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14. ABSTRACT

The purpose is to develop and evaluate an outcome measure that can identify progression of disability in people with MS by being responsive to changes in sensorimotor function that precede an increased rate of disability. Specific Aim 1 investigates sensorimotor function (plantar cutaneous sensation, lower limb proprioception, and central motor drive), posture and mobility to assess what measures of somatosensory and motor function best discriminate between individuals with progressive MS (PMS) and nonprogressive relapsing-remitting MS (RRMS), and compare these to an age- and sex-matched healthy control group. In Specific Aim 2 we assess changes in sensorimotor function over a 2-year period in the same three cohorts and determine what measures (or combination thereof) are most sensitive in detecting changes in a progressive disease course. All three sensorimotor function measures (cutaneous sensitivity, tapping ability, proprioception) were reduced in both MS cohorts compared to controls. Cutaneous sensitivity was reduced for both hands and feet in PMS compared to RRMS; tapping ability was reduced for the foot but not the hand in PMS compared to RRMS. Proprioceptive function in the arm declined from non-MS controls to RRMS to PMS. The main result for Aim 2 is that changes over a 2-year time span were observed in the PMS but not in the RRMS group, with the PMS group showing decline in both hand and foot cutaneous sensitivity.

15. SUBJECT TERMS
Multiple Sclerosis; Relapsing-remitting MS; progressive MS; sensorimotor function; proprioception; cutaneous sensation; central motor drive; postural control; walking;

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1. Introduction

Multiple sclerosis (MS) is a chronic, neurological disease that currently affects more than one million people. Progressive MS (MS*p*) is a subtype of MS that is characterized by a steadily worsening disease course, generally leading to profound disability. While only a small proportion of individuals are diagnosed with MS*p* at the outset, it is estimated that as many as 90% of those with relapsing-remitting (or non-progressive) MS (MS*np*) will ultimately transition to progressive MS. Despite the high prevalence of those developing a progressive course, existing treatments have been shown to be ineffective in forestalling the decline in body functions associated with this progression. Before new treatments can be developed and tested, outcome measures that can accurately and reliably identify and quantify progression must be found. The purpose of this 3-year project is to develop and evaluate an outcome measure that can identify progression of disability in people with MS by being responsive to changes in sensorimotor function that precede an increased rate of disability. This project has two Specific Aims: In Specific Aim 1 we investigate sensorimotor function differences (plantar cutaneous sensation, lower limb proprioception, and central motor drive) as well as postural and gait differences to assess what measures of somatosensory and motor function best discriminate between individuals with MS*p* (n=30) and MS*np* (n=30), and age- and sex-matched healthy controls (CON; n=30). In Specific Aim 2 we assess changes in sensorimotor function over a 2-year period in the same three cohorts and determine what measures (or combination thereof) are most sensitive in detecting changes in a progressive disease course. We anticipate that the to be developed MS neuromotor test will ultimately provide a low cost, non-invasive, sensitive clinical outcome measure that can be used to evaluate progression of disability and efficacy of therapeutic interventions.

2. Keywords

Relapsing-remitting MS; progressive MS; sensorimotor function; proprioception; cutaneous sensation; central motor drive; postural control; walking;

3. Accomplishments

3.1 Major goals of the project

Table 1*:* Major Tasks for Aims 1 & 2 based on submitted Statement of Work (SOW)

Specific Aim 1	**Original Time line**	**Completion**
Major Task 1: Human Subjects Approval	Months	10/26/2016
IRB review at UMass Amherst and Worcester	-3-0	11/18/2016
Review USAMRMC ORP HRPO	1-3	1/11/2017
Milestone(s) Achieved: Full IRB/HRPO approval	3	1/11/2017
Major Task 2: Pilots and Recruitment	Months	
Patient Recruitment	1-3	Completed
Pilot and equipment testing	1-3	2/17/2017

Milestone(s) Achieved: Completion of pilots and recruitment	3	2/17/17 (pilot testing) 6/27/17 (recruitment)
Major Task 3: Baseline Assessment	Months	
Three groups: MS progressive and MS nonprogressive, N=62 in total (N=31 in Each group) Age and sex matched control group (N=30)	3-6	9/26/17 3/5/18
Milestone(s) Achieved: Completion of baseline testing	6	Completed
Milestone(s) Achieved: Data and statistical analysis of baseline testing for Aim 1	9	Completed

Specific Aim 2	Original Time line (Months)	Completion
Major Task 4: Aim 2		
Subtask 1: MS groups (MSp and MSnp) 12 months post baseline perform same tests as in baseline.	15-18	Completed
Subtask 2: Control group 12 months post baseline perform same tests as in baseline.	15-18	Completed
Subtask 3: MS groups (MSp and MSnp) 24 months post baseline perform same tests as in baseline.	27-30	Completed
Subtask 4: Control group 24 months post baseline perform same tests as in baseline.	27-30	Completed
Milestone(s) Achieved: Completion of data collection	30	Completed
Milestone(s) Achieved: Data and statistical analysis of Aim 2	9-35	ongoing
Major Task 5: Reporting		
Subtask 1: Preparation and writing of reports	30-36	Reports year 1 and 2 completed
Milestone(s) Achieved: Final report completed	36	11/27/20

3.2 Accomplishment of these goals

In the first reporting period the following major Tasks in **Specific Aim 1** were completed: Task 1 human subjects approval, Task 2 pilot testing and MS participant recruitment, and Task 3, baseline data collection for both MS groups: n=31 participants with progressive MS and n=32 with non-progressive MS. For the **second reporting period** we completed the baseline data collection for n=30 non-MS control participants and accomplished the major goals in **Specific**

Aim 1 and began testing for the first follow-up in **Specific Aim 2** (subtasks 1 & 2). **In the 3rd reporting period** we completed the follow-up data collection after 12 months (Visit 2), subtask 1 (for MS group) and subtask 2 (for Control group), as well as the complete data analysis of our basic measures for both MS groups and the control group for subtasks 1 and 2. For the first follow-up we tested a total of n=51 MS participants for Specific Aim 2, subtask 1. There were a total of n=11 dropouts on follow-up 1 (7 nonprogressive and 4 progressive). **In the final year of the project** we completed data collection and analysis on the 2nd follow-up (visit #3) for Specific Aim 2 24 months after baseline data collection, Major Task 4, Subtasks 3 and 4. For this 2nd follow-up we tested a total of n=46 MS participants. Two participants that were scheduled at the last progress report could not be tested due to COVID-19. For the non-MS control group a total of n=26 participants were retested on visit 3. Three participants that were scheduled at the last progress report could not be retested due to COVID-19.

3.2.2 Specific Aim 1 – Baseline results

The baseline testing results have been presented in previous reports and have now been published in *Multiple Sclerosis Journal; Experimental, Translational and Clinical and Multiple Sclerosis and Related Disorders*. The MSJ paper contains the results of all sensorimotor measures in this study comparing both MS groups and MS vs. non-MS controls. The second paper (MSRD) focuses on an in-depth analysis and assessment of tapping performance in the upper and lower extremities (see Section 6.1 publications for references to these papers).

Results from the baseline paper in MSJ showed that cutaneous sensation differed between RRMS and PMS at the foot and to a lesser extent the hand. Proprioception function in the upper but not the lower extremity differed between RRMS and PMS, but was different for both upper and lower extremities between MS and non-MS controls. Central motor drive was slowed in MS, but foot-tap and not hand-tap speed was slower in PMS compared to RRMS. In addition, the non-ambulatory sensorimotor measures were more sensitive in detecting differences between RRMS and PMS than mobility assessed with the 25-Foot Walk Test. We concluded that assessment of both upper and lower extremity sensorimotor changes in comparing PMS and RRMS subtypes may improve our sensitivity in detecting early and subtle changes associated with a transition to secondary progressive MS prior to overt mobility impairment.

Overall these results demonstrate sensorimotor changes in MS overall as well as in the progressive MS cohort compared to the non-progressive MS group. Our analyses suggest that both assessment of upper extremity and lower extremity sensorimotor variables may be important, their efficacy dependent upon the type of variable.

The 2nd paper in *Multiple Sclerosis and Related Disorders* focuses in more detail on the tapping data. The title of the paper is "Rapid foot-tapping but not hand-tapping ability distinguishes between Multiple Sclerosis subtypes." Tapping tests have been previously shown to be a more reliable measure of upper motor neuron disease than the widely used Babinski test and have also been shown to examine motor function differences between multiple sclerosis (MS) and healthy controls, and between MS sub-types. However, it is not clear why tapping ability is different between disease sub-types. The objective of this study was to examine whether performance during rapid hand- and foot-tapping tests is different between relapsing-remitting (RRMS) and progressive (PMS) forms of MS as well as how both sub-types differ from non-MS controls. We predicted that: (1) inter-tap interval would be longer in both MS groups compared to controls,

and longer in PMS compared to RRMS, based on outcomes of prior studies on tap count, and (2) inter-tap variation will be increased in MS compared to controls.

Participants in this study included 30 non-MS controls, 31 RRMS, and 31 PMS. Participants wore inertial sensors on both hands and feet and were instructed to tap as fast as possible for 10 seconds. Inter-tap interval (ms), coefficient of variation (COV), up- and down-movement characteristics (duration (ms), COV, peak angular velocity (rad/s)) were examined for a difference between group means and within-group directional differences (up- vs. down-phase movement components). Both hand- and foot-tapping inter-tap interval differed between controls and MS, but only foot tapping was different between RRMS and PMS. Both up- and down-movement duration differences were consistent with the results for inter-tap interval, but up-movement duration showed larger mean group differences than paired differences during the down-movement. No significant group differences in overall inter-tap interval variation were detected for either hand- or foot-tapping; however, up-movement foot-tapping variation but not down-movement variation was different between controls and MS. Up- and down-peak angular velocity during foot-tapping was different between controls and PMS, and up-movement peak angular velocity differences showed larger mean group differences than the down-movement peak angular velocity between controls and PMS.

We concluded that foot-tapping but not hand-tapping differs between MS disease sub-types. Overall tapping variability did not differ between groups; however, when parsed into up- and down-movement variability, up-movement variability was greater in RRMS and PMS compared to controls. Furthermore, up-movement duration during hand- and foot-tapping showed larger group differences than the down-movement, suggesting that the up-movement during tapping may be more important diagnostically.

3.2.3 Specific Aim 2 – Follow-up (after 12 months; visit 2) results

Data collection for the first follow-up (visit 2) has been finalized and analysis has been completed for all major outcome variables. This full data set will be first analyzed separately from the baseline data (same analysis procedures as reported in the previous reports). The second type of analysis will involve (1) comparison between baseline and follow-up data using ANOVA, and (2) evaluation of difference scores between the two assessments. We are reporting here on the first analysis type and will present the results of the second type on the changes from visit 1 to visit 2 in section 3.2.5 below.

Lower extremity variables

Vibration Perception threshold (VPT). Significant differences were observed for VPT at the big toe, 5th metatarsal, and heel between the three groups (Figure 1; p-values <.0001); post-hoc pairwise comparisons showed that VPT systematically increased (sensitivity declined) from controls to RRMS to PMS groups for the big toe, 5th metatarsal, and heel (Figure 2).

Proprioception. For the absolute matching error at the ankle a significant group effect was observed (p<.0001). Pairwise comparisons revealed differences between controls and both RRMS and PMS groups, but not between the two MS groups (Figures 1 & 2).

Foot Tapping. For the number of foot tap counts a significant group effect was observed (p<.0001). Pairwise comparisons showed the number of foot taps systematically decreasing from controls to RRMS to PMS groups (Figures 1 & 2).

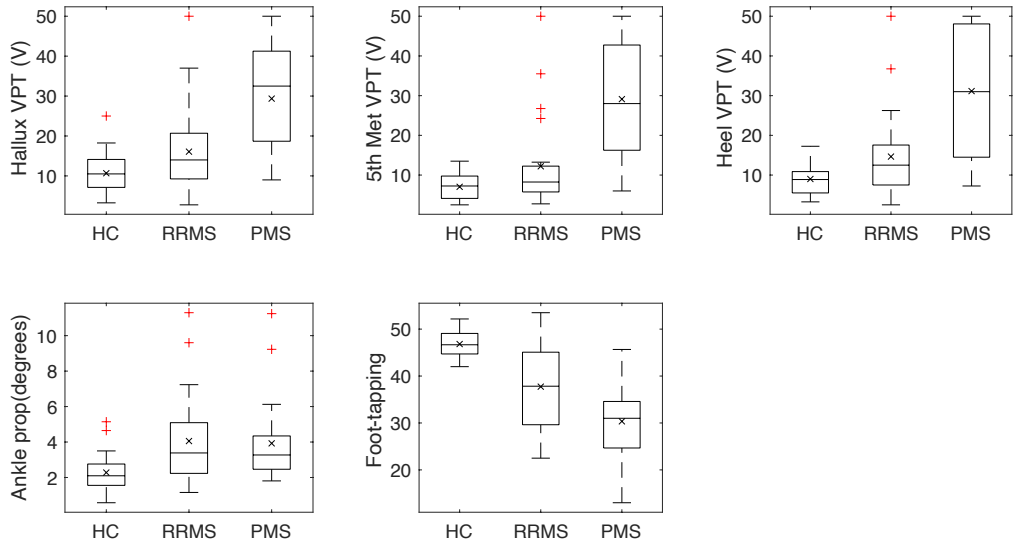

Figure 1. Box plots of *between groups comparisons for lower extremity variables. Vertical lines represent the median, and the black X's the mean for the different groups. Red crosses represent outliers.*

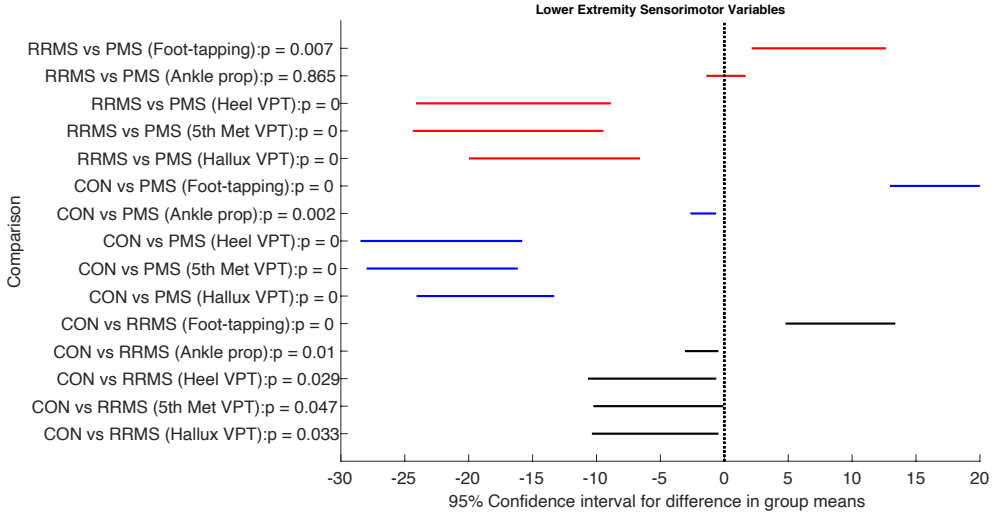

Figure 2. Lower extremity results of pairwise comparisons and *95% confidence interval for the difference in group means. Red lines represent comparisons between RRMS and PMS. Blue lines represent comparisons between CON and PMS. Black lines represent comparisons between CON and RRMS.*

Upper extremity variables

Vibration Perception threshold. VPT for all three sites showed significant group effects (p-values <.001). Pairwise comparisons showed significant differences between controls and both MS groups, with the control group showing lower thresholds (Figures 3 & 4). Significant

differences between RRMS and PMS were observed for all three sites (palm, index finger and thumb), with the PMS showing a higher threshold than the RRMS group.

