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Sensorimotor Function in Progressive Multiple Sclerosis

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Abstract

Background: A sensitive test reflecting subtle sensorimotor changes throughout disease progression independent of mobility impairment is currently lacking in progressive multiple sclerosis.

Objectives: We examined non-ambulatory measures of upper and lower extremity sensorimotor function that may reveal differences between relapsing–remitting and progressive forms of multiple sclerosis.

Methods: Cutaneous sensitivity, proprioception, central motor function and mobility were assessed in 32 relapsing–remitting and 31 progressive multiple sclerosis patients and 30 non-multiple sclerosis controls.

Results: Cutaneous sensation differed between relapsing–remitting and progressive multiple sclerosis at the foot and to a lesser extent the hand. Proprioception function in the upper but not the lower extremity differed between relapsing–remitting and progressive multiple sclerosis, but was different for both upper and lower extremities between multiple sclerosis patients and non-multiple sclerosis controls. Foot-tap but not hand-tap speed was slower in progressive compared to relapsing–remitting multiple sclerosis, suggestive of greater central motor function impairment in the lower extremity in progressive multiple sclerosis. In addition, the non-ambulatory sensorimotor measures were more sensitive in detecting differences between relapsing–remitting and progressive multiple sclerosis than mobility assessed with the 25-foot walk test.

Conclusion: This study provides novel information about changes in sensorimotor function in progressive compared with relapsing–remitting forms of multiple sclerosis, and in particular the importance of assessing both upper and lower extremity function. Importantly, our findings showed loss of proprioceptive function in multiple sclerosis but also in progressive compared to relapsing–remitting multiple sclerosis.

Keywords: Relapsing–remitting multiple sclerosis, progressive multiple sclerosis, cutaneous sensation, proprioception, tapping performance

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Introduction

Progressive multiple sclerosis (PMS) is a subtype of multiple sclerosis (MS) characterized by a steadily worsening disease course, generally leading to profound disability. While only a small proportion of individuals are diagnosed with primary progressive multiple sclerosis (PPMS) at disease onset, it is estimated that as many as 90% of those with relapsing–remitting multiple sclerosis (RRMS) will ultimately transition to a secondary progressive form of multiple sclerosis (SPMS).[1] Despite the high prevalence of transitions from relapsing to PMS, existing treatments are ineffective in forestalling the decline in body functions associated with PMS.[2] Mobility is a key construct included in many scales used to assess function and disease progression in MS, including the most widely used instrument, the Expanded Disability Status Scale (EDSS),[3–5] as well as the 25-foot walk (25FWT)[6] and timed up-and-go test (TUG).[4] While early changes in EDSS and 25FWT are predictive of long-term disability,[5] a sensitive test reflecting subtle sensorimotor changes throughout disease progression and independent of mobility impairment is lacking, thus hampering

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early and appropriate treatment during the transition to PMS.

There is a high prevalence of somatosensory impairments in people with multiple sclerosis (PwMS)[7–11] and strong associations between impaired somatosensation and balance.[7,8] Plantar cutaneous sensation appears to worsen with disease duration and in PMS, independent of age-related changes.[10,12] Despite the recognition that proprioception is commonly affected in balance-impaired PwMS,[13] relatively little is known about the role of proprioception in disease progression. Fling and colleagues[13] found poorer balance control on high-demand proprioceptive tasks, as well as reduced white matter integrity of the cortical proprioceptive tracts in PwMS, especially those related to lower extremity proprioceptive pathways to Brodmann area 3a. Jamali and colleagues[14] assessed a variety of sensorimotor function tests in RRMS, and found that proprioceptive impairments were more prominent in MS than cutaneous deficits. However, from this study it is not known how proprioceptive function in PMS relates to RRMS, although it has been suggested that proprioception may be worse in PMS compared to RRMS.[10]

Alterations in motor function, including muscle weakness and spasticity, are commonly reported by PwMS.[12,15–19] Importantly, changes in motor function that reflect altered central motor function or power asymmetry correlate with balance or mobility impairment more so than strength.[15,16,20] Dorsiflexor muscle weakness is associated with poor foot-tap performance in PwMS, and foot-tap speed is lower in PwMS compared to non-MS controls.[15,20,21] A recent study[22] found reduced foot and finger-tapping performance in PMS compared to RRMS, but observed no differences in foot or finger tapping between people with RRMS and non-MS controls.

