Published in final edited form as:

J Neurol Sci. 2011 June 15; 305(1-2): 103–111. doi:10.1016/j.jns.2011.03.003.

Quantitative measures detect sensory and motor impairments in multiple sclerosis

Scott D. Newsome, DO^a, Joseph I. Wang, BS^c, Jonathan Y. Kang, BA^c, Peter A. Calabresi, MD^a, and Kathleen M. Zackowski, PhD, OT^{a,b,c}

^aDepartment of Neurology, Johns Hopkins University, Baltimore, MD, USA

^bDepartment of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD, USA

^cMotion Analysis Laboratory, Kennedy Krieger Institute, Baltimore, MD, USA.

Abstract

Background—Sensory and motor dysfunction in multiple sclerosis (MS) is often assessed with rating scales which rely heavily on clinical judgment. Quantitative devices may be more precise than rating scales.

Objective—To quantify lower extremity sensorimotor measures in individuals with MS, evaluate the extent to which they can detect functional systems impairments, and determine their relationship to global disability measures.

Methods—We tested 145 MS subjects and 58 controls. Vibration thresholds were quantified using a Vibratron-II device. Strength was quantified by a hand-held dynamometer. We also recorded Expanded Disability Status Scale (EDSS) and timed 25-foot walk (T25FW). T-tests and Wilcoxon-rank sum were used to compare group data. Spearman correlations were used to assess relationships between each measure. We also used a step-wise linear regression model to determine how much the quantitative measures explain the variance in the respective functional systems scores (FSS).

Results—EDSS scores ranged from 0-7.5, mean disease duration was 10.4±9.6 years, and 66% were female. In RRMS, but not progressive MS, poorer vibration sensation correlated with a worse EDSS score, whereas progressive groups' ankle/hip strength changed significantly with EDSS progression. Interestingly, not only did sensorimotor measures significantly correlate with global disability measures (EDSS), but they had improved sensitivity, as they detected impairments in up to 32% of MS subjects with normal sensory FSS.

Conclusions—Sensory and motor deficits can be quantified using clinically accessible tools and distinguish differences among MS subtypes. We show that quantitative sensorimotor measures are more sensitive than FSS from the EDSS. These tools have the potential to be used as clinical outcome measures in practice and for future MS clinical trials of neurorehabilitative and neuroreparative interventions.

© 2011 Elsevier B.V. All rights reserved.

Corresponding Author: Kathleen M. Zackowski, Ph.D. Motion Analysis Laboratory, Kennedy Krieger Institute 707 N. Broadway Baltimore, MD 21205, USA tel: (443) 923-2717 fax: (443) 923-2715 Zackowski@kennedykrieger.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

multiple sclerosis; demyelinating disease; outcome measures; neurological disability; rehabilitation

INTRODUCTION

Multiple sclerosis (MS) is a complex and clinically heterogeneous disease of the central nervous system that often results in marked disability. The lesions that occur in MS can cause many neurological deficits, depending on their location and extent [1]. Common deficits include impairments of sensation, pyramidal tract dysfunction, and gait abnormalities. Evaluating MS disability has consistently relied on rating scales such as the Expanded Disability Status Scale (EDSS) [2], the Scripps Neurologic Rating Scale [3], the 12-item MS Walking Scale [4], and the Ambulation index [5]. These rating scales provide a good overall assessment of an individual's functional status; however, it is well-known that they are insensitive to subtle abnormalities and provide limited information about which impairments may be specifically contributing to an individual's loss of function [1,6,7]. Clinical rehabilitation studies could gain both statistical power and meaning from the use of more specific outcome measures that are sensitive to subtle neurological impairments [6,7].

Quantitative functional testing devices such as the Vibratron II (for vibration sensation) and the hand-held dynamometer (for strength) have been used to evaluate impairments in sensation and strength for various neurological conditions including adrenomyeloneuropathy, cerebral palsy, traumatic brain injury, and peripheral neuropathy [8-14]. These devices are clinically accessible and have the potential for systematically quantifying specific impairments in MS; however, this has not been investigated. Using the same devices in a previous study, we found that impairments in vibration sensation and strength were significantly correlated with column-specific abnormalities in the spinal cord of MS subjects [15,16]. What remains unclear is whether these tools can reliably differentiate MS impairments from control's, distinguish impairments between MS subtypes, and whether they are as sensitive or more sensitive than categorical rating scales in detecting impairments.

