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Distribution and relation of two arm function tests, Box and Blocks test and Nine Hole Peg test, across disease severity levels and types of Multiple Sclerosis

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Highlights

- Both fine and gross manual dexterity were altered in most persons with MS;
- Alterations in gross manual dexterity were predominant early in the disease course;
- Bilateral alterations in gross manual dexterity were more prevalent than in fine manual dexterity;
- Progressive types of MS presented more alterations in dexterity than did RR type.

Abstract

Background: Regular upper limb evaluation in persons with multiple sclerosis to detect early alterations and to monitor possible deterioration, both in gross and fine motor dexterity, is important for optimal levels of participation in life activities across the life span. The purpose of the present study was to inquire upon alterations in bilateral gross and fine manual dexterity, measured with the Box and Block test(BBT) and the

Nine Hole Peg test (NHPT), in persons with MS(PwMS) across a wide range of disability levels and across MS types.

Methods: This is a secondary cross-sectional analysis of BBT and NHPT administered to 215 PwMS at all disability levels and three MS phenotypes, relapsing-remitting, primary progressive and secondary progressive (RRMS, PPMS, SPMS). To inquire on the prevalence of alterations in upper limb gross and fine dexterity, PwMS test scores were compared to normative healthy subjects' values, Abnormal values were defined as scores equal or exceeding 2 standard deviations from the normative values for NHPT and the BBT. The data of both arms was analyzed by disability level and by the type of MS. For characterization and comparisons based on disability level, the sample was divided in four groups according to the EDSS score: 0-3.5 were categorized as Mild (EDSS-Mi), EDSS>3.5 to 5.5 were categorized as Moderate (EDSS-Mo), EDSS>5.5 to 6.5 were categorized as Severe (EDSS-Se), and disability levels of 7 and beyond were categorized as Severe-non-ambulant (EDSS-SeN). Finally, correlations between UL dexterity measures bilaterally were carried out.

Results: Mean(SD) age of the sample was 54.07(±12.81) years, with a mean(SD) disease duration of 18.91(±10.95) years and a median EDSS(IQR) of 6.5(5.5/7). Fifty-three% had RRMS, 19% PPMS and 28% SPMS. Almost the whole sample (96.2%) showed abnormal scores on the BBT; 91.5% had abnormal bilateral scores. Abnormal scores were present on the NHPT in 85.4% of the whole sample, with 68.9% having bilateral abnormal scores. With increase in disability levels the mean number of blocks moved was reduced and time taken to finish the NHPT was increased. The BBT and the NHPT in each arm were highly correlated over all disability levels, with correlation ranging from 0.74 to 0.86.

Overall, right and left arm had statistical differences in median scores on the NHPT peg/sec ($p=0.004$) but similar scores on the BBT ($p=0.57$).

Abnormal bilateral scores were recorded in 85% of PwRR, in 96% of PwSP and 100% of PwPP for the BBT and in about 56% of PwRR, increasing up to 80 and 85% in PwPP and PwSP. Progressive forms of MS presented statistically different values on the BBT ($p<0.001$) and the NHPT with respect to the RRMS type ($p<0.001$).

Conclusion: We found that both fine and gross manual dexterity were altered with respect to normative values in most persons with MS, but abnormalities in gross manual dexterity were more prevalent and pronounced earlier in the disease course. Similarly, with regard to MS types, bilateral alterations in gross manual dexterity were more prevalent than were fine manual dexterity in all three phenotypes considered.

Keywords

Upper limb; Arm function; Outcome measures; rehabilitation; multiple sclerosis.

1. Introduction

People with multiple sclerosis (PwMS) experience multidimensional functional limitations during their life and while their disability status is often tied to mobility function, MS impacts on most daily life actions(1).In this population, changes in hand dexterity, along with cognitive status and functional mobility, have been found to highly influence participation and community activities(2,3).

Recent kinematic analysis of the upper limb demonstrated that people with MS have to cope with alterations in arm functioning since the first stages of the disease(4,5). Moreover, with the progressing of the disease, upper limb (UL) alterations become increasingly prevalent, with PwMS often presenting bilateral worsening in arm function that impacts considerably on activities of daily living(6).

The importance of regular UL evaluation in PwMS to detect early alterations and to monitor possible deterioration, is paramount. To date, the gold standard measure recommended for UL function is the Nine Hole Peg Test (NHPT) which measures fine manual dexterity(7). It has been found to have high correlations with UL tests assessing ADL-like tasks and with patient reported outcome measures. Recently, however, some questions have been raised towards the use of NHPT as the only measure of arm function. Solaro et al, reporting on NHPT in PwMS, found ceiling and floor effects at mild and severe disability levels and recommended caution when using NHPT in studies involving these two sub-populations(8). Similarly, Lamers and Feys recommend to employ other functional tests to adequately capture overall differences in arm function in response to rehabilitation interventions(9).

In fact, due to the complexity of the interaction of the UL with the environment, and since MS causes impairments that could impact both on gross and fine manual dexterity, the NHPT may not alone be able to depict upper limb function(7).

The Box and Blocks test (BBT) is an easy to apply, standardized measure of UL function that captures gross manual dexterity and it has shown good responsiveness and low floor and ceiling effect when applied to PwMS(10–12). Validity and normative data for gender and age have already been reported in literature(13,14). Moreover, BBT showed moderate correlations with NHPT and other tests for the upper limb in MS population(11).