The goal of this study was to examine non-ambulatory outcome measures of sensorimotor function that may be sensitive in finding differences between RRMS and progressive forms of MS. We addressed the following research questions: (a) which lower- and upper-extremity measures of sensorimotor function (cutaneous sensitivity; proprioception; central motor function) differ between PMS and RRMS cohorts and between the MS cohorts and non-MS controls? and (b) how well do the individual sensorimotor variables classify participants into the RRMS and PMS subgroups? We hypothesized that: (a) cutaneous sensitivity will decrease from controls to RRMS to PMS;[10,12] (b) central motor function (reduced foot-tapping ability) in MS groups overall will be impaired compared to controls;[15,20,21] and (c) foot and hand-tapping performance will be lower in PMS compared to RRMS.[22]

Methods

Participants

The study included three cohorts ranging in age from 24 to 80 years: RRMS (n=32); PMS (n=31), including PPMS (n=7) and SPMS (n=24); and healthy, non-MS controls (CON; n=30). The controls were chosen so the sex and age distribution was approximately like that of the combined MS subjects. We did not attempt any age matching of the two MS subgroups, because the onset of the progressive phase of the disease is age-dependent such that people with PMS are inherently older.[23] Group characteristics are reported in Table 1. The MS participants were recruited and tested at the UMass Memorial Medical MS Center, while the non-MS control group was tested at UMass Amherst. The PMS group consisted of people who had been definitively diagnosed with either PPMS or SPMS according to the McDonald criteria.[24] People with PPMS and SPMS were grouped together as their clinical characteristics such as EDSS levels were comparable (see Supplementary file 1).[25,26] People with clinically isolated syndrome or probable MS were excluded. This research was approved by the institutional review boards at UMass Memorial Medical Center and UMass Amherst, and written informed consent was obtained from all participants.

Procedures

For both MS groups a clinical neurologist with training in neuroimmunology research at the MS Center evaluated the following measures bilaterally: muscle spasticity of the elbow flexors and ankle dorsiflexors using the modified Ashworth scale;[27] plantar reflex following the Babinski method; disability status by the EDSS;[3] and MS diagnostic status (i.e. RRMS, PPMS or SPMS) according to the McDonald criteria[24] (Table 1). The following sensorimotor and functional measures were obtained.

Vibration perception threshold. A biothesiometer (Bio-Medical Instruments Co., Newbury, OH, USA) was used to measure cutaneous sensation of both hands (thumb pad, index finger pad, ulnar side of palm) and feet (hallux pad, fifth metatarsal, heel), while blindfolded. Vibration amplitude was steadily

Table 1. Group characteristics and clinical measures.

	Control ($n = 30$)	RRMS ($n = 32$)	PMS ($n = 31$)	P value (all groups)	P value (MS groups)	95% CI (MS groups)
Age (years)	55.1 ± 12.3	52.3 ± 9.9	60.0 ± 8.3	0.006	0.002	–12.3, –3.1
Female (%)	80.0	90.6	64.5	0.048	0.016	–
Height (cm)	166.8 ± 7.7	160.4 ± 6.2	170.4 ± 11.0	<0.001	<0.001	–14.5, –5.4
Body mass (kg)	69.9 ± 10.0	80.1 ± 16.3	88.1 ± 25.6	<0.001	0.146	–18.9, 2.9
BMI ($kg \cdot m^{-2}$)	25.2 ± 4.1	31.2 ± 6.7	30.2 ± 7.8	<0.001	0.559	–2.6, 4.7
Disease duration (years)	NR	12.4 ± 8.6	22.1 ± 12.1	NR	<0.001	–15.1, –4.3
EDSS	NR	3.2 ± 2.2	5.9 ± 1.7	NR	<0.001	–3.6, –1.7
Ashworth right biceps brachii	NR	0.09 ± 0.4	0.3 ± 0.7	NR	0.193	–0.5, 0.1
Ashworth left biceps brachii	NR	0.03 ± 0.2	0.1 ± 0.5	NR	0.213	–0.3, 0.1
Ashworth right TA	NR	0.3 ± 0.7	0.9 ± 1.1	NR	0.015	–1.1, –0.1
Ashworth left TA	NR	0.1 ± 0.3	0.6 ± 1.1	–	0.014	–1.0, –0.1
Babinski Right Foot	NR	3 present	12 present	–	<0.01	–
Babinski Left Foot	NR	3 present	10 present	–	0.03	–
25FWT preferred speed (s)	7.0 ± 1.0	10.7 ± 5.3	14.5 ± 11.1	<0.001	0.169	–9.3, 1.7
25FWT maximal safe speed (s)	4.9 ± 0.5	8.5 ± 4.8	11.8 ± 8.7	<0.001	0.121	–7.7, 0.9
TUG (s)	6.6 ± 1.0	12.4 ± 7.7	18.1 ± 14.0	<0.001	0.109	–12.8, 1.4
Ambulatory (%)	100.0	96.9	77.4	0.003	0.027	–
9HPT (s)	19.7 ± 2.6	31.8 ± 19.6	37.5 ± 26.2	0.002	0.445	–20.9, 9.4