Proprioception. For finger repositioning error a significant group effect was observed ($p<.0001$; Figure 3). Pairwise comparisons found significant differences between the PMS and controls and a trend between the PMS and RRMS groups ($p=.075$), but not between controls and RRMS (Figure 4). A significant group effect was also observed for elbow matching error ($p<.001$). Elbow matching error was significantly increased in both the PMS and RRMS groups compared to the controls group, while there was no difference between the two MS groups (Figured 3 & 4).

Hand Tapping. For the number of hand tap counts a significant group effect was observed ($p<.0001$; Figure 3). Pairwise comparisons showed the number of hand taps to be lower in both MS groups compared to the control group. No difference in hand tap count was observed between the RRMS and PMS groups (Figure 4).

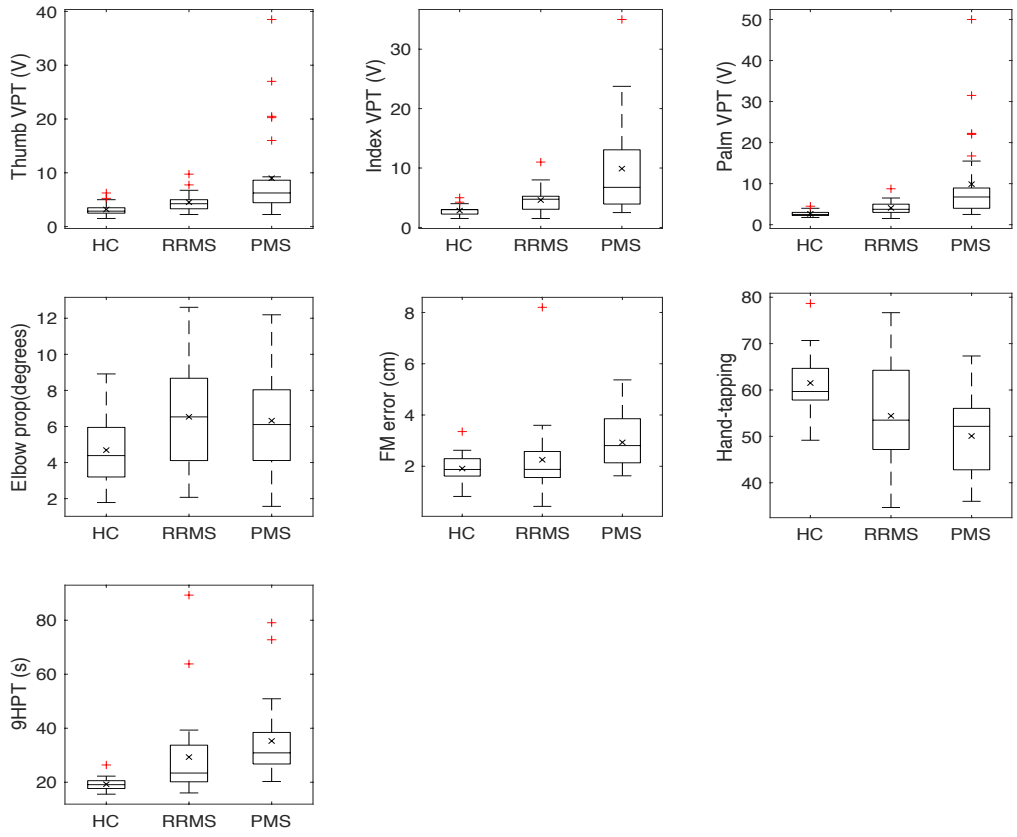

Figure 3. Box plots of *between groups comparisons for upper extremity variables. Vertical lines represent the median, and the black X's the mean for the different groups. Red crosses represent outliers.*

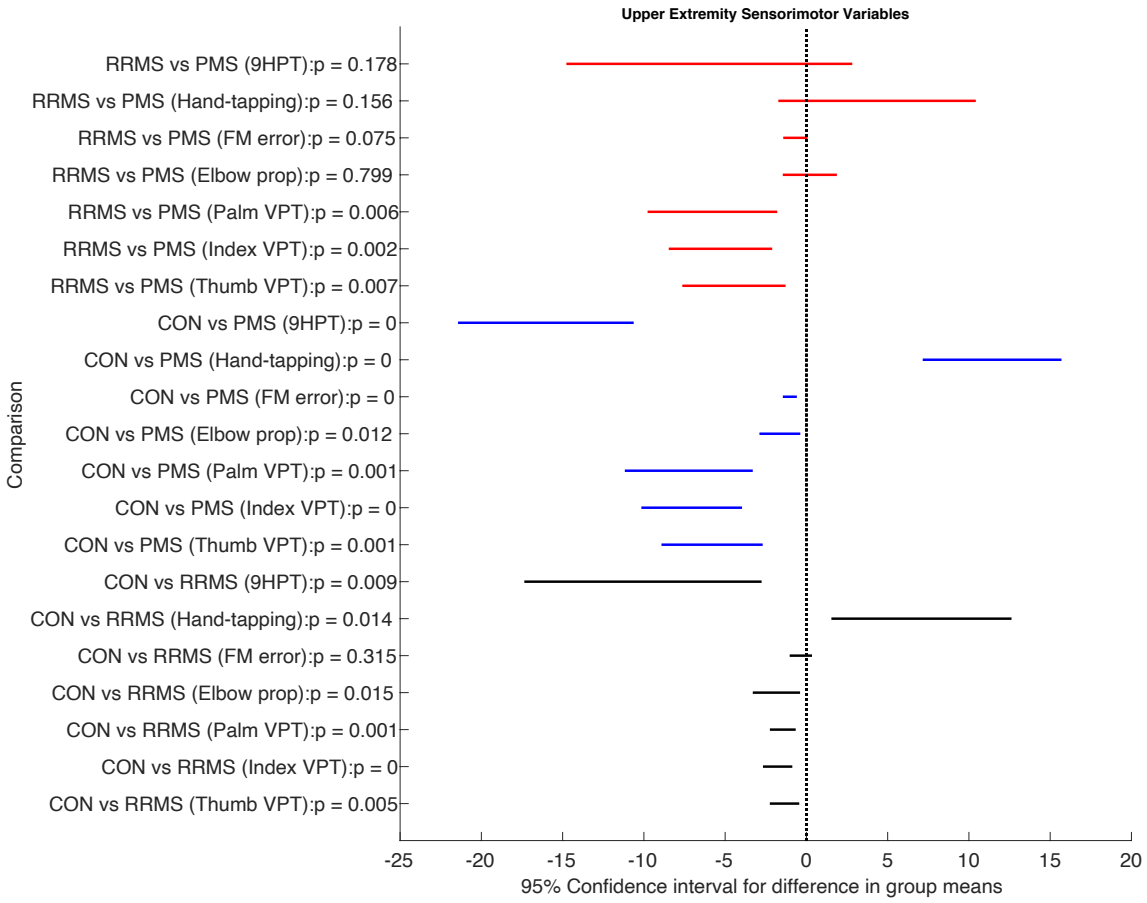

Figure 4. Upper extremity results of pairwise comparisons and *95% confidence interval for the difference in group means. Red lines represent comparisons between RRMS and PMS. Blue lines represent comparisons between CON and PMS. Black lines represent comparisons between CON and RRMS.*

All three mobility tests (25FWTprefered, 25FWTbrisk, and Timed-Up-And-Go [TUG]) showed significant group effects (p-values < .001). Preferred T25FW, briskT25FW, and TUG times were lower in controls compared to RRMS and PMS. Walk times all three tests trended to be faster in RRMS compared to PMS (see Figures 5 & 6).

Consistency results visit 1 (baseline) and visit 2

The reported group differences here on the lower and upper extremity variables are highly consistent with the earlier reported group differences obtained from the baseline measurement. The only exception was for the upper extremity proprioception, where the elbow matching error did not show a difference between the two MS groups during visit 2, but did show a difference at baseline. These group-based results, in addition to a regression analysis will be submitted to *Archives of Physical Medicine and Rehabilitation* in December 2020.

The title of the paper is "Non-ambulatory measures of lower-extremity sensorimotor function are associated with walking function in Multiple Sclerosis" and reveals novel results regarding the link between sensorimotor function measures used in this project and walking performance in different MS subtypes. Main findings indicated that, although all measures of

sensorimotor function were lower in PwMS, foot tapping ability and ankle proprioceptive function but not cutaneous sensitivity were associated with walking performance, and only in RRMS. Why these measures more strongly associate with walking performance in RRMS and not in PMS needs further examination.

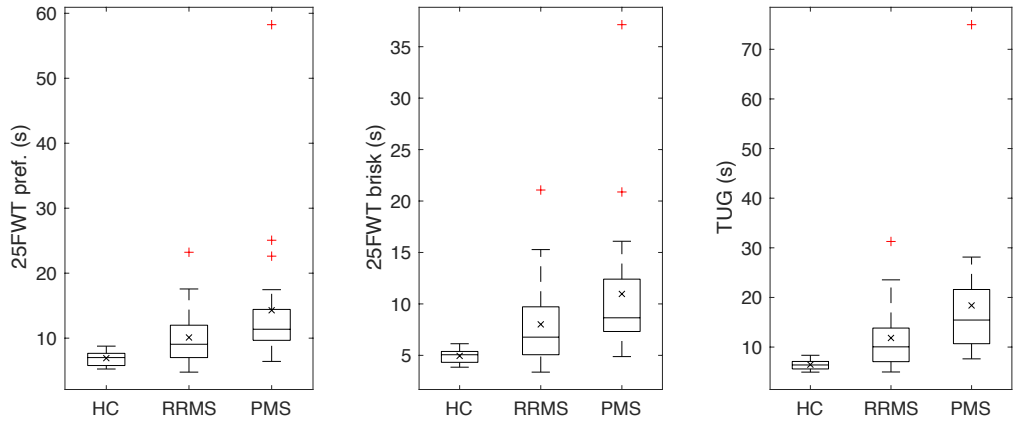

Figure 5. Box plots of *between groups comparisons for mobility test variables. Vertical lines represent the median, and the black X's the mean for the different groups. Red crosses represent outliers.*

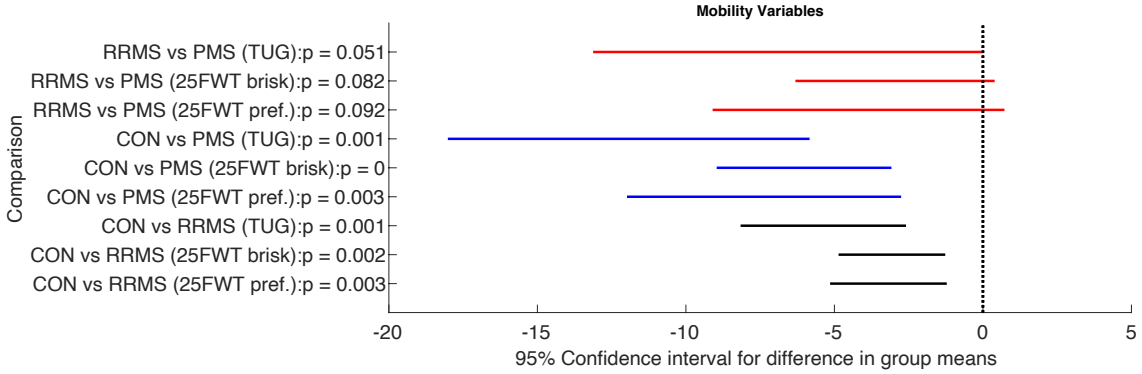

Figure 6. Mobility results of pairwise comparisons and *95% confidence interval for the difference in group means. Red lines represent comparisons between RRMS and PMS. Blue lines represent comparisons between CON and PMS. Black lines represent comparisons between CON and RRMS.*

3.2.4 Specific Aim 2 – 2nd Follow-up (after 24 months; visit 3) results

The overall results of the group comparisons at the 2nd follow-up at visit 3 were again highly consistent with those from the baseline and first follow-up visits. The only exception was for ankle proprioceptive function, where at visit 3 the PMS group showed reduced function compared to RRMS while for visit two there were no differences between the two subtypes. The consistency in reported group differences across all three visits is nicely illustrated in Figure 7 for the sensorimotor variables and in Figure 8 for the mobility variables (T25FW at preferred speed had the same patterns as T25FW at brisk speed).