Already, in the last century, Goodkin et al, inquiring on the prevalence of upper limb disabilities in PwMS, suggested that both tests should be administered to significantly improve the ability of identifying changes in UL over time(15). However, to date, only few papers investigating arm disability in MS have included both measures(16,17).

While relevance of alterations at the BBT across disability levels and types of MS have been explored recently, there are aspects of the BBT that should be better investigated, such as, symmetry of progression between hands across all disability levels(11,18). Moreover, the relationship between fine and gross manual dexterity across disability levels, especially at higher levels, and across different MS types needs further investigation.

Thus, the aims of the present study are to inquire on prevalence of alterations on the BBT and the NHPT bilaterally in a wide sample of PwMS, at different disability levels and across different types of MS.

2. *Materials and Methods*

2.1 Study design

This is a retrospective analysis of secondary data on arm function in PwMS that was collected as part of a series of studies approved by the local Ethical Committee at [Masked] from April 2014 to September 2019.

Two hundred and fifteen persons with clinically definite MS according to the McDonald criteria(19) that had test results from both the NHPT and the BBT were included. Inclusion criteria were an age higher than 17 years, not having had an MS relapse within the preceding two months and not having orthopedic or other neurological conditions that might interfere with arm ability. Written informed consent was obtained from all study participants. All data were collected in agreement with the Declaration of Helsinki.

2.2 Assessment

Demographic variables were collected from participants' medical recordings at the time of the evaluation; a senior physical therapist carried out the testing in a single assessment at the time of the medical check-ups or at the beginning of the rehabilitation program. Hand dominance was recorded.

Gross and fine manual dexterity were assessed with:

Box & Block Test - The test has been validated for PwMS and clinically important worsening over time has been suggested as 3.5 cubes (participant-perception), 5.2 cubes (clinician-perception)(12) or 15%(15).

Nine Hole Peg Test - Is considered the gold standard for manual dexterity in persons with MS(7). Data are recorded as the mean of two consecutive trial for each hand with a maximum time of 300 seconds. Clinically important worsening over time has been suggested as 20%(15).

2.3 Statistical analysis

Normal distribution for clinical variables was verified with the Shapiro-Wilk test; consequently, mean and standard deviation(SD) or median and first and third interquartile were calculated.

For prevalence of alterations in upper limb dexterity, PwMS test scores were compared to normative healthy subjects' values, already available in literature. Abnormal values were defined as scores ≥2SD from the normative values for NHPT(20) and the BBT(13).

The NHPT results are presented in tables and text as time to complete the test (seconds) for comparison with age and sex matched normative data. For data analysis, frequency (peg/s) was used(2,8).

Data were analyzed bilaterally by disability level and by type of MS. The sample was divided in four groups according to the EDSS score: from 0 to 3.5 as Mild (EDSS-Mi); from 4 to 5.5 as Moderate (EDSS-Mo);

from 6 to 6.5 as Severe (EDSS-Se); above 6.5 as Severe-non-ambulant (EDSS-SeN). For comparisons across MS type the group was divided based on their disease course: Relapsing-remitting(PwRR), primary progressive(PwPP) and secondary progressive(PwSP) MS.

Between-group differences for clinical and demographical variables were examined using the Kruskall-Wallis test and the Dunn's post hoc test, while intra-group differences between sides were explored with the Wilcoxon test for paired data. Finally, correlations between UL dexterity measures were explored using Spearman or Pearson correlations test.

Statistical analysis was conducted with R-software (open-source free software http://www.r-project.org).

3. Results

3.1 Overall

Results were collected from 215 PwMS, of these, three subjects were excluded due to incomplete data resulting in a final sample size of 212 PwMS(Table 1). Mean(SD) age was 54.07(±12.81) years, 64% were female, with a mean(SD) disease duration of 18.91(±10.95) years and a median EDSS(IQR) of 6.5(5.5-7).

Six percent of the group was left-handed. Seven subjects were not able to complete the NHPT with either hand, while 7 and 12 subjects did not complete the test respectively with the right and the left hand. All subjects were able to move at least one cube on the BBT unilaterally: 4 subjects were not able to move a cube with the right arm and 5 with the left arm.

Almost the whole sample (96.2%) showed abnormal scores on the BBT; 91.5% had abnormal bilateral scores. Mean(SD) number of cubes moved by right and left arm were 36.98(±16.13) and 36.58(±15.53) respectively, about 20 less cubes with respect to normative values.

Abnormal scores were present on the NHPT in 85.4% of the sample with 68.9% having bilateral abnormal scores. Median(IQR) scores for right and left hand were 33,02(25.37-52.20) seconds and 34,06(26.62-58.33) seconds respectively and were about 10 seconds higher than normative values.

Overall, right and left arm had statistical differences in median scores on the NHPT peg/sec (p=0.004) but similar scores on the BBT (p=0.57).

Correlations between the BBT and the NHPT of the same arm where high and similar for right (r=0.887) and left side (r=0.866). High correlations were also found between arms for the BBT (r=0.787) and the NHPT (r=0.711).