Data are mean ± standard deviation.
RRMS: relapsing–remitting multiple sclerosis; PMS: progressive multiple sclerosis; BMI: body mass index; EDSS: Expanded Disability Status Scale; TA: tibialis anterior; 25FWT: 25-foot walk time; TUG: timed up-and-go; 9HPT: 9-hole peg test; NR: not reported.
TUG is the average of two trials; 9HPT is the bilateral average of two trials.

increased until participants verbally confirmed they felt vibration.[28] The bilateral average over two trials at three sites on both hands and feet was reported, with a lower number (threshold) indicating greater vibration sensitivity.

Proprioception. Custom-built manipulanda (elbow, ankle) coupled with a data acquisition analog-to-digital converter (USB-6000, National Instruments, Austin, TX, USA) and custom-written MATLAB program (The MathWorks, Inc., Natick, MA, USA) were used to assess bilateral elbow and ankle proprioception through contralateral joint position-matching tests,[29] while blindfolded (Figure 1). To assess elbow proprioception,[30,31] the control arm was abducted at an angle of approximately 45° at the shoulder and then passively set to 30° of elbow flexion by the experimenter; participants then actively moved the contralateral test limb until they sensed that the elbow flexion between the two limbs was matched. Similarly, ankle proprioception[32] was assessed by setting the control foot to 15° dorsiflexion and asking participants actively to match the test foot. For both elbow and ankle proprioception, the average joint position (°) during the final 3 seconds was used to obtain the absolute error ($|\Delta^\circ|$) between the set (control) limb and the matched (test) limb, and the bilateral average over a maximum of three trials is reported.

For the finger (whole arm)-matching task, the target position was defined by the index finger of the control limb placed underneath a custom-assembled solid surface (acrylic sheet) in the center of the grid. Participants were instructed to position the index finger of the contralateral test limb directly on top of the acrylic sheet where they sensed it was directly on top of the control limb finger position. The mean radial distance (cm) of each repetition was calculated, and the bilateral average over a maximum of three trials is reported.

Tapping ability. Two wearable inertial sensors (The Opal, Version 2; APDM Wearable Technologies, Portland, OR, USA) were used to evaluate performance during rapid hand and foot tapping. Participants received instructions to tap as fast as possible for 10 seconds based on established procedures.[15,22] Tap count was derived from ascending zero crossings of angular velocity, and the average