We hypothesized that the Vibratron II and the hand-held dynamometer are able to detect abnormalities of sensory and motor impairments in a heterogeneous group of MS patients and that they are more precise than their respective sensory and pyramidal functional system scores of the EDSS (i.e., a global measures of disability in MS). The primary objectives of this study were to: 1) obtain baseline reference values for lower extremity quantitative sensorimotor measures in MS subjects, 2) examine whether these quantitative measures detect differences between MS subjects and matched controls, 3) compare these measures between MS subtypes, 4) evaluate the extent to which these measures correlate with global disability measures such as the EDSS and 5) evaluate their sensitivity compared to their respective EDSS functional systems score (FSS). This study provides the framework to begin validating the use and reliability of the Vibratron II and hand-held dynamometer as relevant MS clinical biomarkers of sensory and motor impairment.

METHODS

Participants

Participants were recruited by convenience sampling from the Johns Hopkins MS Center from November 2004 to July 2009. Participants were excluded if they had an MS relapse within three months of testing or reported a history of peripheral neuropathy. All

participants provided signed, informed consent in accordance with Institutional Review Board regulations at Johns Hopkins University and Kennedy Krieger Institute.

To address our study objectives we examined 145 individuals with MS using quantitative measures of lower extremity sensorimotor impairment (vibration sensation and strength) and overall disease impairment (EDSS and Timed 25-Foot Walk [T25FW]). The participants included 91 with relapsing-remitting MS, 31 with secondary progressive MS, and 23 with primary progressive MS (Table 1). Twenty strength measures and one sensation measure could not be quantified. Subjects' strength measures were not recorded if the joint could not be passively moved to the starting position; the start position was 90 degrees from the plane of the examining table. Vibration sensation measures were not recorded if the subject could not detect the highest amplitude of the Vibratron II device (i.e., 20 vibration units). An EDSS score was not recorded for one participant and 15 participants did not have a T25FW recorded (i.e., subjects were either wheelchair bound, or subjects were not tested because of logistic factors). Disease subtype and duration were obtained by retrospective chart review and interviews with participants by a physician trained in MS disease categorization (SN).

For our healthy cohort we recruited 58 individuals by convenience sample at the Johns Hopkins University and examined them using quantitative lower extremity strength measures. For healthy control vibration sensation, we used information from the Vibratron packaging insert and age-matched mean data provided by courtesy of Dr. Joseph Arezzo [17].

We assessed inter-rater reliability of quantitative sensation and strength in controls. We evaluated inter-rater reliability of strength in MS subjects but did not assess quantitative vibration because the method used for testing sensation is more systematic and objective with less influence from tester technique than for strength testing. For test-retest reliability we repeated the quantitative tests after 24 hours in MS subjects to determine the effects of day to day variability. For the quantitative methods, three examiners (J.W., J.K., S.N.) were trained and tested by one experienced tester (K.M.Z.) to use the same testing technique.

Quantitative and functional impairment measures

In our cohort of 145 MS subjects, we quantified vibration sensation thresholds (vibration units [vu]) for the right and left great toes in 289 of 290 toes using the Vibratron II device (Physitemp, Huron, NJ). For this test an A and a B rod on the Vibratron II are utilized; the experimenter has control of the amplitude and sequence of intensities used for the rods. For each trial, vibration stimulation is present for one rod and the subject is required to determine which of the two rods is actually vibrating using a two-alternative forced choice procedure [18].

As a measure of lower extremity strength (force in kilograms [kg]), we used a Microfet2 hand-held dynamometer (Hoggan Health Industries, West Jordan, UT). For all subjects, we calculated the average of two maximum ankle dorsiflexion and hip flexion efforts for the right and left legs using a break test. For both measures the subject was lying supine on the examining table, for ankle dorsiflexion the ankle was placed at 90° from the plane of the examining table or at neutral ankle dorsiflexion, for hip flexion the start position was 90° of knee and hip flexion. We collected 277 of 290 ankle dorsiflexion measures and 283 of 290 hip flexion measures; controls contributed all strength measures. We chose ankle dorsiflexion and hip flexion strength for several reasons: 1) both could be quantified, 2) these are common sites of weakness for MS patients, and 3) it provided a measure of proximal and distal weakness, which are important for walking.

Ambulation was assessed using the T25FW. We chose this measure because it is easily collected and has been used in MS clinical trials [19-23]. As a measure of overall disease status, we used the EDSS, and then compared the sensory and pyramidal FSS with the quantitative data.

Statistical Analysis

Statistical analyses were completed using Stata 10 (StataCorp LP, College Station, Tex) and Statistica 6 (StatSoft, Tulsa, OK). For reliability, intraclass correlation coefficients (ICCs) were calculated. For strength and sensation we used the worse side (i.e., weaker, or less sensitive) for comparative statistics. All reported p values are two-tailed and statistically significant if $p < 0.05$.