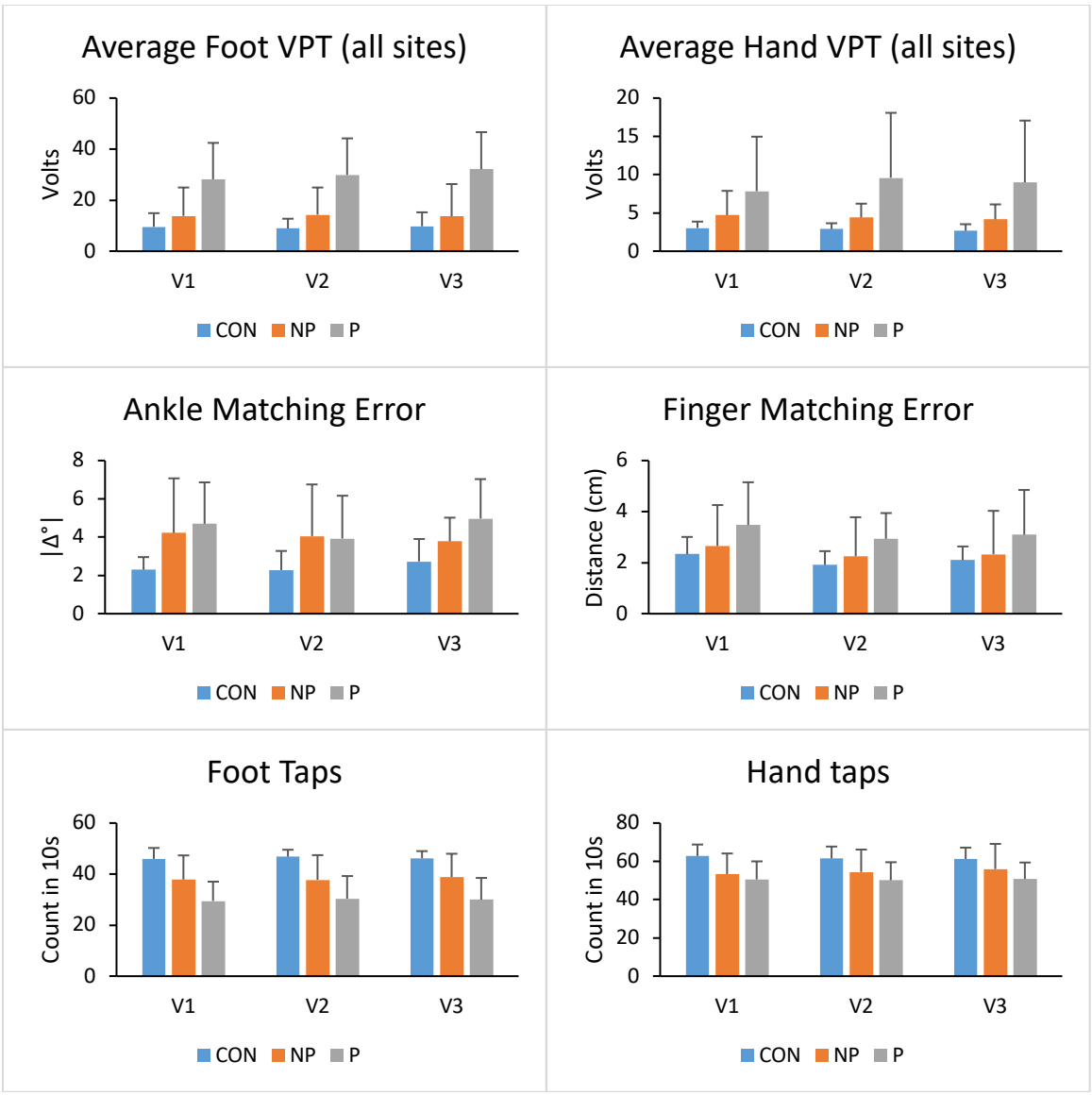

Figure 7. Group differences across all three visits for the upper- and lower-extremity sensorimotor function variables. CON: non-MS control group; NP: Relapsing-remitting or non-progressive MS group; P: Progressive MS group.

3.2.5 Analysis of Change from Baseline to Follow-ups at 12 and 24 months

Change from baseline to follow-up at 12 months

The main change occurred in the PMS group, were overall the cutaneous sensitivity in the hand decreased (threshold increased) from baseline to V2 (p=0.020; mean change 1.39V; 95% CI [0.23,2.55]; see Figure 9). No changes in hand VPT were observed in the RRMS group. Interestingly, mobility in the RRMS group improved as shown by faster walk and TUG times: for TUG (p=.019, mean change -3.33s, CI=[-2.796,-0.279] and T25FW tests (preferred p=.035, mean change -2.36s, 95% CI=[-2.08,-0.08], brisk p=.032, mean change -2.32s, 95% CI=[-2.00,-0.09]); no mobility changes were observed in the PMS group at V2 (see Figure 11).

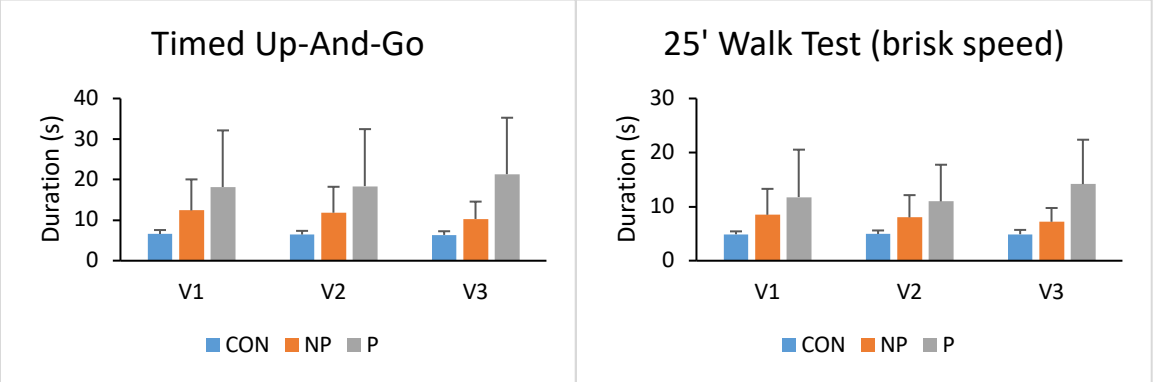

Figure 8. Group differences across all three visits for mobility variables. CON: non-MS control group; NP: Relapsing-remitting or non-progressive MS group; P: Progressive MS group.

Change from Follow-up at 12 to 24 months

No changes were observed in the RRMS group. For the PMS group there was a decrease in the VPT in the foot (p=.04, mean change 3.57V, 95% CI=[0.164,7.24]; Figure 10). There was also a decrease in walk time for the T25FW at brisk pace (p=.020, mean change 1.77s, 95% CI=[0.31,3.23]; see Figure 11).

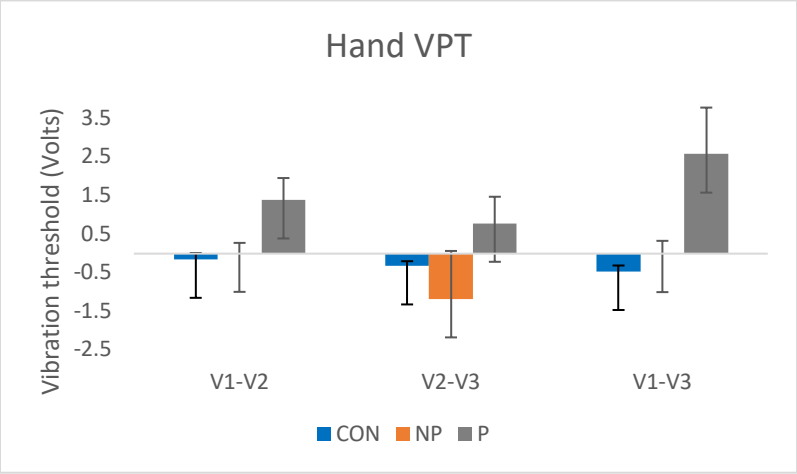

Figure 9. Change from baseline (V1) to V2 (12 month) and V3 (24 month) follow-ups for hand vibration perception threshold (VPT). Positive values indicate increase in vibration threshold and reduced cutaneous sensitivity. CON: non-MS control group; NP: Relapsing-remitting or non-progressive MS group; P: Progressive MS group.

Change from baseline to follow-up at 24 months

No changes were observed in the RRMS group. For the PMS group there was decrease in foot and hand sensitivity (increases thresholds): foot VPT (p=.055, mean change 5.08V, 95% CI=[-0.13,10.29], hand VPT (p=.041, mean change 2.58V, 95% CI=[0.12,5.04]. There also was a trend for decreased TUG ([=.063) and T25FW brisk (p=.080) walk times in the PMS group (see Figures 9-11).

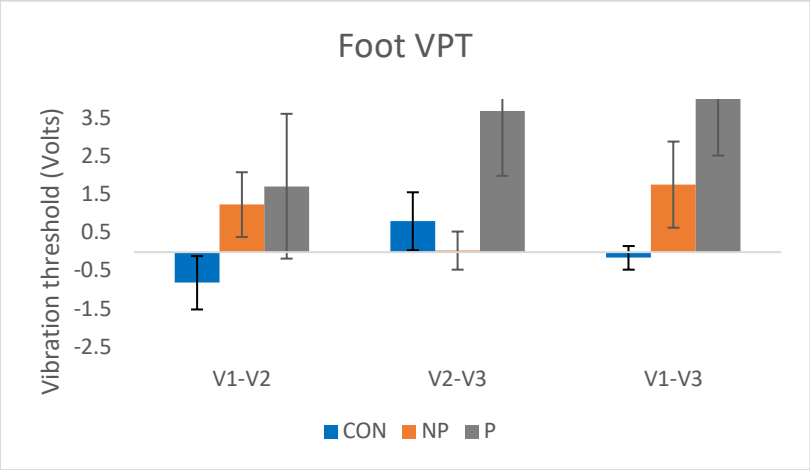

Figure 10. Change from baseline (V1) to V2 (12 month) and V3 (24 month) follow-ups for foot vibration perception threshold (VPT). Positive values indicate increase in vibration threshold and reduced cutaneous sensitivity. CON: non-MS control group; NP: Relapsing-remitting or non-progressive MS group; P: Progressive MS group.

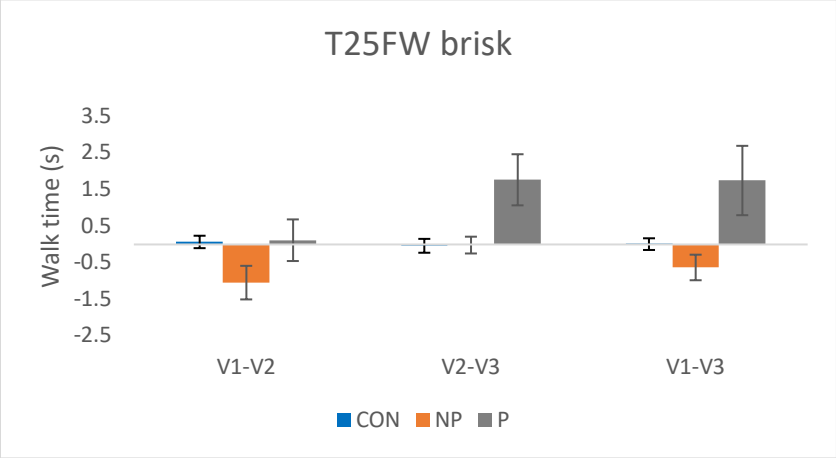

Figure 11. Change from baseline (V1) to V2 (12 month) and V3 (24 month) follow-ups for Times 25 foot walk test (brisk). Positive values indicate increase in walk time and reduced performance on the T25FW test. CON: non-MS control group; NP: Relapsing-remitting or non-progressive MS group; P: Progressive MS group.

3.2.6 Summary of main results

Before summarizing the main results, an important highlight is the overall consistency in the reported differences between the groups across the three measurements in this study, baseline, visit 2 at 12 months follow-up and visit 3 at 24 months follow-up (see Figure 7).

Group comparisons at three visits

Overall our results demonstrate differences in sensorimotor function between healthy 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; while no differences existed between MS groups during the baseline and 12-month follow-up at visit 2, at the 2nd follow-up 24 months later the PMS and RRMS differed, with reduced proprioceptive function for the PMS group. Whether or not this difference at visit 3 is due to dropouts or points at a real change is currently under investigation. Upper arm (i.e., finger matching) proprioceptive function showed systematic declines (greater error) from non-MS controls to RRMS to PMS (see Figure 7). 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 assessments of both upper- and lower-extremity sensorimotor variables are important in assessing differences between RRMS and PMS subtypes.

Analysis of Change from Baseline to Follow-ups at 12 and 24 months
The main result is that changes were observed in the PMS but not in the RRMS group. The changes in the PMS group were mainly observed for cutaneous sensitivity and mobility. The PMS group reduced cutaneous sensitivity in the hand from baseline to 12-month follow-up and for the foot from 12 to 24 month follow-up. Therefore, over the 2-year period both hand and foot cutaneous sensitivity decreased (VPT increased). Finally, although no mobility changes were observed in the RRMS group, for the PMS groups there was a significant decrease in walk times during the brisk T25FW test after 24 months. These findings suggest that of all the sensorimotor function measures the cutaneous sensitivity as measured through vibration tests may be most sensitive in detecting changes due to disease progression. In addition, these changes are most clearly documented through the assessment of the timed 25 foot walk test at a brisk pace for those people with progressive MS that are independently mobile.

3.2.7 Ongoing analyses and plans for papers

Logistic regression and classification of MS subtypes
To complement the group comparisons in our MS baseline paper (Miehm et al., 2020; MSJ: ETC), 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. We are currently performing the logistic regression analysis on the entire sample, including baseline and follow-up visits at 12 and 24 months. The results of this analysis will inform us which sensorimotor variables or combination of these variables are best at classifying the MS subtypes.

Assessment of change in individual participants and transitions MS subtypes
This analysis will focus on identifying patterns of change in individual participants and identification of transition from relapsing-remitting MS to secondary progressive MS. We will also relate subject-specific patterns of change to other clinical data such as EDSS and MRI.

Assessment of changes in mobility in MS subtypes
This analysis assesses how walking performance change over a 1-year time period in relapsing-remitting (RRMS) and progressive MS (PMS) subtypes. So far we have focused in our analyses on walk time changes during the T25FW and TUG tests, but here we will perform a detailed analysis of the changes in locomotor stride parameters and variables that relate to gait stability. The paper resulting from this analysis will be submitted to the premier journal in this area, *Gait & Posture*.

3.3 Opportunities for training and professional development

In the first year the project offered training opportunities for 1 postdoctoral fellow, 2 graduate research assistants at UMass Amherst, and one physician in training in the MS center at UMass Worcester. In the 2nd year of the project we offered training opportunities for 4 graduate research assistants and 3 undergraduate students at UMass Amherst, as well as one physician in training in the MS center at UMass Worcester. The research also formed the foundation for a Master's thesis by a graduate student and research assistant on the project (Jules Miehm). In the 3rd year of the project we offered training opportunities for 3 graduate research assistants and 3 undergraduate students at UMass Amherst, as well as one physician in training in the MS center at UMass Worcester. The postdoctoral fellow was Dr. Jongil lim; the four graduate students were: Jules Miehm, Sumire Sato, Julianna Averill and Caitlin Rajala. The three undergraduate students were: Megan Kelly, Maayan Landy, and Niya Bhatt. The physician in training at the UMass Worcester MS center was Farnaz Khalighinejad.

3.4 Dissemination of results

The results of this project have been disseminated across a wide variety of communities. These included professional societies in the area of Exercise Science and Kinesiology (American College of Sports Medicine; ACSM; American Society of Biomechanics; ASB), the European Consortium for Research and Treatment in MS (ECTRIMS), the Consortium of Multiple Sclerosis Centers (CMSC), and Consortium on Gait and Balance in MS, Society for Neuroscience annual meeting (see publications in section 6.1)

4. Impact

4.1 Impact on development of principal discipline

The data obtained from this project so far will have significant impact on our understanding of sensorimotor function changes in people with progressive MS and how these relate to those diagnosed with relapsing-remitting MS (non-progressive). The major findings of the baseline assessment have been published in two major journals in the field of MS, and a third is currently finalized for submission to the *Archives of Physical Medicine and Rehabilitation.* We are currently preparing a paper detailing the longitudinal changes from baseline to 12- and 24-month follow-up visits and this paper will be submitted to the *Multiple Sclerosis Journal*.