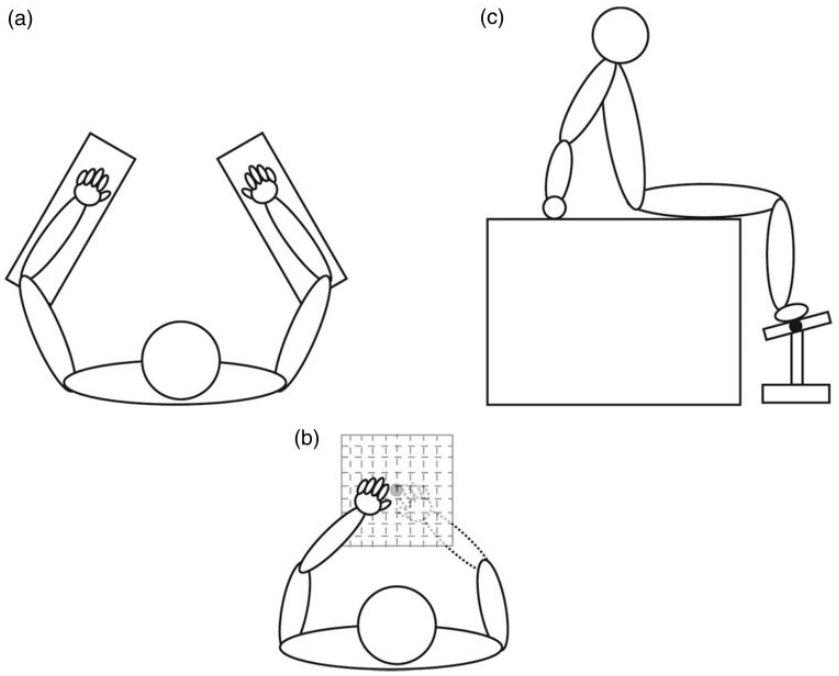

Figure 1. Set-up of proprioceptive matching tasks. (a)–(c) Schematics of upper (a) and (b) and lower-extremity proprioception (c) during a joint position-matching task at the elbow (a) and ankle (c) and a whole upper-limb-matching task using a target grid and matching with the index finger (b). For elbow-matching (a), the set elbow was positioned to 30° in the transverse plane. For ankle-matching (c), the set foot was positioned to 15° dorsiflexion. For whole-limb-matching (b), the set index finger was positioned underneath the grid (10 × 10 cm) to *x*, *y* coordinates [0, 0].

10-second tap count over three bilateral trials was recorded.

Mobility and upper extremity function. Mobility function was assessed with the 25FWT (preferred and maximal safe speed) and average TUG test (two trials).[33] Nine RRMS and 12 PMS participants used walking aids during the mobility tests, ranging from ankle-foot orthotics to rollators. Upper limb function was assessed bilaterally twice using the nine-hole peg test (9HPT).[6,34]

Statistical analysis

The primary dependent variables were upper and lower-extremity measures of sensorimotor function including vibration perception threshold (VPT), proprioception and tapping ability. Secondary dependent variables included clinical, mobility and upper extremity function measures (Table 1). For each continuous outcome, the three groups were compared using analysis of variance (ANOVA), allowing unequal variances (Welch's test). This was complemented by 95% confidence intervals and *t*-tests for differences in group means, again allowing for unequal variances (Satterthwaite's method). Categorical clinical measures were compared between RRMS and PMS using Fisher's exact test. As the ability to classify individuals into groups is a function of both group means and their variability, logistic regression[35] was used to explore the ability of the individual measures, and combinations of them, to assign an MS participant into the RRMS or PMS group. In our main analysis we did not explore the effects of possible confounding variables, such as disease duration or age, which by nature of MS differ between MS subtypes.[1] Unlike randomized control trials in which a potential confounder gets unbalanced due to the randomization, this was an observational study and correcting for a variable, which by nature differs between groups, will change the research question.[36] However, we did perform additional analyses comparing the non-MS control group and each MS subgroup, matched for age (see Supplementary file 2 data). Statistical significance was established at an alpha level of less than 0.05. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Group and functional measures

There was a main effect of group for age, height, body mass and body mass index (BMI) (Table 1). Pairwise comparisons that assumed unequal

variances indicated that RRMS and PMS had similar body mass and BMI, but that PMS was older and taller (Table 1). There was a longer disease duration in PMS than RRMS ($P<0.001$, 95% CI –15.1, –4.3), and a main effect for EDSS ($P<0.0001$, 95% CI –3.6, –1.7), indicating a greater degree of disability in PMS compared to RRMS. There was a main effect of group for all mobility tests and the 9HPT, but no difference between RRMS and PMS in these measures.

Sensorimotor function

Foot VPT. Group differences were observed for VPT at the fifth metatarsal ($F_{2,87}=21.15$, $P<0.0001$); post hoc pairwise comparisons showed that the ability to sense vibration declined from CON to RRMS to PMS groups (Table 2; Figure 2). The same results were obtained for sensitivity at the hallux and heel.

Hand VPT. VPT showed group effects for all three sites: index finger ($F_{2,88}=6.99$, $P=<0.001$), thumb ($F_{2,88}=9.81$, $P<0.001$) and palm ($F_{2,88}=5.16$, $P<0.001$). Pairwise comparisons indicated differences between controls and both MS groups, with CON showing lower thresholds (Table 3; Figure 3). Differences between RRMS and PMS were observed for the thumb and a trend for differences at the index finger, with PMS showing a higher threshold than RRMS. No difference was observed between RRMS and PMS for the palm.

Table 2. Lower-extremity sensorimotor variables.