For our study aim 2: we compared vibration sensation between MS subtypes and controls, we divided each subtype into age-matched groups, and used t-tests with unequal variance to compare age-matched groups. For strength, we divided each MS subtype into age and gender-matched groups and compared these with our control data using Wilcoxon rank-sum. In the few instances in which there were fewer than five individuals in a group, comparative statistics were not performed.

For our study aim 3: we compared vibration sensation among MS subtypes, we normalized each MS participant's vibration sensation value using the age-matched control values provided in the Vibratron package insert. For strength, we calculated the mean strength for age and gender-matched groups in our controls and used these values to normalize the strength values. Wilcoxon rank-sum was used to compare vibration sensation, strength, EDSS, and T25FW among MS subtypes.

For our study aim 4: Spearman correlation coefficients were used to evaluate the relationships between normalized vibration sensation, normalized strength, T25FW and EDSS for each MS subtype. T25FW values were normalized using previously published age and gender-matched control values before assessing its relationship to vibration sensation and strength measures [24]. We also used Spearman tests to assess the associations between normalized sensory or motor measures, EDSS, and specific FSS. Stepwise linear regression analysis was used to assess the extent to which normalized sensory or motor measures could explain the variance in their respective FSS.

For our study aim 5: we examined whether abnormalities in vibration sensation and strength could be detected in MS subjects with normal sensory and pyramidal FSS by using the aforementioned quantitative tools. We defined *abnormal* for quantitative vibration sensation as thresholds ≥ 2.5 standard deviations above matched controls and for quantitative ankle and hip strength as ≥ 2 standard deviations below matched controls.

Lastly, to determine whether normalized vibration sensation, normalized strength, and/or overall disease impairment varied significantly with disease duration within a given MS subtype, we divided each MS participant into one of three groups, based on disease duration, prior to comparative statistical analysis: 1) 0-9 years, 2) 10-19 years, or 3) ≥ 20 years. We compared individuals who were in early (0-9 years) versus later disease (≥ 10 years). If the ≥ 20 years group had five or fewer participants, we added them to the 10-19 years group for analysis. Wilcoxon rank-sum was used to evaluate the effects of disease duration on the measured impairments.

RESULTS

Study population

In the cohort of 145 MS subjects, there was a mean age of 43.6 ± 11.9 years (mean $\pm$ SD) (range: 20-67), mean disease duration of 10.4 ± 9.6 years (range: 1-44), and 66% were females. Our MS subjects represented a wide range of disease disability (EDSS: 0-7.5) and their characteristics divided by disease subtype are presented in Table 1. Table 2A summarizes our MS cohort's vibration sensation with raw and normalized values. Table 2B summarizes our MS cohort's strength with raw and normalized values.

Our healthy controls included 31 women and 27 men with a mean age of 43.3 ± 13.5 years (range: 21-68). Quantitative ankle dorsiflexion and hip flexion strength were also obtained in this control population (Table 3).

Differences between MS subtypes and controls

All three MS subtypes had significantly poorer vibration sensation compared to the age-matched control group (Table 4A). Similarly, SPMS and PPMS groups had significantly weaker ankle and hip muscles compared to age and gender-matched controls. By contrast, the RRMS group was not consistently weaker in the ankle or hip muscles when compared to controls (Table 4B).

Differences among MS subtypes

Fig. 1 A-D illustrates that the RRMS group performed better in all measures of disease impairment than the progressive groups. Specifically, when compared with the SPMS group, the RRMS group had better vibration sensation (Normalized Mean Diff. = -1.70, C.I. [-2.41, -0.99], $p < 0.0001$), stronger ankle dorsiflexion and hip flexion (Normalized Ankle Mean Diff. = 0.28, C.I. [0.18, 0.38], $p < 0.0001$) (Normalized Hip Mean Diff. = 0.37, C.I. [0.27, 0.47], $p < 0.0001$), walked faster in the T25FW (Mean Diff. = -6.24, C.I. [-11.03, -1.45], $p < 0.0001$), and less overall disability, as measured by the EDSS (Mean Diff. = -2.64, C.I. [-3.27, -2.01], $p < 0.0001$). Similarly, when compared with the PPMS group, the RRMS group had better vibration sensation (Normalized Mean Diff. = -0.84, C.I. [-1.36, -0.32], $p < 0.0001$), stronger ankles and hips (Normalized Ankle Mean Diff. = 0.22, C.I. [0.08, 0.36], $p = 0.0001$) (Normalized Hip Mean Diff. = 0.25, C.I. [0.14, 0.36], $p < 0.0001$), walked faster in the T25FW (Mean Diff. = -4.15, C.I. [-7.52, -0.78], $p = 0.0001$) and better EDSS scores (Mean Diff. = -2.58, C.I. [-3.37, -1.79], $p < 0.0001$). By contrast, the PPMS group had similar impairments to the SPMS group ($p > 0.05$).