4.2 Impact on other disciplines

Noting to report

4.3 Impact on technology transfer

Noting to report

4.4 Impact on society beyond science and technology

The data from this research are anticipated to impact the nature of physical rehabilitation programs in MS, as well as providing a more sensitive measure to assess changes in MS disease course.

5. Changes/Problems

5.1 Changes in approach and reasons for change

In the first reporting period, because of the greater than anticipated complexity of scheduling and in order to maintain consistent and optimal points of measurements, we requested that the number of scheduled assessment of the MS participants be changed from 5 to 3 visits (from 6-month to 12-month intervals). This request was approved by our Scientific Officer Dr. Amie Bunker on 9/21/2017. This modification did not change the scope of the project and does not impact our ability to address Aim 2 in the proposal. The benefits of this modification were reported in the previous annual reports.

In the previous 2nd annual report, we noted that the 2nd follow-up assessment was scheduled to start for both MS groups in early 2019 with control group testing following that. The scheduling was anticipated to be tight regarding the 2nd follow-up as the project formally ended on 8/31/19. We therefore request a no-cost extension, and were granted that extension until 8/31//20, to adequately complete all data collection and analyses of the 2nd follow-up.

5.3 Significant changes in use or care in human subjects
None

6. Products

6.1 Publications

Journal papers (see Appendix 1 & 2)

Sato, S., Lim, J., Miehm, J.D., Buonaccorsi, J., Rajala, C., Kent, J.A., Ionete, C., Van Emmerik, R.E.A. (2020). Rapid foot-tapping but not hand-tapping ability is different between Relapsing-Remitting and Progressive Multiple Sclerosis. *Multiple Sclerosis and Related disorders*, *41, 102031.*

Miehm, J.D, Buonaccorsi, J., Lim, J., Sato, S., Rajala, C., Averill, J., Khalighinejad, F., Ionete, C., Jones, S.A., Kent, J.A., Van Emmerik R.E.A (2020). Sensorimotor Function in Progressive Multiple Sclerosis. *Multiple Sclerosis Journal- Experimental, Translational and Clinical, 6(3), 2055217320934835.*

Sumire Sato, John Buonaccorsi, Jules D. Miehm, Jongil Lim, Caitlin Rajala, Farnaz Khalighinejad, Carolina Ionete, Jane A. Kent, Richard E.A. van Emmerik (2020). Relationship between non-ambulatory sensorimotor function and clinical walking measures in multiple sclerosis subtypes. To be submitted to *Archives of Physical Medicine and Rehabilitation* 12/15/20.

Presentations

Miehm, J.D., Averill, J.L., Lim, J., Buonaccorsi, J., Kent, J.A., van Emmerik, R. Effects of Multiple Sclerosis Sub-Type On Lower-Limb Sensorimotor Function and Mobility. Free communication/slide session at New England American College of Sports Medicine Fall Conference, Providence, RI, October 2017.

Miehm, J.D., Sato, S., Lim, J., Rajala, C., Kelly, M., Averill, J.L., Ionete, C., Buonaccorsi, J., Van Emmerik, R.E.A., Kent, J.A. Vibration Sensitivity and Foot-Tapping Distinguish Non-Progressive from Progressive Multiple Sclerosis in the Absence of Overt Gait Differences. Poster Presentation at 8th International Symposium on Gait and Balance in Multiple Sclerosis, Portland, OR. September 2018.

Miehm, J.D., Averill J.L., Lim, J. Buonaccorsi, J., Ionete, C., Kent, J.A., van Emmerik, R. Lower-Extremity Vibration Threshold, But Not Proprioception or Mobility, Distinguishes Non-Progressive from Progressive Multiple Sclerosis Sub-Types. Free communication/slide session at the 2018 Annual Meeting, World Congress on Exercise is Medicine, and World Congress on the Basic Science of Muscle Hypertrophy and Atrophy of the ACSM, Minneapolis, MN. June 2018. Med Sci Sports Exerc. 2018; 50(5).

Sato, S., Lim J., Miehm, JD., Averill, JL., Rajala, C., Buonaccorsi, J., Kent, JA., Ionete, C., van Emmerik, REA. (2018). Rapid foot-tapping but not hand-tapping ability distinguishes between Multiple Sclerosis subtypes. European Committee for Treatment and Research in Multiple Sclerosis, Berlin, Germany. October 10-12 2018.

Sato, S., Lim J., Miehm, JD., Averill, JL., Buonaccorsi, J., Kent, JA., Ionete, C., van Emmerik, REA. (2018). Rapid foot tapping ability distinguishes between Multiple Sclerosis sub-types and is associated with mobility function. Annual meeting of the Consortium of Multiple Sclerosis Centers (CMSC), Nashville, TN, May 30- June 1st 2018.

Miehm, JD., Sato, S. , Rajala, C. , Lim, J., Averill, JL., Buonaccorsi, J., Khalighinejad, F., Ionete, C., Kent, JA., Van Emmerik R.E.A. Progressive Vs. Relapsing-Remitting Multiple Sclerosis:

Sensorimotor Function is Affected Differently in Upper and Lower Extremities. 2019 meeting of the Consortium of Multiple Sclerosis Centers (CMSC), Seattle, Washington 5/28/19 – 6/1/19.

Sato S, Miehm JD, Buonaccorsi J, Rajala C, Lim J, Khalighinejad F, Ionete C, Kent JA, van Emmerik REA (2020) Foot-tapping ability is associated with walking ability in relapsing-remitting and progressive multiple sclerosis (4578). Neurology 94:4578.
Paper was to be presented at the American Academy of Neurology Annual Meeting, April 25 to May 1, 2020 in Toronto Canada, but cancelled due to COVID-19.

Jules D. Miehm, Sumire Sato, John Buonaccorsi, Caitlin Rajala, Jongil Lim, Farnaz Khalighinejad, Carolina Ionete, Richard van Emmerik, Jane A. Kent, FACSM. Longitudinal Changes in Sensorimotor and Mobility Function in People with Progressive Multiple Sclerosis. 2020 Annual meeting of the American College of Sports Medicine, San Francisco, California. Cancelled due to COVID-19. Published in the June supplement of *Medicine and Science in Sports and Exercise* (MSSE) journal.

Sumire Sato, Yeun Hiro, Danielle Zoppo, John Buonaccorsi, Jules D. Miehm, Caitlin Rajala, Jongil Lim, Jane A. Kent, Richard E.A. van Emmerik (2020). Spatiotemporal gait characteristics in multiple sclerosis subtypes during brisk walking. Presented at the (virtual) meeting of the American Society of Biomechanics, August 4-7.

Published Conference Abstracts

Miehm, J.D., Sato, S., Lim, J., Rajala, C., Kelly, M., Averill, J.L., Ionete, C., Buonaccorsi, J., Van Emmerik, R.E.A., Kent, J.A. Vibration Sensitivity and Rapid Foot-Tapping Distinguish Non-Progressive from Progressive Multiple Sclerosis in the Absence of Overt Gait Differences. International Journal of MS Care. 2018.

Miehm, J.D., Averill J.L., Lim, J. Buonaccorsi, J., Ionete, C., Kent, J.A., van Emmerik, R. Lower-Extremity Vibration Threshold, But Not Proprioception or Mobility, Distinguishes Non-Progressive from Progressive Multiple Sclerosis Sub-Types. Med Sci Sports Exerc. 2018; 50(5S); 622.

Sato, S., Lim J., Miehm, JD., Averill, JL., Buonaccorsi, J., Kent, JA., Ionete, C., van Emmerik, REA. (2018). Rapid foot tapping ability distinguishes between Multiple Sclerosis sub-types and is associated with mobility function. International Journal of MS Care: Vol. 20, No. s1, pp. 86-87.
Miehm, J.D., Sato, S., Lim, J., Rajala, C., Kelly, M., Averill, J.L., Ionete, C., Buonaccorsi, J., Van Emmerik, R.E.A., Kent, J.A. Vibration Sensitivity and Rapid Foot-Tapping Distinguish Non-Progressive from Progressive Multiple Sclerosis in the Absence of Overt Gait Differences. International Journal of MS Care. 2018.

Miehm, J.D., Averill J.L., Lim, J. Buonaccorsi, J., Ionete, C., Kent, J.A., van Emmerik, R. Lower-Extremity Vibration Threshold, But Not Proprioception or Mobility, Distinguishes Non-

Progressive from Progressive Multiple Sclerosis Sub-Types. Med Sci Sports Exerc. 2018; 50(5S); 622.

Sato, S., Lim J., Miehm, JD., Averill, JL., Buonaccorsi, J., Kent, JA., Ionete, C., van Emmerik, REA. (2018). Rapid foot tapping ability distinguishes between Multiple Sclerosis sub-types and is associated with mobility function. International Journal of MS Care: Vol. 20, No. s1, pp. 86-87.

Undergraduate Students Conference Presentations

Kelly, M.A., Miehm, J.D., Sato, S., Averill, J.L., Lim, J., Buonaccorsi, J., Ionete, C., Van Emmerik, R., Kent, J.A. Plantar Cutaneous Vibration Perception Threshold Asymmetry in People with Non-Progressive and Progressive Multiple Sclerosis. Platform presentation at the Annual Massachusetts Undergraduate Research Conference, Amherst, MA. April 2018.

Landy, M., Bhatt, N., Sato, S., van Emmerik, R.E.A. (April 2019). Comparison of sway angle and velocity during static balance tests between Multiple Sclerosis sub-types. *25th Massachusetts Undergraduate Research Conference*, Amherst, MA USA.

6.2 Websites
Nothing to report

6.3 Technologies or techniques
Nothing to report

6.4 Inventions, patent application, and/or licenses
Nothing to report

6.5 Other Products
Nothing to report

7. Participants and other Collaborating Organizations

7.1 Individuals who worked on the project

Name	Jules Miehm
Project Role	Graduate Student
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Data collection at UMass Worcester and UMass Amherst; MS patient and Control group data and management; conference presentations; preparation of papers.
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

Name	Sumire Sato
Project Role	Graduate Student

Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Data collection at UMass Worcester and UMass Amherst; MS patient and Control group data and management' conference presentations; preparation of papers.
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

Name	Caitlin Rajala
Project Role	Graduate Student
Researcher Identifier (ORCID ID)	
Nearest person month worked	no change
Contribution to project	Data collection at UMass Worcester and UMass Amherst; MS patient and Control group data and management
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

Name	Jane Kent, Ph.D.
Project Role	Co-investigator
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Participation in weekly team meetings and meetings with UMass Worcester investigators and overall advice regarding design and procedures of the MS neuromotor test.
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

Name	John Buonaccorsi, Ph.D.
Project Role	Co-investigator
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Design of the experiments and statistical analyses
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

Name	Richard van Emmerik, Ph.D.
Project Role	Principle Investigator
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Overall direction and management of project and Research Fellow and graduate students. Responsible for IRB submissions and communications and interactions/meetings with UMass Worcester staff
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

Name	Carolina Ionete, M.D.; Ph.D.
Project Role	Co-investigator; Clinical Neurologist MS Clinic UMass Worcester
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Patient recruitment, selection and clinical assessments

Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

Name	Melissa Adams,
Project Role	Clinical Research Coordinator MS Clinic UMass Worcester
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Regulatory and IRB support
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

Name	Farnaz Khalighinejad
Project Role	Clinical Research Coordinator MS Clinic UMass Worcester; clinical data entry/management
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Scheduling and organization of MS participants at UMass MS Clinic in Worcester; recruitment
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351
Name	Jongil Lim, Ph.D.
Project Role	Postdoctoral Research Fellow
Nearest person month worked	No change
Contribution to project	Dr. Lim was responsible for overseeing equipment, data collection at UMass Worcester and UMass Amherst, development of data analytic procedures and daily management of the project.
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351
Name	Carolyn Griffin, RN
Project Role	Clinical Research Coordinator MS Clinic UMass Worcester
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Scheduling and organization of MS participants at UMass MS Clinic in Worcester; recruitment
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351
Name	Julianna Averill, M.S.
Project Role	Graduate Student
Researcher Identifier (ORCID ID)	
Nearest person month worked	No change
Contribution to project	Data collection at UMass Worcester and UMass Amherst; acted as main liaison and logistics person between the two institutions related to patient recruitment and care
Funding Support	CDMRP – MSRP Award number W81XWH-16-1-0351

7.2 Change in active support for PI and other personnel

Nothing to report

7.3 Other organizations
Both Umass Amherst and Umass Worcester are involved in this project. See section 7.1 for complete personnel listing

8. Special Reporting requirements

N/A

9. Appendices

Appendix 1: Miehm et al. paper in *Multiple Sclerosis Journal- Experimental, Translational and Clinical*
Appendix 2: Sato et al. paper in *Multiple Sclerosis and Related disorders*

MSJ Experimental Translational Clinical

Original Research Paper

Sensorimotor function in progressive multiple sclerosis

Multiple Sclerosis Journal — Experimental, Translational and Clinical

July–September 2020, 1–10

DOI: 10.1177/2055217320934835

Jules D Miehm, John Buonaccorsi, Jongil Lim, Sumire Sato, Caitlin Rajala, Julianna Averill, Farnaz Khalighinejad, Carolina Ionete, Stephanie L Jones, Jane A Kent and Richard EA van Emmerik

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

Date received: 22 January 2020; accepted: 24 May 2020

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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Stephanie L Jones,
Department of Exercise and Sport Studies, Smith College, USA

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Department of Kinesiology, University of Massachusetts Amherst, USA

Richard EA van Emmerik ,
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Neuroscience and Behavior Program, University of Massachusetts Amherst, USA

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

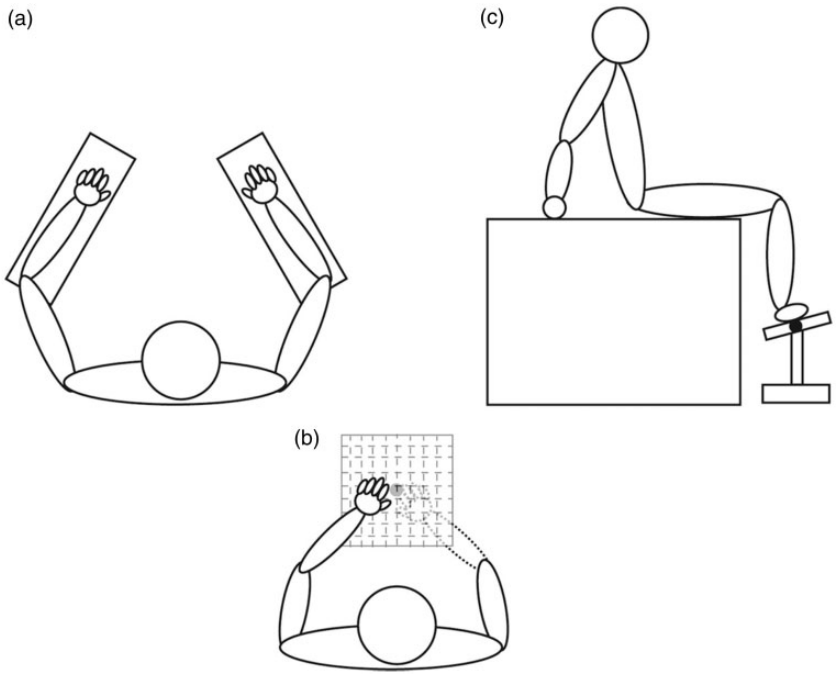

Figure 1. Set-up of proprioceptive matching tasks. (a)–(c) Schematics of upper (a) and (b) and lower-extremity proprioception (c) during a joint position-matching task at the elbow (a) and ankle (c) and a whole upper-limb-matching task using a target grid and matching with the index finger (b). For elbow-matching (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.