Table1. Demographical and clinical characteristics of the sample

		EDSS Category				
Characteristic	**Overall, N = 212[1]**	**Mild, N = 28[1] (13.2%)**	**Moderate, N = 31[1] (14.6%)**	**Severe, N = 85[1] (40.1%)**	**Severe Non Ambulant, N = 68[1] (32.1%)**	**p-value[2]**
Age, years	54.07 (12.81)	41.43 (11.01)[a]	53.65 (11.85)[b]	56.21 (11.47)[b]	56.79 (12.64)[b]	<0.001
Gender						0.99
Female	135 (64%)	18 (64%)	19 (61%)	55 (65%)	43 (63%)	
Male	77 (36%)	10 (36%)	12 (39%)	30 (35%)	25 (37%)	
Disease Duration, years	18.91 (10.95)	9.46 (8.75)[a]	18.19 (9.99)[b]	18.91 (9.46)[b]	23.13 (11.59)[b]	<0.001
EDSS	6.50 (5.50 – 7.00)	2.00 (1.50 – 2.50)[a]	5.00 (4.25 – 5.50)[b]	6.50 (6.00 – 6.50)[c]	7.50 (7.00 – 8.00)[d]	<0.001
Type						<0.001
RR	112 (53%)	28 (100%)	25 (81%)	50 (59%)	9 (13%)	
PP	40 (19%)	0 (0%)	4 (13%)	18 (21%)	18 (26%)	
SP	60 (28%)	0 (0%)	2 (6.5%)	17 (20%)	41 (60%)	
BBT, n of cubes						
Right	36.98 (16.13)	58.04 (12.54) [a]	42.55 (11.66) [b]	37.58 (11.80) [b]	25.03 (13.25)	<0.001
Left	36.58 (15.53)	58.25 (10.15) [a]	40.58 (11.16) [b]	36.31 (11.21) [b]	26.18 (13.83)	<0.001
NHPT, seconds						
Right	33.02 (25.37 – 52.20)	19.58 (17.78 – 24.80) [a]	28.75 (24.95 – 38.96) [b]	31.62 (25.78 – 42.80) [b]	52.73 (33.36 – 113.75) [c]	<0.001
Left	34.06 (26.62 – 58.33)	20.88 (18.50 – 25.57) [a]	30.00 (26.35 – 35.95) [b]	33.19 (27.50 – 49.00) [b]	63.50 (34.53 – 152.92) [c]	<0.001
NHPT, peg/sec						
Right	0.27 (0.17 – 0.35)	0.46 (0.36 – 0.51) [a]	0.31 (0.23 – 0.36) [b]	0.28 (0.21 – 0.35) [b]	0.17 (0.08 – 0.27) [c]	<0.001
Left	0.26 (0.15 – 0.34)	0.43 (0.35 – 0.49) [a]	0.30 (0.25 – 0.34) [b]	0.27 (0.18 – 0.33) [b]	0.14 (0.06 – 0.26) [c]	<0.001

[1]Mean (SD) or Median (IQR) or Frequency (%); [2]One-way ANOVA; Pearson's Chi-squared test; Kruskal-Wallis rank sum test.; EDSS = Expanded Disability Status Scale; RR = relapsing remitting; PP = primary progressive; SP = secondary progressive; BBT = Box and blocks test; NHPT = Nine Hole Peg Test; [a,b,c,d] = differences between groups at post-hoc test.

3.2 Arm function across EDSS levels

3.2.1 Demographical and clinical Differences

PwMS at the mild (EDSS-Mi) and moderate (EDSS-Mo) EDSS levels were respectively 13.2% and 14.6% of the sample, while 40% were severe (EDSS-Se) and 32.2% were severe non-ambulant (EDSS-SeN). Across all disability levels females were from 61-65% of the sample(Table 1).

Regarding demographic and clinical characteristics, PwMS at the EDSS-Mi level were statistically younger ($p<0.001$) and had a shorter disease duration ($p<0.007$) than PwMS at all three more severe disability levels. No differences were found in demographic characteristics between the other disability levels.

3.2.2 Box and Blocks Test

Seventy-five% of EDSS-Mi, 98.8% of EDSS-Se and100% of EDSS-Mo and EDSS-SeN showed abnormal values compared to age-matched healthy subjects(HS).

Percentages of abnormal bilateral scores was about 53% in EDSS-Mi, rising to about 95% in PwMS at the EDSS-Mo and EDSS-Se and 100% in EDSS-SeN(Figure 1A).

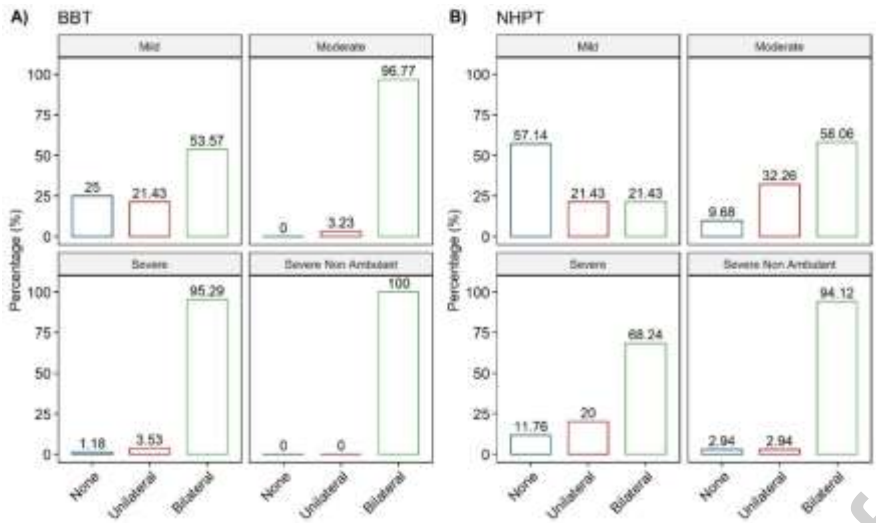
With increase in disability levels the mean number of blocks moved was increasingly lower with respect to aged-matched HS. Regarding between hands symmetry, EDSS-Mi had similar mean (±SD) scores for right and left arm: 58.04(±12.54) and 58.25(±10.15) cubes, a reduction of about 8 and 4 cubes with respect to normative values(Figure 2A). EDSS-Mo moved 42.55(±11.66) and 40.58(±11.16) cubes with right and left arm respectively, a reduction of 16 cubes compared to HS. Similarly, EDSS-Se moved on average 37.58(±11.80) and 36.31(±11.21) blocks with right and left arm, respectively, about 18 cubes less than HS. EDSS-SeN moved 25.03(±13.25) cubes with the right arm and 26.18(±13.83) cubes with the left arm; for both arms cubes moved were 30 cubes fewer than HS.

