001	0.028
HGS (best, kg)	0.246, *p* < 0.001	0.181, *p* = 0.072	0.293, *p* < 0.001	0.183
HGS (worst, kg)	0.413, *p* < 0.001	0.382, *p* < 0.001	0.420, *p* < 0.001	0.365
HGS (mean, kg)	0.356, *p* < 0.001	0.317, *p* = 0.001	0.374, *p* < 0.001	0.311
BBT (best)	0.421, *p* < 0.001	0.433, *p* < 0.001	0.367, *p* < 0.001	0.275
BBT (worst)	0.492, *p* < 0.001	0.540, *p* < 0.001	0.420, *p* < 0.001	0.117
BBT (mean)	0.474, *p* < 0.001	0.521, *p* < 0.001	0.402, *p* < 0.001	0.124

impairment (SDMT ≤ 34). Overall, both the 9-HPT and HGS measures appeared to be slightly stronger in size when computed in the subgroup of patients with no cognitive impairment (SDMT > 34) than in the subgroup showing cognitive impairment (SDMT ≤ 34). In turn, the BBT measures showed an opposite pattern, with stronger correlations in the subgroup showing cognitive impairment (SDMT ≤ 34). Note, however, that only the 9-HPT show significant differences in the size of correlation with the MAM-36 across subgroups. Note that partial correlations controlling for potential confounding variables (see supplementary material, Table S2) revealed an identical pattern, although the effect size of correlations appeared to be generally lower.

Discussion

The present study aimed to evaluate the influence of cognition, assessed trough the SDMT, on UL measures and its effect on the correlation between subjective (MAM-36) and objective (9-HPT, BBT and HGS) measures of upper limb function in a large sample of PwMS, with or without cognitive impairments.

Beyond processing speed, SDMT scores are expected to reflect individual differences in attention and working memory, which in turn are the most involved cognitive skills in the completion of PROMs [15].

When comparing subjects showing no cognitive impairment with those reporting mild-to-moderate impairment, we found significant differences in the distribution of 9-HPT, BBT, and MAM-36 measures (but not of HGS), indicating that lower cognitive ability is associated with poorer UL function as assessed by these measures. Coherently, processing speed, assessed by the SDMT raw score, significantly correlated with all UL measures but HGS.

The results are in line with other studies [25, 28–31], reporting correlations between SDMT and 9-HPT ranging from – 0.24 for the dominant hand [29] to – 0.65 [30] for the right-left mean. However, to our knowledge, no previous study showed correlations between the SDMT, gross motor,movement or muscle strength in PwMS. In a previous study [36], a small-to-moderate correlation between MAM-36 and objective UL measures (i.e., 9-HPT, BBT, and HGS) has been reported. Extending these findings, in the present study, we found evidence that processing speed may influence the association between perceived manual ability (i.e., MAM-36 scores) and hand dexterity. In subjects showing no cognitive impairment, the correlation between MAM-36 and 9-HPT scores was stronger (ρ ranging from – 0.52 to – 0.48), while decrease in subjects with mild-to-moderate cognitive impairment (ρ ranging from – 0.31 to – 0.29). An opposite pattern was found for the BBT, with slightly stronger effect sizes in subject with mild-to-moderate cognitive impairment; in turn, HGS showed the least difference in correlations between the groups. Note however that differences between correlation were relatively small, and significance emerged only for the 9-HPT measures. The weak influence of cognition on the correlation between objective and subjective measure is consistent with the results reported by Gold et al. [32].

The present study is not without limitation. As a matter of fact, processing speed is the unique cognitive function evaluated in the study. Although SDMT is the gold standard to assess processing speed in PwMS [23], its score is also expected to reflect other cognitive domains, such as attention and working memory, involved in PROMs completion [15]. Despite that, the influence of other cognitive domains, such as episodic memory, executive function, verbal fluency, and visuospatial perception, on the correlation between objective and subjective UL measures, was not addressed in the present study, and needs further evaluation. Additionally, in our study, the SDMT score was not adjusted for age, sex, and education, potentially affecting emerging findings. Instead, the raw, unadjusted SDMT score was used in the analyses. This approach (i.e., use of the raw SDMT score) more closely aligns with the methodology used by previous authors exploring a similar dataset (i.e., Gold et al. [32]). Additionally, note that in an effort to establish the role of potential confounding variables, namely, age, EDSS, disease duration, and disease course, the linear association between study measures was explored by computing both zero-order correlations, and partial correlations controlling for confounding variables. Results of partial correlations revealed a similar pattern of associations, but were generally reduced in size.

To sum up, the present study reports novel evidences on the association between processing speed and both objective and subjective measures of UL function.

In conclusion, findings suggest that cognitive impairment is associated with subjects' performance on 9-HPT, BBT and MAM-36, resulting in poorer UL function, while the hand grip strength, assessed through the HGS, seems to be the only parameter not correlated to cognitive function.

Cognitive impairment was found to affect the congruence between subjective and some of the objective UL measures, albeit only minor differences in the correlation pattern across groups with different cognitive performances emerged.

Specifically, self-perception of UL function better complies with gross UL motor function in subjects with mild-to-moderate cognitive impairment, while fine manual dexterity show a stronger association in subjects showing no cognitive impairment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-023-07286-7.

Author contribution CS conceived the study and designed the study protocol. CS, DM, DC, RDG, EG, BG, MM, AT, RB, FP, AP, LP, LC, and RR recruited the subjects and carried out the experiments. DM analyzed the results. CS, DM, RDG, and EG wrote the manuscript. DC, LP, AT, FP, and AP revised the manuscript. All authors have read and approved the final version of the manuscript.

Funding The study was supported by a Grant 2014/20 from the Italian Multiple Sclerosis Foundation (FISM).

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Each ethical committee of each participating centre allowed the ethical approval for this study (P.R.196REG2015). Signed informed consent was obtained from each patient prior to enrolment in the study according to the Declaration of Helsinki.

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