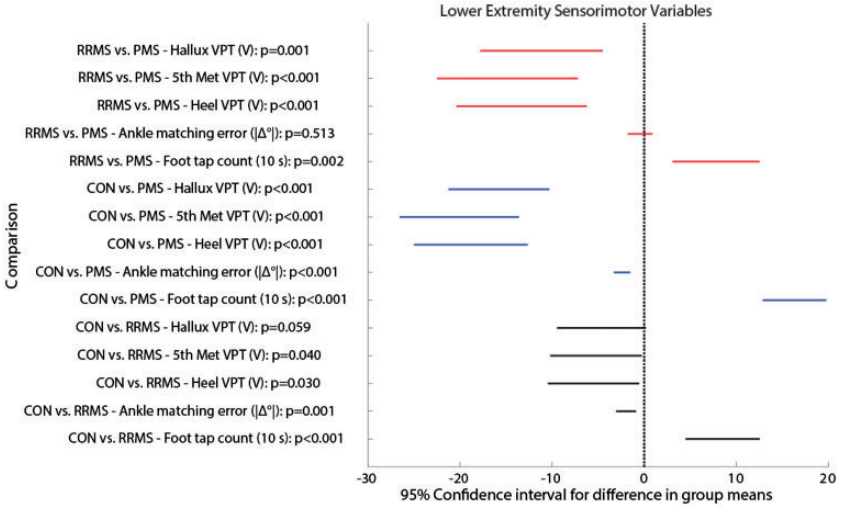

Figure 2. Analysis of differences in group means for the lower extremity sensorimotor variables. RRMS: relapsing–remitting multiple sclerosis; PMS: progressive multiple sclerosis; CON: non-multiple sclerosis control group; VPT: vibration perception threshold; Met: metatarsal. Lines that do not cross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

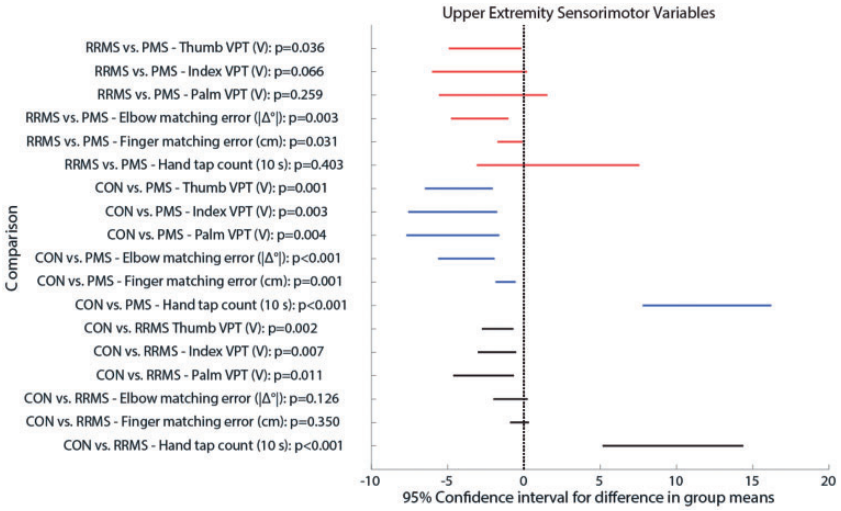

Figure 3. Analysis of differences in group means for the upper extremity sensorimotor variables. RRMS: relapsing–remitting multiple sclerosis; PMS: progressive multiple sclerosis; CON: non-multiple sclerosis control group; VPT: vibration perception threshold; Met: metatarsal. Lines that do not cross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

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publicationof this article.

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Supplemental Material

Supplemental material for this article is available online.

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Original article

Rapid foot-tapping but not hand-tapping ability is different between relapsing-remitting and progressive multiple sclerosis

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ABSTRACT

Background: Rapid tapping tests have been shown to be reliable measures of upper motor neuron disease, and effectively examine motor function differences between multiple sclerosis (MS) and non-MS controls (CON), and between relapsing-remitting and progressive MS subtypes. To successfully perform rapid repetitive movements such as tapping, a person must be able to consistently turn on and off motor units to switch between the up and down movement phases. However, it is not clear which specific movement phase that occurs during tapping is different between MS subtypes. The objective of this study was to quantify and characterize performance differences during rapid hand- and foot-tapping tests between relapsing-remitting (RRMS) and progressive (PMS) forms of MS, as well as how both subtypes differ from non-MS controls.

Methods: Participants in this study included 30 non-MS controls, 32 RRMS, and 31 PMS. Participants wore inertial sensors on all hands and feet and were instructed to tap as fast as possible for 10 s. Angular velocity from the gyroscope was used to quantify inter-tap interval (ms), coefficient of variation of inter-tap interval (COV), and up- and down-movement characteristics (duration (ms), COV, peak angular velocity (rad/s)). Differences between groups were examined with ANOVA and independent t-tests. Inter-tap interval was examined for its ability to distinguish between RRMS and PMS by a binary logistic regression analysis. Up-down movement characteristics were further evaluated for within-group directional differences (up- vs. down-phase movement components) with paired-sample t-tests.

Results: Inter-tap interval for both hand- and foot-tapping differed between controls and MS, but only foot tapping was different between RRMS and PMS (RRMS = 286.7 ± 83.0 ms; PMS = 379.5 ± 170.9 ms; mean difference (d) = -92.8 ms). Logistic regression analysis showed foot-tap interval but not hand-tap interval has the potential to distinguish between RRMS and PMS (Area under the ROC = 0.71). Both up- and down-movement duration differences were consistent with the results for inter-tap interval, but up-movement duration showed larger mean group differences than down-movement differences. No significant group differences in overall inter-tap interval COV were detected for either hand- or foot-tapping; however, up-movement foot-tapping variation (CON = 18.7 ± 6.1; RRMS = 25.5 ± 11.2; PMS = 23.3 ± 8.6; CON vs RRMS d = -6.8; CON vs PMS d = -4.7), but not down-movement variation was different between controls and MS. Up- and down-peak angular velocity during foot-tapping were different between controls and PMS (CON Up = 1.4 ± 0.5 rad/s; PMS Up = 1.0 ± 0.4 rad/s; Up d = 0.4 rad/s; CON Down = 1.5 ± 0.6 rad/s; PMS Down = 1.2 ± 0.5 rad/s; Down d = 0.3 rad/s), and up-movement peak angular velocity differences showed larger mean group differences than the down-movement peak angular velocity between controls and PMS.

Conclusion: Foot-tapping differs between MS disease subtypes and has greater potential than hand-tapping to distinguish between subtypes. Performance in the up-movement showed larger group differences than the down-movement, suggesting that the anti-gravity up-movement during tapping may be more important diagnostically. Future studies should be conducted on the nature of the physiological mechanisms underlying impairments in anti-gravity movements in people with MS.

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1. Introduction

Multiple sclerosis (MS) typically begins in early adulthood and is the second most frequent cause of disability in young adults (Adelman et al., 2013). Clinical features of MS vary between patients, but the overall clinical course of the disease can be categorized into relapsing-remitting MS (RRMS) and progressive MS (PMS). RRMS is characterized by exacerbations of neurological dysfunction with full recovery or residual deficit upon recovery (Lublin et al., 2014). PMS can be further classified into primary and secondary progressive MS. Primary progressive MS is characterized by the accumulation of disability over time, while secondary progressive MS patients start from a RRMS disease course followed by gradual transition into accumulating disability (Koch et al., 2010). Both progressive subtypes show an accumulation of disability without recovery to baseline, are associated with increased disability, and are treated with different medications compared to RRMS (Rae-Grant et al., 2018a). Breakthroughs in medicine have identified treatments that are able to decrease relapse rate or slow accumulation of MRI lesions (Montalban et al., 2018; Rae-Grant et al., 2018b), but there is still a lack of treatment options to prevent disability worsening (Mulero et al., 2018). To effectively address this treatment gap, it is important to characterize differences in MS subtypes for a future diagnostic test that can correctly identify MS disease course for each individual (Bitsch and Bruck, 2002; Rae-Grant et al., 2018a).

Rapid upper and lower extremity tapping tasks involve the corticospinal tract, and cerebellar and sensory pathways (Campbell and DeJong, 2013). Tapping tasks have been shown to be a reliable measure of upper motor neuron disease burden (Kent-Braun et al., 1998; Shirani et al., 2017) and corticospinal impairments (Appasamy et al., 2018; Maher et al., 1992; Miller and Johnston, 2005; Mitsumoto et al., 2007; Van Gijn and Bonke, 1977), and are currently a common component of the bedside neurologic exam. In regards to MS, tapping ability has also been shown to be different between MS subtypes and healthy controls (Bonzano et al., 2013; Tanigawa et al., 2017), and correlated to MS disease progression (Tanigawa et al., 2017). However, it is not clear which specific movement phase that occurs during tapping is different between MS subtypes.

For successful rapid, repetitive, and alternating movements, a person must be able to make consistent changes in movement. Variability in movement patterns may help quantify the quality of the movement (Konig et al., 2016). To our knowledge, no studies have explored the effects of MS on tapping consistency. However, it has been shown that compared to healthy controls, there is an increased variability in hand-tapping in patients with Parkinson's disease (Luft et al., 2019) and Essential tremor (a type of action tremor) (Farkas et al., 2006; Luft et al., 2019). By identifying group differences in variation in inter-tap interval, we may be able to infer differences in quality of tapping in MS populations. Measurements of movement quality may be more sensitive than mobility differences and may have the potential to be utilized to track functional disability status in MS patients.

In addition to consistency, faster tapping depends on the capacity for fast recruitment and de-recruitment of motor units of agonist and antagonist muscles (Desmedt and Godaux, 1978; Wakeling et al., 2011). In MS, the rapid-alternating up-down movements may be affected by impaired motor unit recruitment and rate coding due to demyelination and axonal loss, and/or the decreased ability to control the activation and deactivation of muscles due to spasticity (Ng et al., 2004). Spasticity most often affects anti-gravity muscles, causing uneven stiffness between the agonist and antagonist muscle groups (Brown, 1994; Dietz and Sinkjaer, 2012; Haselkorn and Loomis, 2005). By parsing out the effects of MS on duration and peak velocity achieved during the up- and down-phases, we may be able to identify whether tapping performance in MS is affected differently in anti-gravity movements.

The objective of this study was to examine whether rapid hand- or foot-tapping performance measured from inertial sensors is different between RRMS and PMS and from non-MS controls. Our specific research aims were: (1a) to determine whether there are group differences between RRMS, PMS, and non-MS controls in inter-tap interval duration (i.e., tap *ability*) and (1b) whether tapping ability is able to distinguish between RRMS and PMS; (2) to determine whether groups differ in inter-tap interval coefficient of variation (i.e. tapping *consistency*); and (3) to explore whether there are differences in the up vs. down movements of tapping in the MS groups compared to controls for duration, duration variability, or peak angular velocity. We predicted: (*hypothesis 1)* that inter-tap interval would be longer in both MS groups compared to controls, and longer in PMS compared to RRMS, based on outcomes of prior studies on tap count (Shirani et al., 2017; Shribman et al., 2018; Tanigawa et al., 2017), and (*hypothesis 2)* that inter-tap variation would be greater in MS compared to controls, based on studies in other populations with CNS pathology (Farkas et al., 2006; Luft et al., 2019).

2. Materials and methods

2.1. Participants

This study is a cross-sectional design which included 32 RRMS, 31 PMS and 30 non-MS control participants. MS participants were recruited at the Multiple Sclerosis Center at University of Massachusetts Memorial Medical Center in Worcester. Inclusion criteria for the MS groups were: a definitive diagnosis of MS using the McDonald criteria (Polman et al., 2011), and ages 21 −80 years. MS subtype was classified by one experienced clinical neurologist with training in MS clinical and translational research after reviewing the medical records for each

Table 1
Participant characteristics (mean ± SD) for the participants who were included in this study. Numbers in parentheses reflect those who completed foot-tapping. Spasticity was measured by the Modified Ashworth Scale (MAS) on the biceps brachialis and tibialis anterior muscles. Participants who scored a 1+ on the MAS were scored as a 1.5. F = Female, M = Male, BMI = Body mass index, EDSS = Expanded disability status scale, UE = Upper extremity, LE = Lower extremity, NR = Not reported, NA = Not applicable.

	Controls	RRMS	PMS
n	28	29 (28)	29 (26)
Age (yrs)	55.11 ± 12.53	52.03 ± 9.94 (52.25 ± 10.06)	60.38 ± 8.32 (59.19 ± 7.69)
Sex (F:M)	23:5	26:3 (25:3)	19:10 (17:9)
BMI (kg x m^{-2})	25.3 ± 4.15	32.11 ± 6.27 (31.77 ± 6.10)	30.24 ± 7.78 (28.55 ± 4.80)
EDSS	NA	3.26 ± 2.19 (3.14 ± 2.13)	5.98 ± 1.72 (5.77 ± 1.69)
UE Spasticity	NR	0.05 ± 0.20 (0.05 ± 0.21)	0.22 ± 0.55 (0.25 ± 0.57)
LE Spasticity	NR	0.21 ± 0.45 (0.16 ± 0.39)	0.83 ± 0.99 (0.79 ± 1.00)
Disease Duration (yrs)	NA	12.75 ± 8.73 (12.48 ± 8.79(	21.85 ± 12.35 (21.69 ± 12.36)
Baclofen:No baclofen	NR	14:15 (14:14)	13:16 (12:14)
Dalfampridine:No dalfampridine	NR	0:29 (0:28)	7:22 (7:19)

patient. The control participants were approximately age- and sex-matched to the overall MS group, and were recruited at the University of Massachusetts Amherst. Some participants were not able to complete the task due to severe motor impairments or equipment malfunction. As a result, 29 RRMS, 29 PMS, and 28 controls completed the hand-tapping test, and 28 RRMS, 26 PMS, and 28 controls completed the foot-tapping test (Table 1).

Participants' written informed consent were obtained prior to the study. This study was approved by the Institutional Review Boards of the University of Massachusetts Amherst and Medical School in Worcester.

2.2. Data collection

Participants wore inertial sensors (Opal, Version 2, APDM Wearable Technologies Inc., Portland, OR) on both hands and feet (Fig. 1). Acceleration (m/s^2) and angular velocity (rad/s) signals measured from the Opal tri-axial accelerometer and gyroscope were collected at 128 Hz.