Variable	Controls	RRMS	PMS	*P* value
Hallux VPT (V)	10.60 ± 5.44	15.23 ± 12.10	26.38 ± 13.52	<0.001
Fifth Met VPT (V)	8.39 ± 4.93	13.62 ± 12.72	28.46 ± 16.42	<0.001
Heel VPT (V)	9.68 ± 6.56	15.19 ± 11.97	28.50 ± 15.07	<0.001
Ankle matching (|Δ°|)	2.29 ± 0.66	4.26 ± 2.82	4.70 ± 2.17	<0.001
Foot-tap count (10 s)	45.95 ± 4.29	37.43 ± 9.57	29.63 ± 7.67	<0.001

Data are mean ± standard deviation.
RRMS: relapsing–remitting multiple sclerosis; PMS: progressive multiple sclerosis; VPT: vibration perception threshold; V: volts; Met: metatarsal; |Δ°|: absolute difference in degrees between the set and matched limb; s: seconds. Measurements for each variable represent the bilateral average of two trials (VPT) and three trials (matching and tapping).
P values for main effect of group are from one-way analyses of variance (ANOVAs). See Figure 2 for post hoc pairwise comparisons.

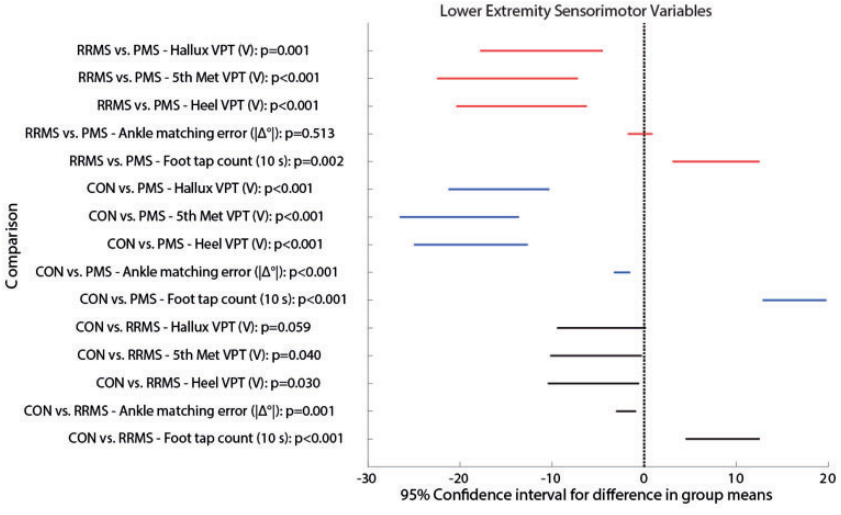

Figure 2. Analysis of differences in group means for the lower extremity sensorimotor variables. RRMS: relapsing–remitting multiple sclerosis; PMS: progressive multiple sclerosis; CON: non-multiple sclerosis control group; VPT: vibration perception threshold; Met: metatarsal. Lines that do not cross zero indicate a difference between groups.

Table 3. Upper-extremity sensorimotor variables.

Variable	Controls	RRMS	PMS	*P* value
Thumb VPT (V)	3.06 ± 0.94	4.78 ± 2.67	7.33 ± 5.88	<0.001
Index VPT (V)	3.17 ± 0.94	4.93 ± 3.31	7.83 ± 7.76	<0.001
Palm VPT (V)	2.88 ± 0.79	5.52 ± 5.36	7.54 ± 8.12	<0.001
Elbow-matching error (|Δ°|)	4.81 ± 2.08	5.68 ± 2.33	8.58 ± 4.40	<0.001
Finger-matching error (cm)	2.33 ± 0.67	2.62 ± 1.59	3.53 ± 1.67	0.002
Hand-tap count (10 s)	62.80 ± 5.98	53.03 ± 10.70	50.80 ± 9.50	<0.001

Data are mean ± standard deviation.
RRMS: relapsing–remitting multiple sclerosis; PMS: progressive multiple sclerosis; VPT: vibration perception threshold; V: volts; |Δ°|: absolute difference in degrees between the set and matched limb; cm: centimeters; s: seconds. Measurements for each variable represent the bilateral average of two trials (VPT) and three trials (matching and tapping).
P values for main effect of group are from one-way analyses of variance (ANOVAs). See Figure 3 for post hoc pairwise comparisons.