3.2.3 Nine Hole Peg Test

Fine manual dexterity, when compared with HS's values, was altered in 43% of EDSS-Mi. In EDSS-Mo and EDSS-Se alterations increased considerably to around 90%, reaching 97% in the EDSS-SeN. Bilateral involvement increased from 21.5% of EDSS-Mi to 58.4% and 68% of EDSS-Mo and EDSS-Se, reaching 95% in EDSS-SeN(Figure 1B).

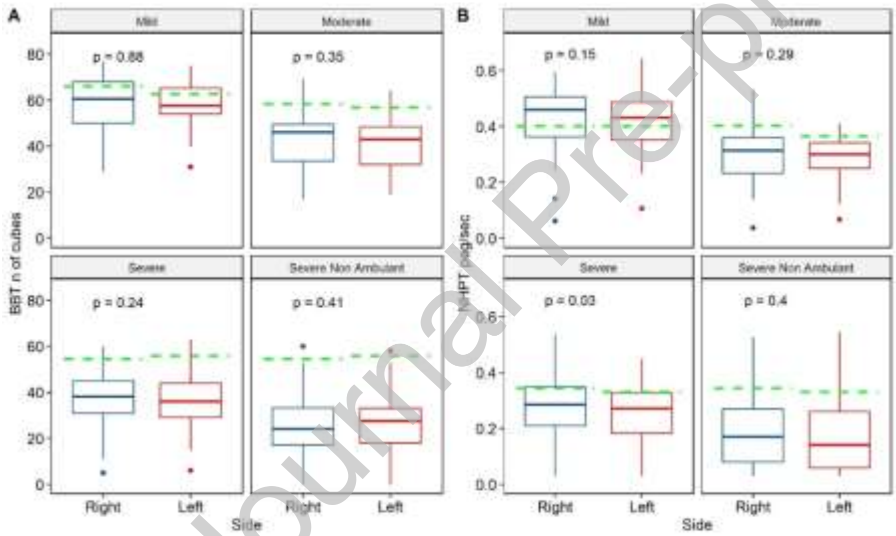
Compared to HS, NHPT median(IQR) scores were within normal ranges in the EDSS-Mi, with a median score of 19.58(17.78-28.40) and 20.88(18.50-25.57) seconds for right and left hand(Figure 2B). EDSS-Mo recorded 28.75(24.95-38.96) and 30.00(26.35-35.95) seconds for right and left hand, while EDSS-Se scored 31.62(25.78-42.80) and 33.19(27.50-49.00) seconds. Both, EDSS-Mo and EDSS-Se, had about 6 seconds higher medians values with respect to HS. In the EDSS-SeN, scores for right and left hand increased to 52.73(33.36-113.75) and 63.50(34.53-152.92), respectively 26.5 and 36 seconds higher than HS.

Figure 1. Percentage laterality abnormality relative to normative values by EDSS category



A) BBT = Box and Blocks test; B) NHPT = Nine Hole Peg Test.

Figure 2. BBT and NHPT mean and median scores by EDSS Category



A: BBT = Box and Blocks test; B: NHPT = Nine Hole Peg Test. The green dashed line represents the lower limit for normative values; ●= outliers; p: differences between arms.

3.2.4 Correlations between measures and side

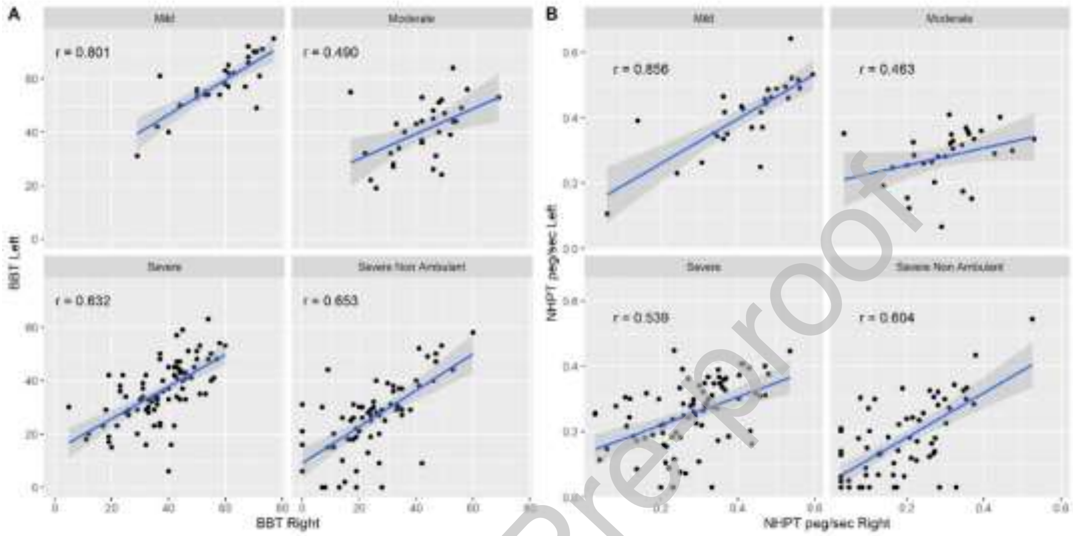
There were statistical differences between BBT and NHPT values ($p<0.001$) at almost all disability levels with only EDSS-Mo and EDSS-Se showing similar results on both ($p>0.2$).