Participants were instructed to tap as fast as possible for 10 s while seated, repeated 3 times for both hands and feet. At least 1 min of rest was given between repetitions to mitigate fatigue effects. For hand-tapping, participants were instructed to tap with their whole hand, hinging at the wrist, with the forearm on the table at all times. Elbow flexion angle was self-selected by the participant. For foot-tapping, participants were instructed to tap with their toe portion with shoes on, hinging at the ankle and heel on the floor at all times. Knee flexion angle was self-selected by the participant.

2.3. Data processing

All data was processed using MATLAB (The Mathworks, Natick, MA). The gyroscope signal was de-trended and low-pass filtered at 12 Hz for hand-tapping and at 8 Hz for foot-tapping. Accelerometer data from the inertial sensors was used to detect the start of the movement (start threshold = 75% of average acceleration deflection within trial). Angular velocity from the gyroscope was used to quantify tapping interval, variability, and performance metrics (direction specific movement duration, COV, and peak angular velocity).

Bilateral average tap interval duration across a maximum of 6 trials was obtained from the number of taps over the 10-s period (see Fig. 2A). Intra-individual inter-tap variability was calculated as the coefficient of variation (COV; standard deviation/mean interval x 100) and was averaged across the left and right trials performed by that participant. Next, separation of zero-crossings into either ascending or descending angular velocities (Fig. 2A) was used to determine movement duration, variability (COV) and peak angular velocity for the up-movement and down-movement components. The bilateral average for all tapping variables was calculated and used for statistical analyses for both hand and foot tapping.

2.4. Statistical analysis

Differences in group mean in overall tap interval and COV were examined by a one-way analysis of variance (ANOVA) allowing unequal variances (Welch's test). This was accompanied by pairwise t-tests and 95% confidence intervals for differences among group means, also allowing for unequal variance (Statterthwaite's method).

For the MS groups, logistic regression was used to model the probability of group membership (RRMS or PMS) and estimate the ability to classify individuals using a cross-validation method. Since the study design had approximately equal numbers of participants in each group, a cutpoint of 0.5 was used in the classification.

For the up- and down-movement variables (duration, duration COV, and peak angular velocity), we first compared the groups for each variable in the same manner as the group comparisons for tap interval and variation described above. In addition, we compared the up- and down-movement in each group using a paired *t*-test.

We explored the effects of disease duration and age using analysis of covariance (ANCOVA).

Statistical significance was identified at $p < 0.05$. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

The 95% confidence intervals for differences between groups (CI) and p-values for pairwise comparisons are presented in the figures, and means and standard deviations for each group in the tables below.

3.1. Tap interval

There was a statistically significant group effect for average hand-tap interval ($p < 0.001$; Table 2, Fig. 3A). Post-hoc analysis showed that average hand-tap interval was significantly shorter in controls compared to RRMS and PMS subtypes, but RRMS was not different compared to PMS (Fig. 3C).

There was a statistically significant group effect for average foot-tap interval ($p < 0.001$; Table 2, Fig. 3B). Post-hoc analysis showed that average foot-tap interval was significantly shorter in controls compared to RRMS and PMS subtypes, and RRMS was significantly shorter

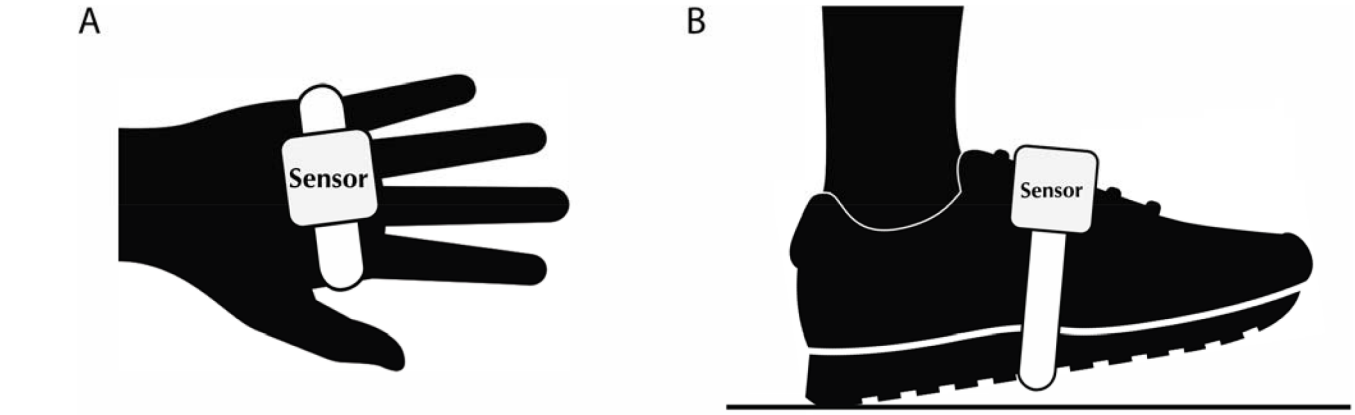

Fig. 1. *Experimental setup*. A. Inertial sensor placement on the hand. Participants wore inertial sensors on the dorsum of the hand wrapped around the 2nd to 5th metacarpal bones. B. Inertial sensor placement on the foot. Foot sensors were placed on the dorsum of the foot with the sensor display facing upwards and positioned near the center of the shoelace region. .

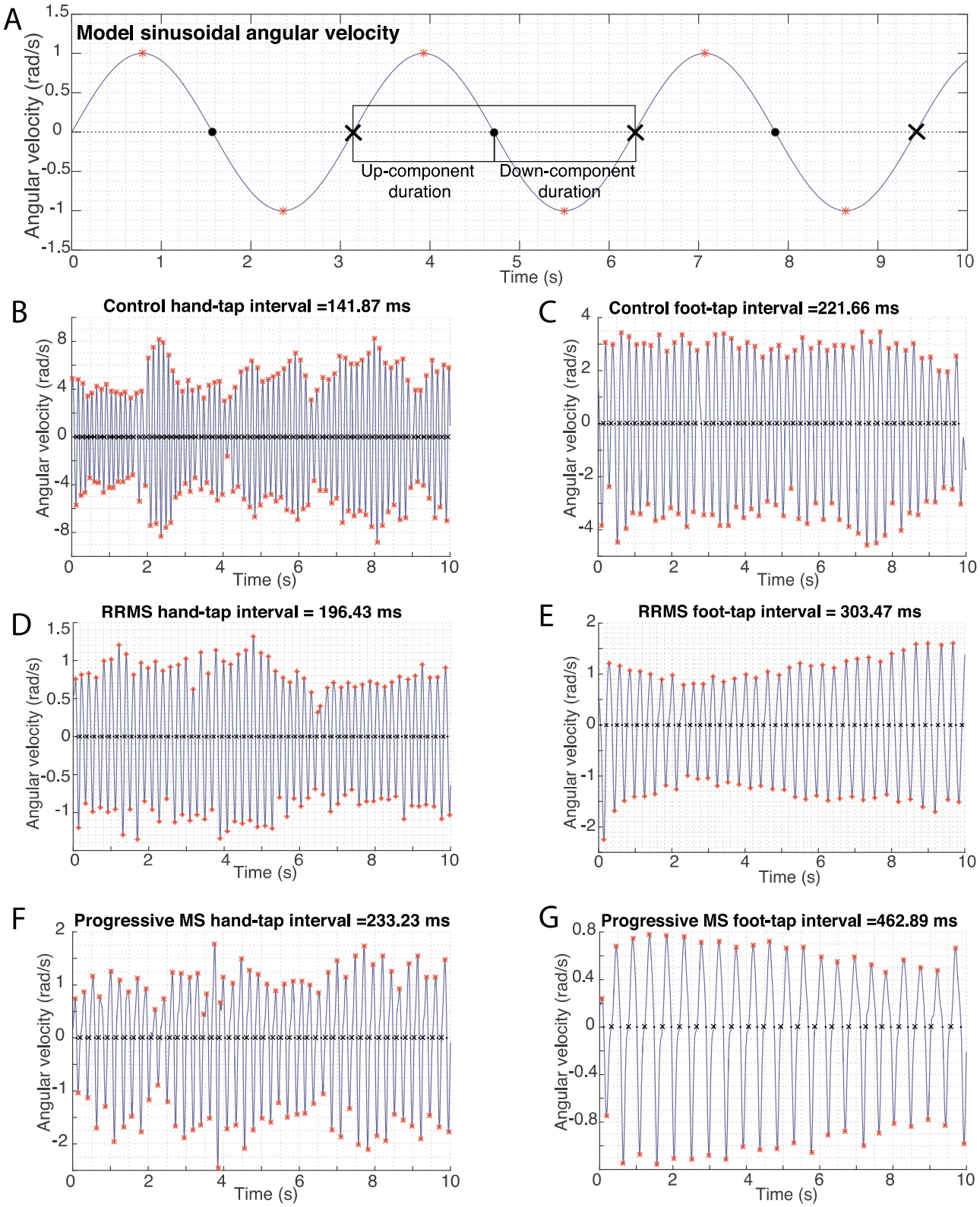

Fig. 2. *Examples of gyroscope data.* A. Model sinusoidal gyroscope plot. Black X's represent where a tap is identified, dots are where the extremity is at its top-most position. Red *'s represent peak positive and negative angular velocities during the up- and down-movement, respectively. Tap signals were cropped 10-s post start point. From the gyroscope data, all zero-crossings of angular velocity were identified to determine the number of taps. Peak positive angular velocity is the peak angular velocity achieved during the up-phase of the tap movement (i.e., lifting the foot) and peak negative angular velocity is the peak angular velocity achieved during the down-phase of the tap movement (i.e., lowering of the foot). Up-movement duration is the duration of the gravity-resisting movement phase and down-movement duration is the duration of the gravity-assisted movement phase during tapping. B-G. Example hand-tap (B, D, F) and foot-tap (C, E, G) gyroscope plots from representative control (B-C), RRMS (D-E), and PMS (F-G) participants.

Table 2
Main effect of group for one-way ANOVAs; p-value, means and standard deviation for controls, relapsing-remitting MS (RRMS), and progressive MS (PMS) for tap interval and tap interval coefficient of variation (COV).

Variable	p-value	Controls	RRMS	PMS
Hand-tap interval (ms)	< 0.001	159.29 ± 14.43	195.67 ± 43.69	202.54 ± 39.75
Foot-tap interval (ms)	< 0.001	217.53 ± 21.19	286.68 ± 83.04	379.48 ± 170.87
Hand-tap interval COV	0.192	10.84 ± 6.03	15.05 ± 10.96	12.60 ± 7.51
Foot-tap interval COV	0.250	17.46 ± 6.24	20.99 ± 9.41	19.17 ± 7.12

compared to PMS (Fig. 3C).

Consistent with the between groups analysis, foot-tap interval shows more potential for distinguishing groups, with an estimated classification rate of 61% ($p = 0.005$, AUROC = 0.71; Table 3), compared to hand-tap interval (45%, $p = 0.496$, AUROC = 0.55). Classification by foot-tap interval was more specific than sensitive (Specificity = 0.64, Sensitivity = 0.58).

3.2. Tap interval variability

There were no significant group differences in the COV for hand-tap interval ($p = 0.192$; Table 2, Fig. 4A and 4C) or foot-tap interval ($p = 0.250$; Table 2, Fig. 4B and 4C), although Fig. 4C does show the tendency for the COV to be smaller in the controls than in the RRMS group for both hand and foot-tapping (Hand: $p = 0.078$, CI = [−8.9, 0.50]; Foot: $p = 0.104$, CI = [−7.8, 0.76]).

3.3. Up- and down-movement specific variables

3.3.1. Up-and down-movement tap interval

During hand-tapping the group effect was significant for both the up- and down-movement duration (Up: $p < 0.001$; Down: $p < 0.001$; Table 4, Fig. 5A and C). Up- and down-movement duration in controls were significantly shorter compared to RRMS and PMS, but RRMS did not significantly differ from PMS (Fig. 5E). Up-phase duration was longer than down-phase duration for all groups (Table 5).

During foot-tapping the group effect was significant for both up- and down-movement duration (Up: $p < 0.001$; Down: $p < 0.001$; Table 4, Fig. 5B and D). Up- and down-movement duration in controls were significantly shorter compared to RRMS and PMS, and PMS had significantly longer durations compared to RRMS (Fig. 5E). Up-phase duration was longer than down-phase duration for the two MS subtypes but not for controls (Table 5).

3.3.2. Up- and down-movement variability

Neither the up- nor down-movement duration COV during hand-tapping was different among groups (Up: $p = 0.247$; Down: $p = 0.174$; Table 4, Fig. 6A and C). Up-movement duration COV was significantly larger than down-movement duration COV for controls and RRMS, and showed a trend in the same direction for PMS ($p = 0.069$, CI = [−0.09, 2.41]; Table 5).

During foot-tapping the up-movement ($p = 0.009$) but not the down-movement ($p = 0.478$) duration COV was different between groups (Table 4, Fig. 6B and D). Post-hoc analysis showed that up-movement COV during foot-tapping was smaller in controls compared to RRMS and PMS, but not significantly different between the two MS subtypes (Fig. 6E). Up-movement duration COV was significantly smaller compared to the down-movement in controls but not for RRMS and PMS (Table 5).