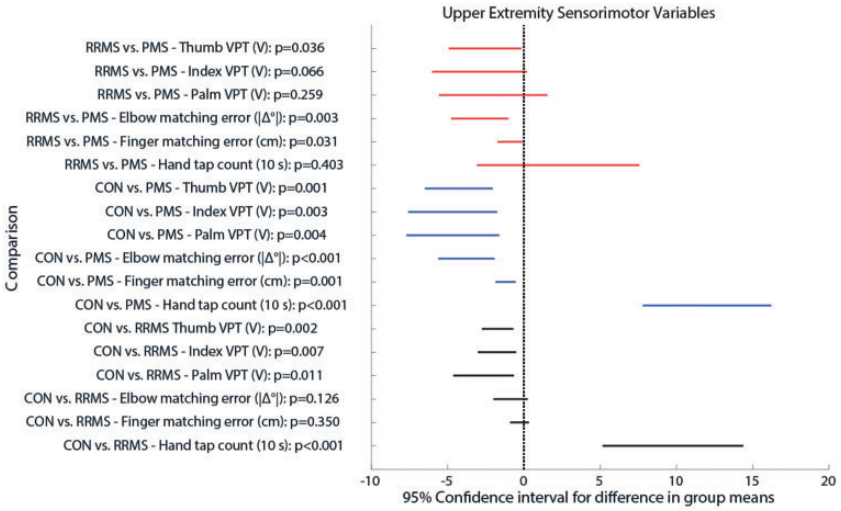

Figure 3. Analysis of differences in group means for the upper extremity sensorimotor variables. RRMS: relapsing–remitting multiple sclerosis; PMS: progressive multiple sclerosis; CON: non-multiple sclerosis control group; VPT: vibration perception threshold; Met: metatarsal. Lines that do not cross zero indicate a difference between groups.

Ankle proprioception. A group effect was observed for the absolute error during ankle-matching ($F_{2,84}$=10.98, P<0.001). Pairwise comparisons revealed differences between CON and both RRMS and PMS, but not between the two MS groups (Table 2; Figure 2).

Finger and elbow proprioception. A group effect was observed for the finger-matching error ($F_{2,89}$=6.08, P=0.002). Pairwise comparisons indicated differences between PMS versus CON and PMS versus RRMS, but not between CON versus RRMS (Table 3; Figure 3). A group effect was also observed for the elbow-matching error ($F_{2,86}$=11.90, P<0.001), which was greater in PMS compared to CON and RRMS. The difference between RRMS and CON was modest and not significant.

Foot tapping. A group effect was observed for foot-tap count ($F_{2,79}$=32.04, P<0.001). Pairwise comparisons showed the number of foot taps was systematically lower from CON to RRMS to PMS (Table 2; Figure 2).

Hand tapping. A group effect also was observed for hand-tap count ($F_{2,83}$=14.30, P<0.001). Pairwise comparisons showed the number of hand taps to be lower in both MS groups compared to CON.

No difference in hand-tap count was observed between RRMS and PMS (Table 3; Figure 3).

We also controlled for age in comparing non-MS controls to RRMS and PMS groups. Matching the non-MS controls to the PMS group resulted in the same outcomes for all sensorimotor and mobility variables presented above. The same result was obtained in matching the non-MS control group to the RRMS group (see Supplementary file 2 for full data).

Classification of participants into MS subgroups: logistic regression

Single variable logistic regression suggested that the most promising individual variables for distinguishing the two MS groups were the average absolute error in the elbow position-matching task, and the cutaneous measures at the hallux, fifth metatarsal and age (classification rate; Table 4). We also considered logistic models combining each of the variables with age (incorporating an interaction term if needed). For some variables the results with age led to substantial increases in the estimated correct classification rate; for the thumb VPT (from 60.7% to 70.4%), 25FWT preferred (54% to 69.4%), ankle-matching error (45.6% to 66.7%) and hand-tap count (44.8% to 64.3%) with all but the model with the thumb involving an interaction term. These age-adjusted improvements did not surpass the best three variables unadjusted for age (Table 4).

For multiple logistic regression, there were too many variables relative to the number of observations to use standard model-building methods on all variables. For pairs of variables, the best combinations (where the model allowed for an interaction effect through the product of the 2 variables) included the average error at the elbow, with an estimated correct classification rate of 78.9% when combined with the sensitivity in any of hallux, fifth metatarsal or heel, and 75.4% with the palm and index finger. Stepwise selection resulted in the optimal model including VPT at the fifth metatarsal, the elbow-matching error and their interaction. These potential gains are rather modest with respect to what was achieved using a single variable at a time (Table 4).