Effects of disease duration within each respective MS subtype

To determine the effect of disease duration on our MS cohort's impairments, we divided individuals into groups based on their MS subtype and disease duration (Table 1). Comparison of early (0-9 years) versus later disease (≥ 10 years) were made to examine sensitivity to cumulative disease impairment. The early RRMS group had better hip flexion strength than the late RRMS group (early: 0.70 ± 0.19 ; late: 0.61 ± 0.11 ; $p = 0.018$) and less overall impairment, as measured by the EDSS (early: 2.3 ± 1.4 ; late: 3.4 ± 1.8 ; $p = 0.015$). The early SPMS group had similar scores to the late SPMS group in the majority of impairments. By contrast, the early PPMS group was much less impaired than the late PPMS group. Specifically, the early PPMS group had stronger hip flexion muscles (early: 0.56 ± 0.21 ; late: 0.23 ± 0.14 ; $p = 0.001$), walked markedly faster on T25FW (early: 6.09 ± 3.23 ; late: 13.25 ± 9.38 ; $p = 0.005$), and had less overall impairment according to EDSS (early: 4.5 ± 1.6 ; late: 6.1 ± 1.5 ; $p < 0.03$) than the late PPMS group.

Correlations between impairment measures within each respective MS subtype

In our MS cohort of 145 patients, significant impairment correlations were made for the entire group and each MS subtype (Table 5). All measures were significantly correlated with each other for the entire cohort. Within each subtype, as expected, slower T25FW correlated with higher EDSS scores. Similarly, for each subtype, weaker ankle strength correlated with weaker hip strength; however, these strength measures did not correlate with vibration sensation. Only in the RRMS group did poorer vibration sensation correlate with a worse EDSS score. Unlike ankle strength, the RRMS group's hip flexion strength correlated with the EDSS. By contrast, both ankle and hip strength in the progressive groups correlated with the EDSS. T25FW correlated with vibration sensation and hip strength in the RRMS group, both ankle and hip strength in the SPMS group, and only hip strength in the PPMS group.

How well do quantitative vibration sensation measures relate to sensory FSS?

Vibration sensation means (in vibration units [vu]) organized by sensory FSS were: 0=2.21, 1=4.27, 2=4.91, 3=8.92, and 4=14.22 (Fig. 2). Poorer vibration sensation correlated with a worse sensory FSS and EDSS (both: $R=0.64$; $p<0.0001$) (Table 6). Hierarchical regression showed that vibration sensation followed by diagnosis were the most significant predictors of sensory FSS ($R=0.41$; $p<0.0001$); age and disease duration were not strongly related. Surprisingly, we found that approximately 30% of subjects with a sensory FSS of 0 (i.e. normal) actually had abnormal quantitative vibration sensation (i.e., at least 2.5 standard deviations outside of age-matched control values). This finding suggests that quantitative vibration measures can detect impairments before abnormalities are rated in the FSS.

How well do strength measures relate to pyramidal FSS?

Ankle dorsiflexion strength means (in kilograms of force [kg]) organized by pyramidal FSS were: 0=23.1, 1=20.0, 2=20.1, 3=16.7, and 4=7.8. Hip flexion strength means (kg) organized by pyramidal FSS were: 0=21.8, 1=20.0, 2=16.8, 3=14.1, and 4=5.4 (Fig. 2). Weak ankle and hip strength correlated with a worse pyramidal FSS and EDSS (ankle: $R=-0.49$, -0.48 ; hip: $R=-0.65$, -0.62 ; all $p<0.0001$) (Table 6). Hierarchical regression showed that hip flexion strength followed by diagnosis were the most significant predictors of pyramidal FSS ($R=0.54$; $p<0.0001$); age, disease duration, and ankle strength were not strongly related. Similar to the sensory measures, we found that 32% of subjects with a pyramidal FSS of 0 had abnormal quantitative ankle strength and 4% had abnormal quantitative hip strength (i.e., at least 2 standard deviations outside of age and gender matched control values).

Inter-rater and test-retest reliability of quantitative sensorimotor measures

Inter-rater reliability ICCs for each quantitative measure was high. We report ICCs, as well as (absolute mean difference, and standard error) in healthy control subjects and MS subjects. For inter-rater reliability in healthy controls: vibration sensation, ICC=0.96 (0.22 vu, 0.06 vu) N=13; ankle dorsiflexion strength, ICC=0.83 (2.61 kg, 0.36 kg) N=21; hip flexion strength, ICC=0.93 (1.66 kg, 0.23 kg) N=27. For MS subjects: ankle dorsiflexion strength, ICC=0.97 (2.35 kg, 0.29 kg) N=22, hip flexion strength, ICC=0.98 (1.26 kg, 0.19 kg) N=22. Test-retest reliability for MS subjects: vibration sensation, ICC=0.91 (0.67 vu, 0.13 vu) N=20; ankle dorsiflexion, ICC=0.77 (2.24 kg, 0.41 kg) N=18; hip flexion, ICC=0.95 (1.28 kg, 0.21 kg) N=20.