Differences between arms were found only for the NHPT in EDSS-Se(right: 0.28(0.21-0.35); left: 0.27(0.18-0.33) peg/sec); a further in-between group analysis highlighted that only in PwMS with an EDSS of 6 this difference ($p=0.03$) was statistically significant.

The correlation between arms was high for both tests in the EDSS-Mi (BBT: r=0.80; NHPT: r=0.86) while it was lower in PwMS at EDSS-Mo (BBT: r=0.49; NHPT: r=0.46), EDSS-Se (BBT: r=0.63; NHPT: r=0.54) and EDSS-SeN (BBT: r=0.65; NHPT: r=0.60) (Figure 3).

The BBT and the NHPT (pegs/sec) in each arm were highly correlated at all disability levels, with correlations ranging from 0.74 to 0.86(Table 2).

Figure 3. Correlations between arms of NHPT and BBT by EDSS category



A: BBT = Box and Blocks test; B: NHPT = Nine Hole Peg Test.

Table 2. Correlations between BBT and NHPT for each upper limb by EDSS category

EDSS Category	Right UL	Left UL
Mild	0.844	0.784
Moderate	0.755	0.742
Severe	0.787	0.776
Severe Non Ambulant	0.836	0.824

EDSS= Expanded Disability Status Scale; UL= upper limb

3.3 Arm function across MS Types

3.3.1 Demographical and clinical differences

Persons with RRMS (PwRR) were the biggest group, 52,8% of the sample (112 persons), while 47.2% had progressive type of MS. Forty persons had PPMS (PwPP, 18.9%) while 60 persons had SPMS (PwSP, 28.3%). Female ratio ranged from 55% in the PwSP group to 68% in the PwRR group.

PwSP were statistically older than PwRR (p<0.001) and had a longer disease duration (p<0.001). Between all MS types there was a statistically significant difference in disability level as measured by EDSS (p<0.001) with PwRR having a median(IQR) EDSS of 6.00(3.88-6.50), PwPP having an EDSS of 6.5(6.5-7) and PwSP an EDSS of 7(6.5-8)(Table 3).

Table 3. Demographical and clinical characteristics by MS Type

	MS Type			
Characteristic	**RR, N = 112[1] (52.8%)**	**PP, N = 40[1] (18.9%)**	**SP, N = 60[1] (28.3%)**	**p-value[2]**
Age, years	50.88 (12.58)[a]	55.77 (13.61)[b]	58.90 (11.01)[b]	<0.001
Gender				0.3
Female	76 (68%)	22 (55%)	37 (62%)	
Male	36 (32%)	18 (45%)	23 (38%)	
Disease Duration, years	16.81 (10.30)[a]	14.80 (11.11)[a]	25.57 (9.11)[b]	<0.001
EDSS	6.00 (3.88 - 6.50)[a]	6.50 (6.50 -7.00)[b]	7.00 (6.50 - 8.00)[c]	<0.001
BBT, n of cubes				
Right	43.83 (15.02)[a]	32.05 (13.45)[b]	27.48 (13.77)[b]	<0.001
Left	42.36 (14.31)[a]	31.45 (14.63)[b]	29.22 (14.13)[b]	<0.001
NHPT, seconds				
Right	27.79 (21.55 - 38.89)[a]	42.26 (29.29 - 75.00)[b]	41.21 (32.64 - 93.75)[b]	<0.001
Left	29.97 (24.32 - 41.28)[a]	37.28 (29.38 - 77.96)[b]	51.11 (31.27 - 90.38)[b]	<0.001
NHPT, peg/sec				
Right	0.32 (0.23 - 0.42)[a]	0.21 (0.12 - 0.31)[b]	0.22 (0.10 - 0.28)[b]	<0.001
Left	0.30 (0.22 - 0.37)[a]	0.24 (0.12 - 0.31)[b]	0.18 (0.10 - 0.29)[b]	<0.001

[1] Mean (SD) or Median (IQR) or Frequency (%); [2] One-way ANOVA; Pearson's Chi-squared test; Kruskal-Wallis rank sum test. EDSS = Expanded Disability Status Scale; RR = relapsing remitting; PP = primary progressive; SP = secondary progressive; BBT = Box and blocks Test; NHPT = Nine Hole Peg Test; [a,b,c] = differences between groups at post-hoc test.

3.3.2 Box and Blocks Test

All MS types had overwhelmingly abnormal values on the BBT with respect to HS. Respectively, 94% of PwRR, 100% of PwPP and 98,8% of PwSP showed abnormal values (≥2 SD). Abnormal bilateral scores were recorded in 85% of PwRR, in 96% of PwSP and 100% of PwPP(Figure 4A).