Table 4. Single variable logistic regression analyses.

Variable	b	SEb	*P* value	Classification rate	Low	Up
Hallux VPT (V)	1.490	0.454	0.001	71.7	60.3	83.1
Fifth Met VPT (V)	1.397	0.395	<0.001	75.0	64.0	86.0
Heel VPT (V)	1.478	0.441	0.001	65.0	52.9	77.1
Index VPT (V)	1.390	0.574	0.015	65.6	53.7	77.5
Thumb VPT (V)	1.341	0.592	0.023	60.7	48.4	72.9
Palm VPT (V)	0.788	0.473	0.095	65.6	53.7	77.5
Finger-matching error (cm)	0.363	0.176	0.039	66.7	55.0	78.3
TUG (s)	0.064	0.041	0.115	59.2	45.4	72.9
25FWT preferred (s)	0.064	0.050	0.199	54.0	40.2	67.8
25FWT brisk (s)	0.087	0.060	0.145	60.0	46.4	73.6
Ankle-matching error ($\|\Delta^\circ\|$)	0.070	0.107	0.512	45.6	32.7	58.5
Elbow-matching error ($\|\Delta^\circ\|$)	0.291	0.107	0.006	72.9	61.5	84.2
Foot-tap count (10 s)	–0.108	0.039	0.005	61.1	48.1	74.1
Hand-tap count (10 s)	–0.023	0.027	0.396	44.8	32.0	57.6
9HPT (s)	0.016	0.017	0.330	53.8	38.2	69.5
Age	0.09	0.03	<0.001	68.3	56.8	79.7

Univariate logistic regression results for modeling and classifying MS group status (PMS vs. RRMS).
Based on a combination of diagnostics and goodness-of-fit tests, the cutaneous measures are log transformed for use in the logistic model.
b: estimate of β; SEb: standard error for b; *P*: *P* value for testing H_0: $\beta = 0$; Classification Rate: estimated correct classification rate using a 0.5 cut point and cross-validation; Low, Up: approximated 95% confidence interval for the classification rate; RRMS: relapsing–remitting multiple sclerosis; PMS: progressive multiple sclerosis; VPT: vibration perception threshold; V: volts; Met: metatarsal; TUG: timed up-and-go test; 25FWT: 25-foot walk test; $|\Delta^\circ|$: absolute difference in degrees between the set and matched limb; 9HPT: 9-hole peg test.

Discussion

Overall, these results demonstrate differences in sensorimotor function between non-MS controls and PwMS and, most importantly, between PMS and RRMS cohorts, that are independent of ambulation. First, vibration sensation was lower in both MS groups, more so in the progressive group. This reduction in vibration sensitivity was observed at most of the sites tested on both hands and feet. Second, proprioceptive function during the ankle-matching task was lower in both MS groups compared to controls, but no differences existed between MS groups. In contrast, performance during elbow and finger-matching differed between PMS and RRMS. The logistic regression analysis also identified elbow proprioceptive function as a potential significant classifier of MS subtype. This novel set of results indicates that proprioceptive function may not be impacted similarly across the body among different MS subtypes. Third, central motor function, as assessed by tapping ability, was systematically reduced from controls to RRMS to PMS for foot but not hand tapping, although both MS groups showed lower hand-tapping ability compared to controls. Our analyses suggest that both upper and lower-extremity sensorimotor variables are important in assessing differences between RRMS and PMS subtypes.

In agreement with previous studies[12,14,15] we found differences in cutaneous sensation between RRMS and controls for sites on the hands and feet. A novel finding in this study was that we detected differences in cutaneous sensation between RRMS and PMS at all sites on the foot and, to a lesser extent, on the hand. The more pronounced differences between RRMS and PMS for locations on the foot suggest that, although MS is a central nervous system disease, longer axons that serve mechanoreceptors on the foot could be more susceptible to changes over time or due to differences in disease processes in PMS compared to RRMS. These findings highlight the importance of testing cutaneous sensitivity changes at the feet in MS, especially given its relevance to balance control.[11,13,15,21] The potential for these measures to provide insight into the transition from RRMS to SPMS is worth further exploration.