DISCUSSION

Our data show that we can validly quantify lower extremity vibration sensation and strength in individuals with MS using clinically accessible tools and that these tools can detect

differences among MS subtypes (i.e., RRMS, SPMS, and PPMS) and healthy controls. Vibration sensation and strength were significantly correlated to MS subtype and we found significant differences that were dependent on disease duration. Overall, all MS subtypes had significantly worse vibration sensation and strength when compared to matched controls. As expected, the RRMS group had better sensation, were stronger, walked more quickly than the progressive groups, and had the lowest EDSS scores. More importantly, our quantitative sensorimotor measures significantly correlated with global disability measures (i.e. EDSS, FSS, and T25FW) and remarkably these quantitative measures were able to detect abnormalities in MS subjects with documented *normal* sensory and pyramidal FSS.

Since MS is a heterogeneous and unpredictable disease with very limited medical and neurorehabilitation interventions, many investigators have emphasized the need for more sensitive and responsive functional outcome measures [6,7]. An international task force was formed by the National MS Society to address this need which led to the development of the Multiple Sclerosis Functional Composite (MSFC) [25,26]. The MSFC is a composite measure that evaluates cognition, arm function, and walking and has been shown to have excellent intra-rater and inter-rater reliability [27,28]. As a result, the MSFC is now widely used and has been incorporated into many clinical trials as an outcome measure [21,22]. In this study, we used quantitative tools that measure specific sensory and motor impairments that correlate with functional tract specific MRI pathology in MS [15,16]. These quantitative measures might be more sensitive in evaluating specific and subtle impairments compared to the commonly used rating scales. They offer additional advantages in that they are precise, objective, , and remain more cost-effective and transportable than tools such as an isokinetic device.

Up to this point, it has been very difficult to quantify subtle vibration sensation loss, which often occurs early in MS. Neurological exams which include tuning fork vibration testing is variable and often subjective [29]. The Vibratron II measures vibration sensation in a more objective fashion, and it uses a constant frequency, an adjustable magnitude, and a systematic data collection paradigm [8]. Our data show differences among the MS subtypes along with a significant correlation between vibration sensation and the EDSS in the RRMS group. By contrast, this was not seen within the progressive groups. Vibration sensation dysfunction in RRMS may be a marker for early disease progression and suggests that this is less appreciated in more advanced, progressive disease. Additionally, irrespective of disease subtype, we found that almost 30% of MS subjects who had a *normal* sensory FSS actually had abnormal quantitative vibration sensation (i.e., at least 2.5 standard deviations outside of age-matched controls). We suggest that the Vibratron II has the potential to be a useful clinical outcome measure in MS.

Similar to vibration sensation, traditional strength testing has been reliant on insensitive rating scales and subjective clinical exams. We used a hand-held dynamometer because it is faster to use and clinically more accessible than other devices available [8,16]. In our cohort, the majority of individuals with RRMS and all individuals with SPMS and PPMS were found to have significantly weaker ankle dorsiflexion and hip flexion than matched controls. We also found that the early PPMS group had significantly stronger hip flexion compared to the late PPMS group. This difference corresponds with previous natural history studies as PPMS typically presents with a progressive myelopathy [30,31]. Currently, there are few outcome measures that detect subtle clinical abnormalities in individuals with progressive MS making it difficult to evaluate possible treatments [32]. Irrespective of disease subtype, we found that strength was detected as abnormal in 32% and 4% of MS subjects who had a normal pyramidal FSS (for ankle dorsiflexion and hip flexion, respectively). These findings suggest that quantitative measures might detect even small deficits that are missed by rating scales and that ankle dorsiflexion weakness is an early deficit that is often overlooked. We

suggest that quantitative strength testing could be an effective clinical outcome measure, especially for progressive MS.

Walking is an important functional goal for individuals with MS. Gait abnormalities can often present early in MS without obvious functional impairment [33,34]. Despite this observation, very little research has focused on the details of what may be contributing to these gait problems. Perhaps this is because in MS the clinical gold standard has been to use rating scales or timed walk tests to evaluate global problems with walking [2,4,5]. However, our data show that we can measure lower extremity vibration sensation and strength in a more quantitative fashion than what has been done in the past and that these functions are deficient relative to a control cohort. Previous studies have shown that poor sensation and poor strength result in an increased number of falls and slower walking speeds in individuals with MS [35,36]. As such, our results provide a basis for future studies to evaluate walking in relation to quantitative sensory and motor impairments. We propose that the tools in this study have the potential to assist in predicting who might have future ambulation problems and therefore allow us to intervene earlier with strategic rehabilitation approaches and MS drug therapies.