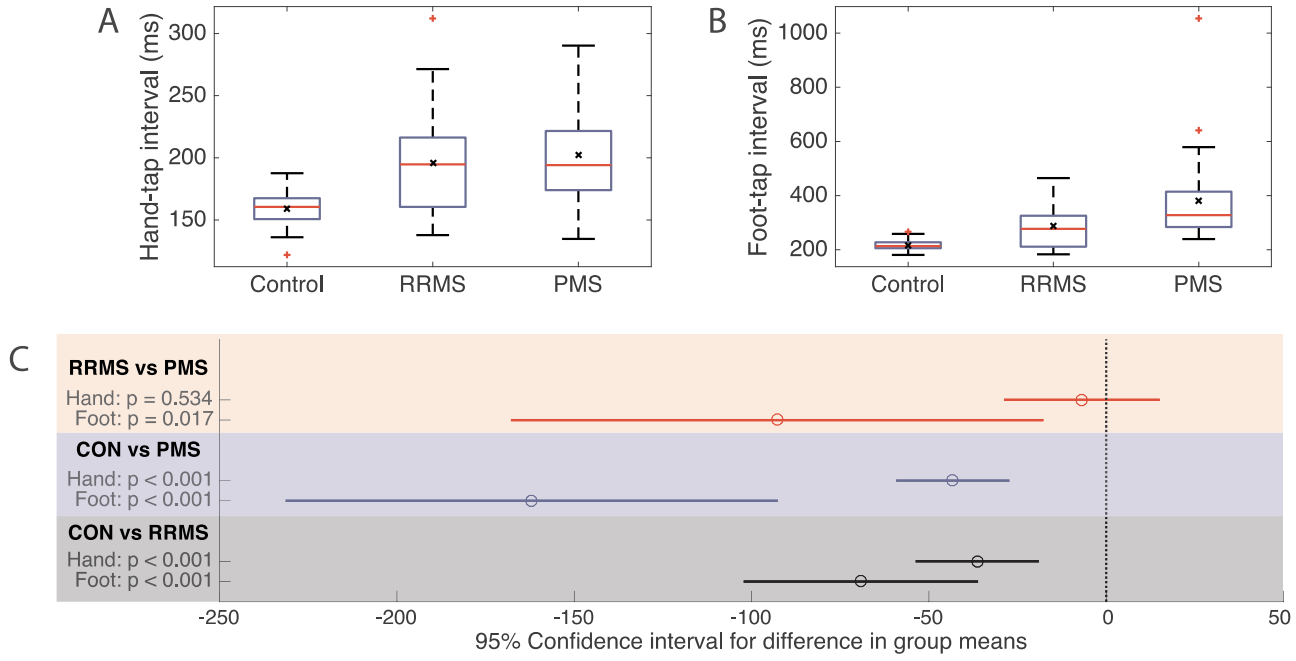

Fig. 3. *Between-group comparisons for tap interval.* A-B. Box plots of average tap interval during hand-tapping (A) and foot-tapping (B). Red line represents the median, and the black X's represent the mean for the different groups. Red crosses represent outliers. C. 95% confidence interval for the difference in group means. Red shaded area and lines represent comparisons between RRMS and PMS. Blue shaded area and lines represent comparisons between controls (CON) and PMS. Black shaded areas and lines represent comparisons between CON and RRMS. Circles on the confidence interval indicate the mean group difference.

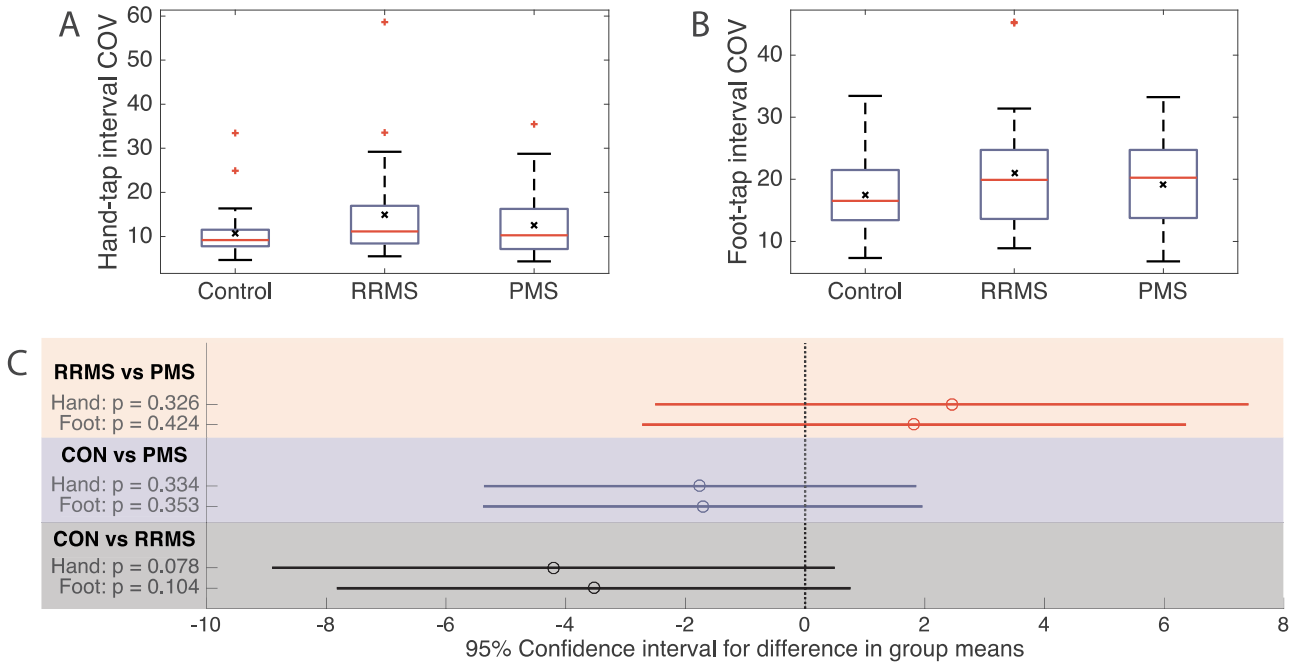

Fig. 4. *Between-group comparisons for tap interval coefficient of variation (COV).* A-B. Box plots of average tap interval COV during hand-tapping (A) and foot-tapping (B). Red line represents the median, and the black X's represent the mean for the different groups. Red crosses represent outliers. C. 95% confidence interval for the difference in group means. Red shaded area and lines represent comparisons between RRMS and PMS. Blue shaded area and lines represent comparisons between controls (CON) and PMS. Black shaded areas and lines represent comparisons between CON and RRMS. Circles on the confidence interval indicate the mean group difference.

3.3.3. Up- and down-movement peak angular velocity

During hand-tapping both up- and down-movement peak angular velocity were not different among groups (Up: $p = 0.299$; Down: $p = 0.397$; Table 4, Fig. 7A and 7C). Up-direction peak angular velocity during hand tapping was significantly slower than down-direction peak angular velocity in all three groups (Table 5).

During foot-tapping overall group differences were significantly different for up-, but not down-direction movement peak angular velocity (Up: $p = 0.011$; Down: $p = 0.106$; Table 4, Fig. 7B and D). Post-hoc analysis showed that average up-movement peak angular velocity was significantly greater in controls compared to PMS, but not different between controls and RRMS and RRMS and PMS (Fig. 7E). Although the ANOVA was nonsignificant, pairwise comparisons do suggest that down-movement peak angular velocity may be greater in controls compared to PMS ($p = 0.037$, CI = [0.02, 0.63]; Fig. 7E). Similar to hand-tapping, foot-tapping up-direction peak angular velocity was significantly slower than down-direction peak angular velocity in all groups (Table 5).

3.4. Analysis of covariance

Secondary analyses where performed using ANCOVA (after verifying common slopes to adjust for age and disease duration (Supplementary Tables 2 and 3). However, since both of these variables differ between subtypes (PMS has a longer disease duration are older compared to RRMS (Weinshenker, 1994)), and this is an observational study, the resulting analyses should not be construed as a comparison of group means adjusting for the covariate (Miller and Chapman, 2001). Rather, these results estimate and test for the difference in groups in the sense of comparing two hypothetical individuals, one in each group, with a common value of the covariate. The significances for group differences agree with the earlier analyses (estimated differences will change because of the change in the mean of the covariate between groups) except a minute disagreement for down-direction peak angular velocity between controls and progressive MS ($p = 0.058$; Supplementary Table 2; Initial analysis: $p = 0.037$, Fig. 7).

4. Discussion

We found that consistent with our hypothesis, both hand- and foot-tapping ability differed between people with MS and non-MS controls; however, only foot-tapping and not hand-tapping ability is different in participants with RRMS compared to those with PMS and able to differentiate between the two MS subtypes. Contrary to our hypothesis, overall inter-tap interval variability was not significantly different between the MS subtypes and control groups. However, the analysis of separate movement phases showed increased variability in both MS groups compared to controls for the up-movement in the foot but not hand-tapping, with no differences between MS subtypes. Peak angular foot-tapping velocity was decreased in the PMS group compared to controls in both movement phases. These results show that foot-tap ability is different between MS and controls and between MS subtypes. In addition, anti-gravity movements seem to show larger differences between groups, indicating that future research should be done on other anti-gravity movement characteristics in people with MS.

4.1. Foot-tapping may be more sensitive to group differences between RRMS and PMS compared to hand-tapping

Our results suggest that tapping ability is not affected equally in the upper and lower extremities in people with MS. Contrary to our results, a previous study by Tanigawa et al. (2017) found that both index finger and foot-tapping ability were different between RRMS and PMS but not between RRMS and controls. We did not exclude participants undergoing medical treatment or involved in clinical trials, but participants with MS in Tanigawa's study were untreated. In addition, Tanigawa et al. (2017) instructed participants to tap with only their index finger and assigned a score of zero for participants who were unable to complete the task, while we instructed participants to use their whole hand and did not include participants who were unable to complete the task, which may have produced the differences in upper-extremity tapping results.

Overall, our current results suggest that lower extremity motor

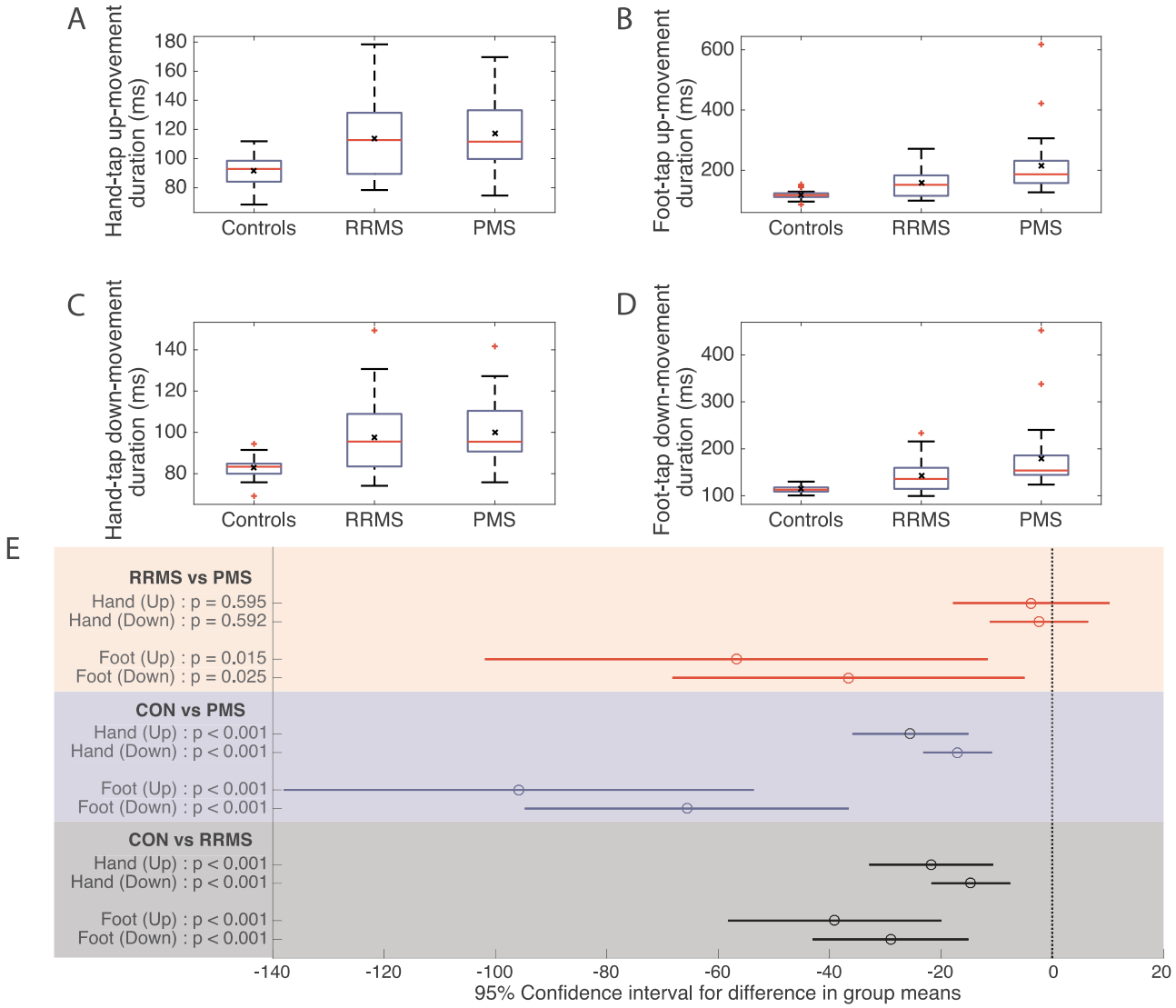

Fig. 5. *Between-group comparisons for up- and down-component duration.* A-D. Box plots of up- (A-B) and down-movement duration (C-D) during hand-tapping (A & C) and foot-tapping (B & D). Red line represents the median, and the black X's represent the mean for the different groups. Red crosses represent outliers. E. 95% confidence interval for the difference in group means for up- and down-phase peak angular velocity. Red shaded area and lines represent comparisons between RRMS and PMS. Blue shaded area and lines represent comparisons between controls (CON) and PMS. Black shaded areas and lines represent comparisons between CON and RRMS. Circles on the confidence interval indicate the mean group difference.

function measured by foot-tapping may be more sensitive to detect group differences between RRMS and PMS (regardless of treatment) compared to upper-extremity motor function. This may be due to the spinal cord syndrome that is a characteristic of primary progressive MS (Rice et al., 2013). This is consistent with our binary logistic regression results that showed foot-tap interval was more specific than sensitive (Table 3), which indicates that foot-tapping may be more useful to rule-in PMS in MS populations than to ruling-out PMS.

4.2. Variability differences in tapping performance emerged only in the up- and not the down-phase of the tapping movement

Overall variability did not differ between groups in either hand or foot-tapping, but when parsed into up- and down-movements, variability was significantly greater in the MS groups (both PMS and RRMS) compared to controls during the up-movement of foot-tapping (Fig. 6E). These results demonstrate the importance of investigating individual movement phases in addition to overall movement, as has traditionally been done in gait analysis where comparisons of MS and controls may reveal different results for swing vs. stance phase of gait (Remelius et al., 2012). Similar to our current results, people with MS may demonstrate higher variability in gait mechanics compared to controls (Crenshaw et al., 2006). However, there were no differences in variability between MS subtypes, suggesting that patients with PMS may tap slower, but the neural mechanism underlying consistency is still intact. Together, our results suggest that overall quality of movement during tapping may not be sensitive for comparisons between MS subtypes and controls, but that loss of movement consistency in MS my occur in the up-phase component where movements are performed against gravity.