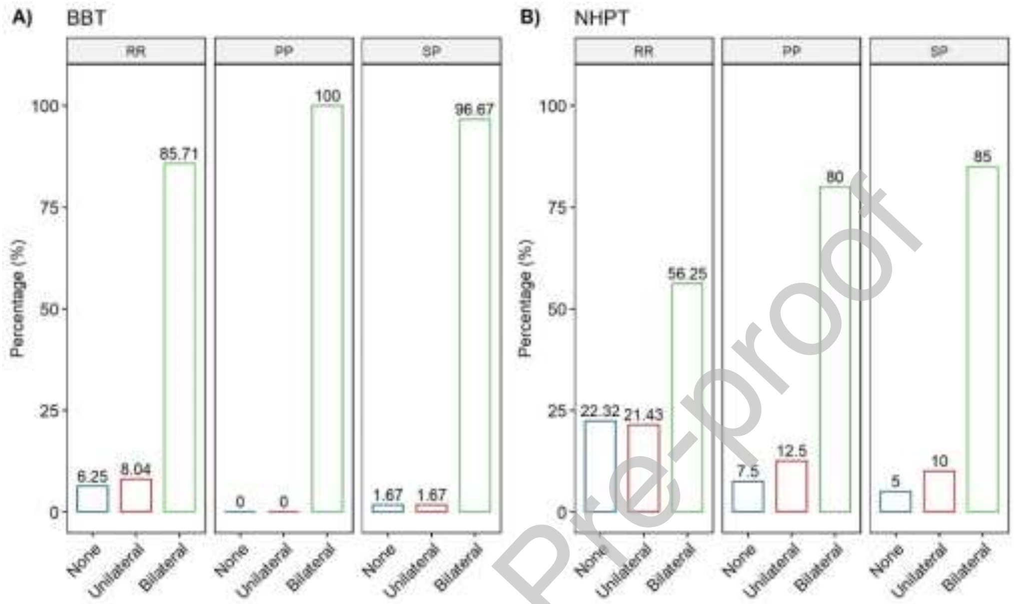
Regarding between hands symmetry, mean(SD) BBT values were similar (P>0.05) for right and left arm in all MS phenotypes: 43.83(15.02) peg/sec and 42.36(14.31) cubes moved by PwRR; 32.05(13.45) and 31.45 (14.63) cubes moved by PwPP; 27.48(13.77) and 29.22(14.13) in PwSP. These values were reduced, with respect to HS, for right and left arms, of 15 and 14 cubes in PwRR, 23 and 24 cubes in PwPP and of 27 cubes for both arms in PwSP(Figure 5A).

3.3.3 Nine Hole Peg Test

Fine manual dexterity was altered relative to HS in about 78% of PwRR, in 92,5% PwPP and 95% PwSP. Bilateral involvement was present in about 56% of PwRR, increasing up to 80 and 85% in PwPP and PwSP(figure 4B).

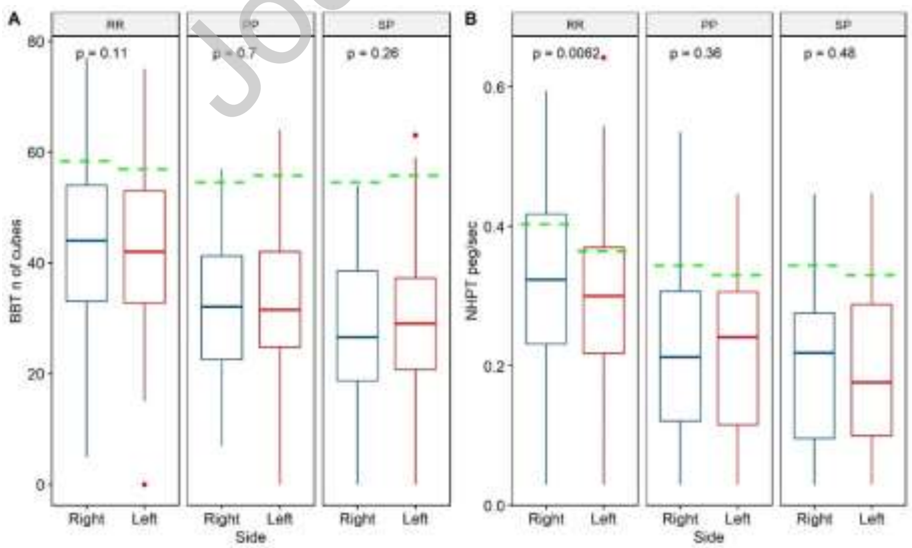
PwRR, recorded a median(IQR) NHPT of 27.79(21.55-38.89) seconds for the right hand and of 29.97(24.32-41.28) for the left hand; values 5 seconds higher compared to HS. PwPP recorded median(IQR) time of 42.26(29.29-75.00) and 37.28(29.38-77.96) for right and left hand, respectively 16 and 10 seconds higher than HS. PwSP had median(IQR) time for right and left hand of 41.21(32.64-93.75) and of 51.11(31.27-90.38) seconds, 15 and 23 seconds higher than HS's values(Figure 5B).

Figure 4. Percentage of abnormality presentation by Type of MS



A) BBT = Box and Blocks test; B) NHPT = Nine Hole Peg Test.