There are several limitations to our study. We performed a cross-sectional study which does not allow for definitive conclusions about the sensitivity and validity of the quantitative devices used over time. To address this we plan to use baseline values from this study in a prospective, longitudinal study. Our measure of vibration sensation is valid and more objective than the tuning fork; however, the Vibratron device can only be used for testing at the great toe and index finger. Ideally, one would like to evaluate vibration sensation at multiple points. Our measure of strength is valid and objective [8,37]; however, we only tested two muscle actions. We chose ankle dorsiflexion and hip flexion strength because clinically these are common sites of weakness in MS. Also, this accounts for proximal and distal impairments, both of which are important in walking [8,38]. Lastly, quantitative strength testing methods requires examiners to be trained for proper testing technique and assumes the patient is participating with their full effort. To control for this we had one experienced tester (K.M.Z.) train and monitor all testers using the same testing technique.

Implications

Abnormalities of sensation and strength are common deficits that affect many people who suffer from MS. Our data demonstrate that we can quantify abnormalities in vibration sensation and strength in MS and distinguish differences among MS subtypes and controls using clinically accessible tools. More broadly, this study shows that sensory and motor impairments can be measured using the Vibratron device and a hand-held dynamometer. We suggest that these tools could be used to evaluate impairments in the upper extremity as well as the lower extremity. Our impairment data strongly correlated with the commonly used EDSS and T25FW, and detected abnormalities in up to 32% of MS subjects with “normal” sensory and pyramidal FSS. These observations support the notion that the Vibratron device and hand-held dynamometer have the potential to be used as outcome measures in future MS clinical trials of neurorehabilitative and neuroreparative interventions. Use of these tools in a longitudinal study would allow for the quantification of early deficits and improve prediction of future changes in functional measures such as ambulation.

Acknowledgments

The authors would like to thank Divya Sambandan and Mike Shteyman for their assistance in collecting parts of this data and Dr. Joseph Arezzo for providing some of the Vibratron control data.

FUNDING

This work was supported by a Sylvia Lawry Physician Fellowship from the National Multiple Sclerosis Society (S.D.N.); NMSS Tissue Repair Grant (K.M.Z. and P.A.C.); NIH NICHD [grant number K01 HD049476] (K.M.Z.); and the Dana Foundation (K.M.Z.).

REFERENCES

- Schwid SR, Goodman AD, Mattson DH, Mihai C, Donohoe KM, Petrie MD, et al. The measurement of ambulatory impairment in multiple sclerosis. *Neurology*. 1997; 49:1419–1424. [PubMed: 9371932]
- Kurtzke JF. Rating neurologic impairments in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983; 33:1444–1452. [PubMed: 6685237]
- Sipe JC, Knobler RL, Braheny SL, Rice GPA, Panitch HS, Oldstone MBA. A neurologic rating scale (NRS) for use in multiple sclerosis. *Neurology*. 1984; 34:1368. [PubMed: 6541311]
- Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology*. 2003; 60:31–6. [PubMed: 12525714]
- Hauser SL, Dawson DM, Leirich JR, Beal MF, Kevy SV, Propper RD, et al. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *NEJM*. 1983; 308:173–180. [PubMed: 6294517]
- Schwid SR, Goodman AD, Apatoff BR, Coyle PK, Jacobs LD, Krupp LB, et al. Are quantitative functional measures more sensitive to worsening MS than traditional measures? *Neurology*. 2000; 55:1901–3. [PubMed: 11134392]
- Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Perkau J, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain*. 1999; 122:871–882. [PubMed: 10355672]
- Zackowski KM, Dubey P, Raymond GV, Mori S, Moser HW, Bastian AJ. Sensorimotor function and axonal integrity in adrenomyeloneuropathy. *Arch Neurol*. 2006; 63:74–80. [PubMed: 16401738]
- Taylor N, Dodd K, Graham HK. Test-retest reliability of hand-held dynamometric strength testing in young people with cerebral palsy. *Arch Phys Med Rehabil*. 2004; 85:77–80. [PubMed: 14970972]
- Katz-Leurer M, Rottem H, Meyer S. Hand-Held Dynamometry in Children with Traumatic Brain Injury: Within-Session Reliability. *Pediatr Phys Ther*. 2008; 20(3):259–263. [PubMed: 18703964]
- Berger AR, Schaumburg HH, Gourevitch MN, Freeman K, Herskovitz S, Arezzo JC. Prevalence of peripheral neuropathy in injection drug users. *Neurology*. 1999; 53:592. [PubMed: 10449125]
- Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, et al. Quantitative sensory testing: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003; 60:898–904. [PubMed: 12654951]
- Deng H, He F, Zhang S, Calleman CJ, Costa LG. Quantitative measurements of vibration threshold in healthy adults and acrylamide workers. *Int Arch Occup Environ Health*. 1993; 65:53–6. [PubMed: 8394840]
- Fatemi A, Smith SA, Dubey P, et al. Magnetization transfer MRI demonstrates spinal cord abnormalities in adrenomyeloneuropathy. *Neurology*. 2005; 64:1739–1745. [PubMed: 15911801]
- Zackowski KM, Smith SA, Reich DS, Zackowski KM, Bastian AJ, van Zijl PC, et al. Sensorimotor dysfunction in Multiple Sclerosis and column-specific magnetization transfer imaging abnormalities in the spinal cord. *Brain*. 2009; 132:1200–9. [PubMed: 19297508]
- Reich DS, Zackowski KM, Gordon-Lipkin EM, Smith SA, Chodkowski BA, Cutter GR, et al. Corticospinal Tract Abnormalities Are Associated with Weakness in Multiple Sclerosis. *Am J Neuroradiol*. 2008; 29:333–9. [PubMed: 17974617]
- Arezzo, JC. Quantitative Sensory Testing of Vibration Threshold: Vibratron II (Rationale and Methods). Physitemp Instruments, Inc.; Clifton: 1993.
- Arezzo JC, Schaumburg HH, Laudadio C. The Vibratron: A simple device for quantitative evaluation of tactile/vibratory sense. *Neurology*. 1985; 35(Suppl1):169.