4.3. Lower foot-tapping ability in MS compared to controls may largely be due to difference in the up-movement

We found that up-direction durations consistently had larger mean group differences compared to the down-direction duration, which may be due to spasticity which affects up to 80% of people with MS (Barnes et al., 2003). Muscle tone is maintained by the upper motor

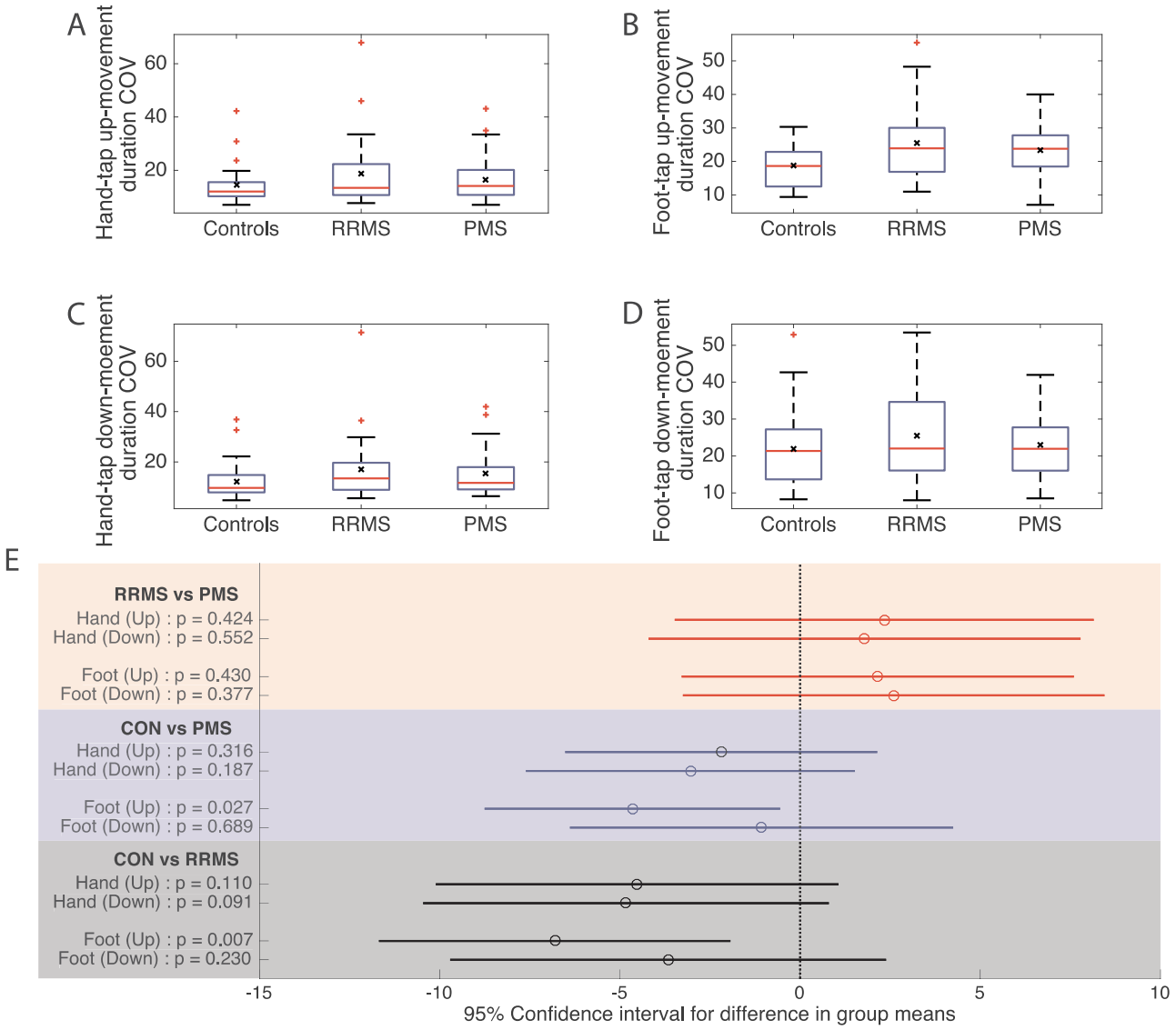

Fig. 6. *Between-group comparisons for up- and down-component duration coefficient of variation (COV).* A-D. Box plots of up- (A-B) and down-movement duration COV (C-D) during hand-tapping (A & C) and foot-tapping (B & D). Red line represents the median, and the black X's represent the mean for the different groups. Red crosses represent outliers. E. 95% confidence interval for the difference in group means for up- and down-phase peak angular velocity. Red shaded area and lines represent comparisons between RRMS and PMS. Blue shaded area and lines represent comparisons between controls (CON) and PMS. Black shaded areas and lines represent comparisons between CON and RRMS. Circles on the confidence interval indicate the mean group difference.

neuron input to the lower motor neuron circuitry to support the body against gravity. When an impairment in upper motor neuron occurs (such as MS), patients demonstrate spasticity, commonly affecting the antigravity muscles such as the upper extremity flexors and lower extremity extensors (Brown, 1994; Dietz and Sinkjaer, 2012; Haselkorn and Loomis, 2005), and this spasticity is worse during rapid-movements since it is velocity-dependent. We speculate the directional-differences are due to spasticity, but the nature of the physiological mechanisms underlying the more affected movements during the up-direction phase of tapping in people with MS should be explored further. Our results suggest that the up-movement during tapping may be more important to characterize differences between tapping ability in MS populations.

4.4. Limitations

This study has a relatively small sample size compared to clinical trials, lacking a validation cohort, and limited clinical information (e.g. neuroimaging) for our MS participants. It is important to note that we are not suggesting tapping alone to be used in the clinic to differentiate between MS subtypes; only 61% of our MS participants were classified correctly as PMS with foot-tapping (AUROC = 0.71), with fairly low sensitivity and specificity (Table 3). However, our data suggests that foot-tapping may distinguish MS subtypes regardless of treatment protocol, and provides the first step for foot-tapping to be explored further.

Another limitation which is a common limitation for research studies that aim to characterize the different MS subtypes, is the heterogeneity of the RRMS subtype. It has been reported that up to 90% of people with RRMS ultimately transition into the SPMS subtype (Weinshenker et al., 1989) and the diagnosis of SPMS is retrospective using clinical history of the patient. Therefore, it will be important to distinguish tapping characteristics in the RRMS cohort between those at higher functional levels and those likely in the transition phase. Future studies should explore the longitudinal changes in tapping ability to determine if worse ability in RRMS patients may indicate the transition into the SPMS subtype.

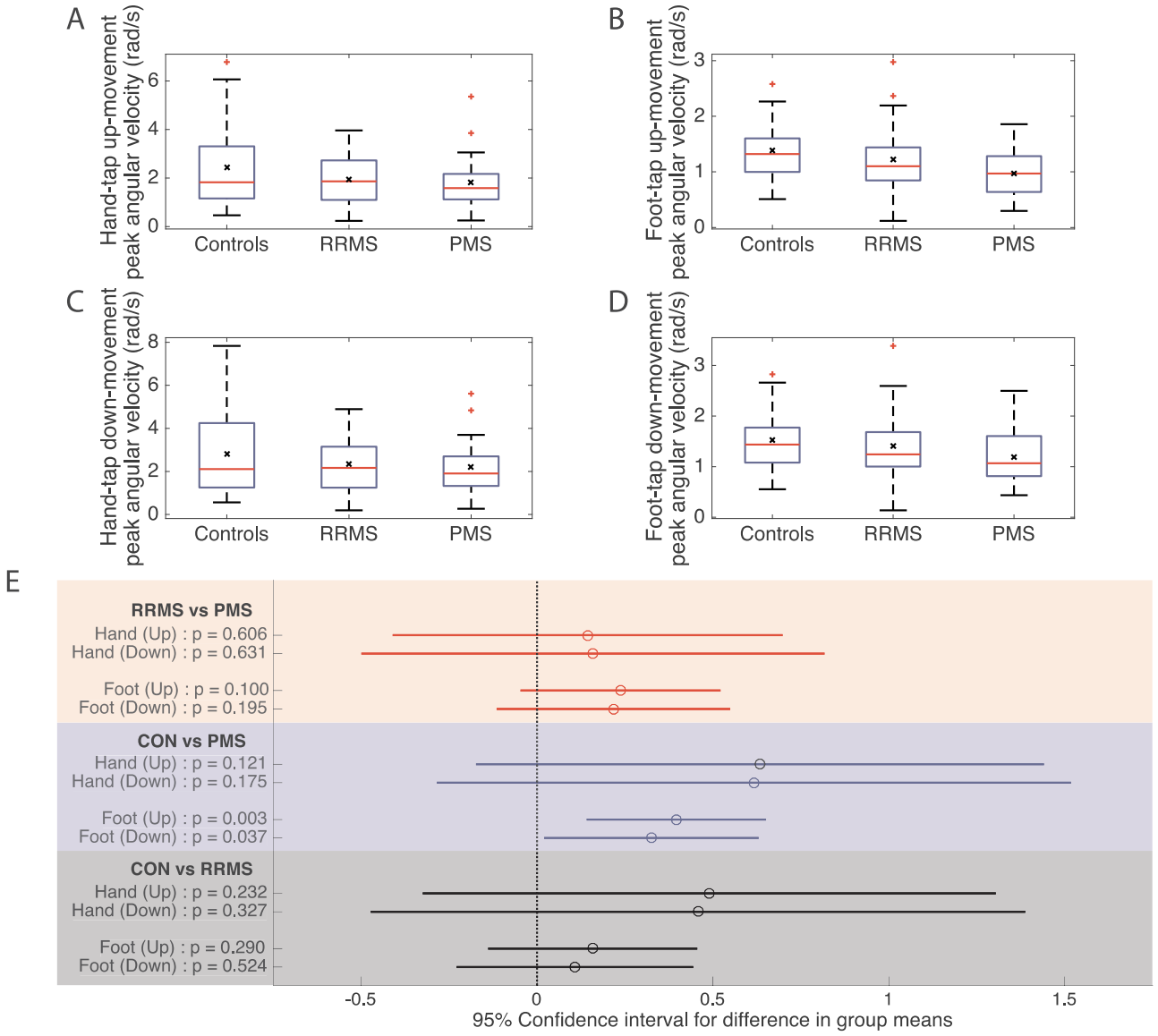

Fig. 7. *Between-group comparisons for up-phase peak angular velocity and down-phase peak angular velocity*. A-D. Box plots of up- (A-B) and down-movement peak angular velocity (C-D) during hand-tapping (A & C) and foot-tapping (B & D). Red line represents the median, and the black X's represent the mean for the different groups. Red crosses represent outliers. E. 95% confidence interval for the difference in group means for up- and down-phase peak angular velocity. Red shaded area and lines represent comparisons between RRMS and PMS. Blue shaded area and lines represent comparisons between controls (CON) and PMS. Black shaded areas and lines represent comparisons between CON and RRMS. Circles on the confidence interval indicate the mean group difference.

Table 3
Logistic regression analysis results for distinguishing between RR and progressive MS. b1 = Slope, SEb1 = Standard error for slope, Correct = Estimated probability of correctly classifying a patient with MS into RRMS or PMS is 50%, CI = Approximate 95% confidence interval for estimated classification rate, Sensitivity = True positive rate for classifying PMS, Specificity = True negative rate for classifying RRMS. AUROC = Area under the ROC curve.

	b1	SEb1	p-value	Correct	CI	Sensitivity	Specificity	AUROC
Hand-tap interval	−0.02	0.03	0.396	0.448	[0.32, 0.58]	0.48	0.41	0.55
Foot-tap interval	−0.11	0.04	0.005	0.611	[0.48, 0.74]	0.58	0.64	0.71

5. Conclusions

Tapping is already a common component of the beside neurological exam, but the tapping performance differences between MS subtypes is unclear. We have shown that both hand- and foot-tapping ability is different between healthy controls and MS groups, but only foot-tapping ability is different and able to differentiate between RRMS and PMS subtypes. Our findings suggest that MS participants perform worse with tapping due to larger mean differences in the antigravity, up-movement as indicated by the 95% confidence intervals. Investigating the difference between movement directions during rapid tapping tests has the potential to enhance the diagnostic sensitivity of the tapping movements.

Table 4
Main effect of group from one-way ANOVAs; p-value, means and standard deviation for controls, relapsing-remitting MS (RRMS), and progressive MS (PMS) for variables with up- and down-components (component duration, component duration coefficient of variation (COV), and peak angular velocity).

Variable		p-value	Controls	RRMS	PMS
Hand: Direction-specific duration (ms)	Up	< 0.001	91.69 ± 10.05	113.43 ± 27.69	117.19 ± 25.80
	Down	< 0.001	83.12 ± 5.35	97.76 ± 17.98	100.13 ± 15.49
Foot: Direction-specific duration (ms)	Up	< 0.001	118.87 ± 15.04	157.95 ± 47.53	214.68 ± 103.69
	Down	< 0.001	114.26 ± 7.27	143.31 ± 35.50	179.90 ± 71.80
Hand: Direction-specific duration COV	Up	0.247	14.39 ± 7.46	18.91 ± 12.86	16.58 ± 8.81
	Down	0.174	12.38 ± 7.56	17.21 ± 12.94	15.43 ± 9.55
Foot: Direction-specific duration COV	Up	0.009	18.68 ± 6.07	25.49 ± 11.25	23.34 ± 8.57
	Down	0.478	21.88 ± 10.33	25.54 ± 12.16	22.95 ± 9.13
Hand: Peak angular velocity (rad/s)	Up	0.299	2.44 ± 1.86	1.95 ± 1.07	1.80 ± 1.03
	Down	0.397	2.80 ± 2.07	2.34 ± 1.33	2.18 ± 1.17
Foot: Peak angular velocity (rad/s)	Up	0.011	1.38 ± 0.50	1.22 ± 0.60	0.98 ± 0.43
	Down	0.106	1.52 ± 0.58	1.41 ± 0.67	1.20 ± 0.54

Table 5
Directional difference (up vs. *down) within groups*. Paired *t*-test p-value, 95% confidence interval for difference in group means (CI), and estimated mean difference (Estimate) between up- and down-movement for controls, relapsing-remitting MS (RRMS), and progressive MS (PMS). Positive estimated mean difference indicates that the up-direction variable is higher than the down-direction variable. Higher absolute value of the estimated mean difference indicates a larger difference between the up- and down-direction.

		Controls			RRMS			PMS		
		p-value	CI	Estimate	p-value	CI	Estimate	p-value	CI	Estimate
Direction-specific duration (ms)	**Hand**	0.003	[3.00, 14.15]	8.57	< 0.001	[10.20, 21.15]	15.68	< 0.001	[11.57, 22.53]	17.05
	Foot	0.449	[−7.43, 16.64]	4.61	0.018	[2.61, 26.68]	14.64	< 0.001	[22.29, 47.27]	34.78
Direction-specific duration COV	**Hand**	0.002	[0.74, 3.28]	2.01	0.008	[0.45, 2.95]	1.70	0.069	[−0.09, 2.41]	1.16
	Foot	0.031	[−6.09, −0.03]	−3.19	0.973	[−2.94, 2.85]	−0.05	0.797	[−2.61, 3.39]	0.39
Peak angular velocity (rad/s)	**Hand**	< 0.001	[−0.50, −0.23]	−0.36	< 0.001	[−0.53, −0.27]	−0.40	< 0.001	[−0.51, −0.25]	−0.38
	Foot	< 0.001	[−0.21, −0.08]	−0.14	< 0.001	[−0.26, −0.13]	−0.19	< 0.001	[−0.28, −0.15]	−0.21

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Declaration of Competing Interest

None.

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Supplementary materials

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