Fling et al.[13] found that balance control in PwMS is especially affected in tasks that put higher demands on proprioceptive function; however, they did not assess the relative loss of proprioceptive function within upper and lower extremities. Jamali and colleagues[14] assessed a variety of sensorimotor function tests in RRMS, and found that proprioceptive impairments were more prominent in MS than cutaneous (e.g. tactile pressure and vibration). Our results indicate that evaluation of both upper and lower-extremity proprioceptive function is important when comparing RRMS and PMS subtypes. For the lower extremity, both MS groups showed impaired ankle proprioceptive function compared to non-MS controls, with no differences between MS subtypes. In contrast, for the upper limb both elbow and whole-limb proprioceptive function was lower in PMS than RRMS, with no differences between RRMS and non-MS controls. This is in contrast to Jamali and colleagues,[14] who found a greater degree of proprioceptive impairment in the lower compared to the upper extremities. These different findings could be the result of the sensitivity of the assessment; Jamali et al.[14] used global assessment of movement and direction in response to passive movement induced by the experimenter and ours was active repositioning focused on precise matching of the contralateral limb. Our findings regarding the PMS group are novel and support the earlier suggestion by Soyuer and colleagues[10] that proprioception may be worse in PMS compared to RRMS. Overall, our results suggest that loss of proprioceptive function due to MS disease progression or duration may happen earlier in the upper compared to the lower extremity, but this hypothesis requires further testing.

In contrast to the results on proprioception, the MS groups differed in lower but not upper-extremity tapping function. A recent study reported similar foot-tap counts between controls and RRMS.[22] We found that RRMS had lower foot-tapping ability compared to controls. This discrepancy might be due to a greater level of disability or dorsiflexor weakness in our RRMS group compared with that of the previous study. In agreement with Tanigawa et al.,[22] we found that PMS had lower foot-tapping ability compared to both controls and RRMS, probably due to more significant spinal cord involvement in PMS. As with foot tapping, we found that the ability to tap the hand rapidly was lower in both MS groups compared to controls. Unlike with foot tapping and contrary to Tanigawa et al., hand-tapping ability did not differ between the two MS groups in the current study. Differences in scoring method for tapping might explain this discrepancy; rather than assign a score of zero for those who were physically unable to perform the tapping task, as done previously,[22] we treated each case as a missing value. Assigning a score of zero for someone who cannot perform a

task would probably artificially lower the scores in the PMS group.

To complement the group comparisons, the logistic regression analysis revealed that the most promising variables for distinguishing the two MS groups reflected elbow proprioceptive function and the lower-extremity vibration sensitivity measures on the plantar surface of the foot. Adjusting for age in the logistic regression analysis also raised the classification rate for the upper extremity cutaneous sensitivity (thumb) and lower extremity ankle proprioception. Overall classification rates of cutaneous and proprioceptive measures were higher than those for mobility and tapping. These findings would need to be confirmed in a larger study sample. Although early changes in EDSS and 25FWT are predictive of long-term disability,[5] these measures are highly dependent on mobility function. The sensorimotor measures in the current study may lead to a more comprehensive assessment of relapsing–remitting and progressive forms of MS. The finger-matching protocol, assessing upper limb proprioceptive ability, in particular, could easily be incorporated in a standard array of clinical tests.

Although the main focus of this study was on non-ambulatory measures of sensorimotor function, we assessed mobility function with the 25FWT and TUG for those who were able to walk. For both tests, the differences between controls and MS groups were greater than those observed between RRMS and PMS. This finding adds to the argument above that that subtle physiological differences between RRMS and PMS may be more detectable in the non-ambulatory, sensorimotor measures presented here compared to standard clinical tests of 25FWT and TUG. Although further investigation is needed to determine whether we can build a battery of tests based on sensorimotor function measures that classify people into either RRMS or PMS cohorts, our preliminary findings on the ability of the sensorimotor measures to detect differences between MS groups are promising.

In summary, this study provides novel information about changes in sensorimotor function in progressive compared with relapsing–remitting forms of MS. Our results show the importance of assessing both upper and lower-extremity sensorimotor changes in comparing PMS and RRMS subtypes. Importantly, our findings provided novel information regarding loss of proprioceptive function in MS and between the MS subtypes; loss of proprioceptive function due to MS disease progression or duration may happen earlier in the upper compared to the lower extremity. Our findings also suggest that proprioceptive and motor pathways may be affected differently for the upper and lower extremities between people with relapsing–remitting and progressive subtypes of MS. Future studies should focus on the potential to exploit these differences in order to detect early and subtle changes associated with a transition to secondary progressive MS prior to overt mobility impairment.

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Conflict of Interests

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Supplemental Material

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