19. Goodman AD, Brown TR, Cohen JA, Krupp LB, Schapiro R, Schwid SR, et al. Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology*. 2008; 71:1134–1141. [PubMed: 18672472]
20. Goodman AD, Brown T, Krupp L, Schapiro R, Schwid SR, Cohen R, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet*. 2009; 373:732–8. [PubMed: 19249634]
21. Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Kooijmans MF, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology*. 2002; 59:679–687. [PubMed: 12221157]
22. Rudick RA, Cutter G, Baier M, Fisher E, Dougherty D, Weinstock-Guttman B, et al. Use of the Multiple Sclerosis Functional Composite to predict disability in relapsing MS. *Neurology*. 2001; 56:1324–1330. [PubMed: 11376182]
23. Burt RK, Loh Y, Cohen B, Stefosky D, Balabanov R, Katsamakis G, et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. *Lancet Neurol*. 2009; 8:244–253. [PubMed: 19186105]
24. Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. *Age and Ageing*. 1997; 26:15–9. [PubMed: 9143432]
25. Rudick R, Antel J, Confavreux C, Cutter G, Ellison G, Fischer J, et al. Clinical Outcomes Assessment in Multiple Sclerosis. *Ann Neurol*. 1996; 40:469–479. [PubMed: 8797541]
26. Rudick RA, Antel JP, Confavreux C, Cutter GR, Ellison GW, Fischer JS. Recommendations from the National Multiple Sclerosis Society Clinical Outcome Assessment Task Force. *Ann Neurol*. 1997; 42:379–382. [PubMed: 9307263]
27. Schwid SR, Covington M, Segal BM, Goodman AD. Fatigue in multiple sclerosis: Current understanding and future directions. *J Rehabil Res Dev*. 2002; 39:211–224. [PubMed: 12051465]
28. Cohen JA, Fischer JS, Bolibrush DM, Jak AJ, Kniker JE, Mertz LA, et al. Intrarater and interrater reliability of the MS functional composite outcome measure. *Neurology*. 2000; 54:802–6. [PubMed: 10690966]
29. Bell-Krotoski JA, Buford WL Jr. The force/time relationship of clinically used sensory testing instruments. *J Hand Ther*. 1997; 10:297–309. [PubMed: 9399179]
30. Weinshenker BG. Natural History of Multiple Sclerosis. *Ann Neurol*. 1994; 36:S6–S11. [PubMed: 8017890]
31. Bashir K, Whitaker JN. Clinical and laboratory features of primary progressive and secondary progressive MS. *Neurology*. 1999; 53:765–771. [PubMed: 10489038]
32. Kragt JJ, Thompson AJ, Montalban X, Tintore M, Rio J, Polman CH, et al. Responsiveness and predictive value of EDSS and MSFC in primary progressive MS. *Neurology*. 2008; 70:1084–1091. [PubMed: 18184917]
33. Benedetti MG, Piperno R, Simoncini L, Bonato P, Tonini A, Giannini S. Gait abnormalities in minimally impaired multiple sclerosis patients. *Multiple Sclerosis*. 1999; 5:363–8. [PubMed: 10516781]
34. Martin CL, Phillips BA, Kilpatrick TJ, Butzkueven H, Tubridy N, McDonald E, et al. Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Multiple Sclerosis*. 2006; 12:620–8. [PubMed: 17086909]
35. Thoumie P, Lamotte D, Cantalloube S, Faucher M, Amarenco G. Motor determinants of gait in 100 ambulatory patients with multiple sclerosis. *Multiple Sclerosis*. 2005; 11:485–491. [PubMed: 16042234]
36. Mazzaro N, Grey MJ, Sinkjaer T, Andersen JB, Pareyson D, Schieppati M. Lack of On-Going Adaptations in the Soleus Muscle Activity During Walking in Patients Affected by Large-Fiber Neuropathy. *J Neurophysiol*. 2005; 93:3075–3085. [PubMed: 15689390]
37. Bohannon RW. Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. *Arch Phys Med Rehabil*. 1997; 78:26–32. [PubMed: 9014953]
38. Byrne CA, O'Keeffe DT, Donnelly AE, Lyons GM. Effect of walking speed changes on tibialis anterior EMG during healthy gait for FES envelope design in drop foot correction. *J Electromyogr Kinesiol*. 2007; 17:605–616. [PubMed: 16990012]