Figure 5. BBT and NHPT mean and median scores by Type of MS



RR = Relapsing Remitting; PP = Primary Progressive; SP= Secondary Progressive. The green dashed line represents the lower limit for normative values; ●= outliers; p: differences between arms. A: BBT = Box and Blocks test; B: NHPT = Nine Hole Peg Test.

3.3.4 Correlations between measures and side

Regarding differences between measures in the different MS phenotypes, progressive forms presented statistically different values on the BBT (p<0.001) and the NHPT with respect to the RRMS type (p<0.001), while differences between arms were present only in the RRMS type on the NHPT (right: 0.32(0.23-0.42) and left: 0.30(0.22-0.37) peg/sec)(p= 0.006).

The BBT and the NHPT(peg/sec) were highly correlated bilaterally in all three MS types, with r values ranging from 0.81 to 0.87(Table 4).

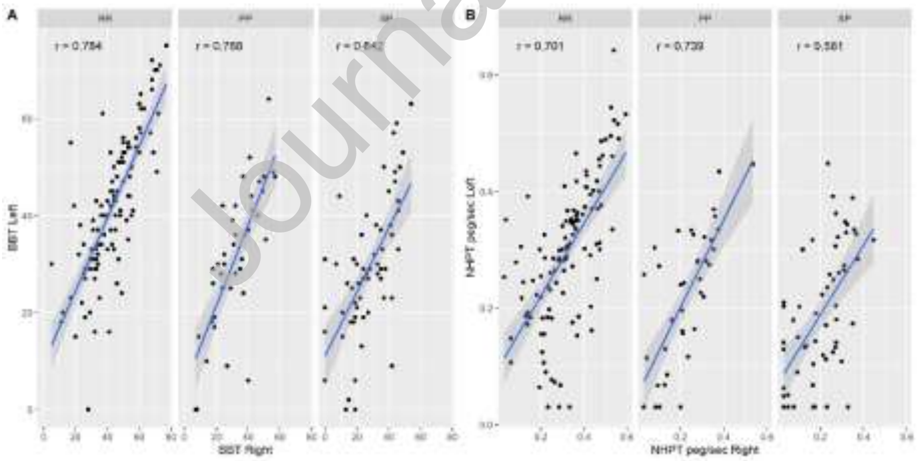
The correlation between right and left arm was high for both BBT and NHPT in PwRR and PwPP(r= 0.70-0.78) while they were more moderate in PwSP(r= 0.64 BBT and r=0.58 NHPT)(Figure 6).

Table 4. Correlations between BBT and NHPT for each upper limb by MS Type

MS Type	Right UL	Left UL
RR	0.865	0.859
PP	0.857	0.813
SP	0.837	0.867

RR = Relapsing Remitting; PP = Primary Progressive; SP= Secondary Progressive; UL = Upper Limb.

Figure 6. Correlations between arms of NHPT and BBT by MS Type



RR = Relapsing Remitting; PP = Primary Progressive; SP= Secondary Progressive;
A: BBT = Box and Blocks test; B: NHPT = Nine Hole Peg Test.

4. Discussion

The purpose of the present study was to inquire upon alterations in fine and gross manual dexterity, measured with the Nine Hole Peg test and Box and Block test, in persons with MS across a wide range of disability levels and MS types. We found that both fine and gross manual dexterity were altered with respect to normative values in most persons with MS, but abnormalities in gross manual dexterity were more prevalent earlier in the disease course. Similarly, with regard to MS types, bilateral alterations in gross manual dexterity were more prevalent than in fine manual dexterity.

Our sample represented all disability levels, including PwMS with no or mild and severe hand dysfunction, as defined by the cut-off value of 33.3 seconds on the NHPT, suggested by Lamers(21). Similarly, MS types (RRMS, SPMS, PPMS) were well represented in the sample, with half of the participants having RRMS.

Floor and ceiling effects were negligible for the BBT and moderate for the NHPT: all participants were able to move at least a block with one arm even if they were not able to place and remove all the pegs in 300 seconds. Moreover, all PwMS presenting normal bilateral scores for fine manual dexterity showed an alteration of gross arm dexterity.

4.1 EDSS Category

Regarding gross manual dexterity, more than half of the mild group and almost all the participants in the other groups demonstrated bilateral alterations. Already in the mild stage our participants tended to move less cubes than healthy age-matched persons and this gap from normative values increased in the successive disability stages.

Fine manual dexterity, on the other hand, presented minor alterations in the mild group, with only about 20% of the participants demonstrating bilateral alterations. Through disability levels, bilateral involvement increased to around 60% in the moderate and severe groups, reaching almost all non-ambulant persons.

The progressive worsening across severity groups was far beyond the established MDC of 20%(15) for both BBT and NHPT, in accordance with findings of Solaro(11); moreover, in the present work, EDSS levels were divided in four groups, rather than three, and we found that dexterity in the Moderate and Severe group appeared to be similar.

Regarding the different sensitivity of the two tests in the milder disability groups, the study by Silva et al(22) observed that the execution of the BBT implicates a higher activation of proximal muscles, while the NHPT requires a prevalent activation of hand and forearm’s muscles. Thus, BBT might be more sensitive to alterations of proximal muscles activity (suggested as a possible biomarker for upper limb impairments in MS)(23) while, NHPT may be more related to alteration in muscle activity of the forearm and to somatosensory impairments(5,24,25).

Alterations in bilateral gross manual dexterity were symmetric across all disability levels with the difference between hands never exceeding 2 cubes. Neither did we observe relevant alterations in symmetry of fine motor dexterity between hands across levels of disability, with the exception, however, of the severe level. These findings are in line with studies from Solaro et al that documented an asymmetry between hands on the NHPT in persons with EDSS levels six and above(18). This asymmetry in fine motor dexterity observed in the severe group might be connected to the use of walking aids that characterize this group. Upon closer inspection of our data, we found however, that only PwMS using a unilateral assistance presented this asymmetry between the two hands. This is interesting, and might suggest that upon beginning to use a unilateral aid there is a temporary worsening in fine manual dexterity in one of the hands that then levels out at higher disability levels. From our data we don't have information on which hand was using the walking aid and so we cannot speculate on cause and effect here, but we recommend investigation of this aspect in future studies.

We found a high correlation between tests that was in line with previous findings(11) proving that BBT and NHPT measures similar but not equal capacities. Test symmetries, measured as correlations of tests between sides, also confirmed the presence of slight differences between arms. Gross manual dexterity was more similar between sides than was fine manual dexterity which may be more influenced by handedness at performance and functional connectivity level(26).

4.2 MS Type

In the present study almost half of the sample had progressive MS, with two fifths of them being of the PP phenotype and three fifths of the SP phenotype. This study thus provides important information on dexterity for this group of people that are often neglected in research on MS.

All three different phenotypes RR, PP and SP had alterations in both fine and gross motor dexterity, with the progressive types of MS being worse overall. This is in accordance with findings of others(11), even if, it has to be considered that there were more PwRR in the lower disability groups and more PwPP and PwSP in the higher disability groups. The progressive MS groups were also older than the RRMS, while disease duration was considerably lower in the RRMS and PPMS groups(27). Considering that disease duration is much higher in PwSP relative to PwPP, this indicates that important manual dexterity alterations arrive much earlier in PwPP. Moreover, it is evident that there are somewhat different influences on dexterity depending on phenotypes that should be further explored in order to tailor prevention and intervention in all MS types.

Regarding fine manual dexterity, bilateral alterations were present in approximately 55% in the PwRR rising to around 80% of bilateral alterations in the progressive types of MS. However, gross manual dexterity was more often altered in RRMS than was fine manual dexterity, with eighty-five% of PwRR demonstrating alterations in gross manual dexterity bilaterally, and all persons with progressive types of MS had bilateral alterations. This is in contrast with findings of Huertas-Hoyas that found no phenotype differences in either fine or gross motor dexterity(28). This could be due to their smaller sample with lower disability levels. Again, the indication is that gross motor dexterity alterations are even more prevalent earlier in the disease course across all MS types than are fine motor dexterity alterations.

Correlation between fine and gross motor dexterity was high both within and between hands, in line with findings of Huertas-Hoyas(28).

It is evident that dexterity is worse overall in persons with the progressive type of MS and that dexterity problems are probably present in PwPP from even earlier on than in RRMS(29). This indicates a fundamental importance of protecting upper limb function in PwPP in particular, in order to delay further disease progression and maintain independence in activities of daily living. Persons with both progressive phenotypes are also the persons with higher EDSS and, on average, they were either using bilateral support for walking or using wheelchairs for moving. It may be necessary to shift the focus to functions that are critical for maintaining independence in ADL, especially at those advanced stages. Future trials should look at upper limb function as a primary outcome for trials including persons with more advanced and progressive MS.

4.3 General discussion

More attention to maintenance of arm and hand function throughout the lifespan of having MS is vital, since there is some evidence that early cortical reorganization in response to upper limb dysfunction may lead to maladaptation that affects present and future motor function(26,30,31). Early detection of dexterity impairments is important since it is possible that low interference interventions, started early in the disease progression, may provide a longer maintenance of upper limb function(26). Building up of neural reserve capacity in order to preserve anatomical functional connectivity might be an important strategy in better preservation of arm function(32). In this perspective periodical testing of both fine and gross manual dexterity is essential to capture early changes(33).

In this cross-sectional study, the prevalence of fine and gross manual dexterity was evaluated bilaterally across a wide spectrum of disability and across MS phenotypes with results that emphasize the present and increasing problem of hand function from early to late in the course of the disability. The ongoing under-recognizing of changes in hand function relative to walking impairments is preoccupying(33) given its importance in participation and level of independence(2,3,34). Both BBT and NHPT are tests that are objective and fast and can be recommended along with patient reported outcomes. Our results suggest also the possibility to use BBT to detect alterations in UL functions not detected by NHPT in PwMS with mild disability, but these findings should be confirmed in a wider sample of this category.

4.4 Strength and limitations

The strength of this cross-sectional analysis is the sample size and good representation of MS disability levels and types. There are limitations, we do not have information on the persons' perceived arm function, or how their arm function relates to quality of life. Further, we do not have measures of muscle activity and how it relates to the two tests. This should be investigated in future studies. Also, the responsiveness of the two tests to disease deterioration and response to rehabilitation should be investigated across all disability levels and types.

5. Conclusions

Both fine and gross manual dexterity were altered with respect to normative values in most persons with MS, but abnormalities in gross manual dexterity were more prevalent and pronounced earlier in the disease course. Similarly, with regard to MS types, bilateral alterations in gross manual dexterity were more prevalent than were fine manual dexterity in all three phenotypes considered. Our results suggest the use of the BBT to detect alterations in UL functions not detected by NHPT in PwMS earlier in the disease course.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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