Figure 1.

Box plots showing group means of disease impairment for RRMS, SPMS, and PPMS groups. (A) Normalized ankle dorsiflexion strength, (B) Normalized hip flexion strength, (C) Normalized great toe vibration sensation, and (D) T25FW in individuals with multiple sclerosis (MS). RRMS= Relapsing-Remitting MS; SPMS= Secondary Progressive MS; PPMS= Primary Progressive MS; ns= not significant; † $p \leq 0.0001$.

Figure 2.

Plot shows mean values for each MS quantitative sensory and motor measure graphed against the corresponding EDSS functional systems score (FSS). Group means and standard deviations are presented. (A) Raw great toe vibration sensation and sensory FSS, (B) Raw ankle dorsiflexion strength and pyramidal FSS, (C) Raw hip flexion strength and pyramidal FSS, (D) Normalized great toe vibration sensation and sensory FSS, (E) Normalized ankle dorsiflexion strength and pyramidal FSS, and (F) Normalized hip flexion strength and pyramidal FSS. Vibration sensation raw values are in vibration units and raw strength values are in kilograms of force.

Table 1

Characteristics of individuals with multiple sclerosis

MS Type	Disease Duration	Gender	Age	Disease Duration	EDSS	Median EDSS
Relapsing-Remitting	Total	65/26	38.5 (10.7)	6.9 (6.4)	2.6 (1.6)	2.5
	0-9 yrs	47/22	36.0 (9.5)	4.0 (2.8)	2.3 (1.4)	2.0
	10-19 yrs	15/2	43.2 (9.5)	13.2 (2.4)	3.1 (1.8)	3.0
	≥ 20 yrs	3/2	57.0 (7.9)	25.4 (6.7)	4.3 (1.9)	4.5
Secondary Progressive	Total	18/13	52.5 (8.1)	19.6 (10.7)	5.2 (1.5)	6.0
	0-9 yrs	3/3	46.7 (4.8)	5.5 (2.4)	4.1 (1.6)	3.8
	10-19 yrs	7/5	49.0 (7.0)	15.3 (2.9)	5.6 (1.4)	6.0
	≥ 20 yrs	8/5	58.3 (6.5)	30.1 (6.5)	5.4 (1.3)	6.0
Primary Progressive	Total	12/11	51.6 (9.0)	11.6 (10.2)	5.2 (1.7)	6.0
	0-9 yrs	6/7	47.5 (8.2)	5.0 (2.7)	4.5 (1.6)	4.0
	10-19 yrs	4/3	55.1 (6.5)	15.0 (2.9)	6.6 (0.9)	6.5
	≥ 20 yrs	2/1	61.0 (8.7)	32.3 (10.7)	4.8 (2.0)	6.0

Values are mean (standard deviation); Disease duration and Age are in years; Gender= number of female/male subjects; yrs= years; EDSS=Expanded Disability Status Scale.

Table 2A

Great toe vibration sensation in individuals with multiple sclerosis

MS Type	Disease Duration	Side	n	Vibration	Vibration Norm.	Worse Vib. Norm.
Relapsing-Remitting	Total	R	90	2.96 (2.79)	1.14 (0.96)	1.34 (1.04)
		L	91	3.04 (2.27)	1.19 (0.87)	
	0-9 yrs	R	69	2.67 (2.09)	1.07 (0.83)	1.23 (0.90)
		L	69	2.81 (2.10)	1.12 (0.82)	
	10-19 yrs	R	17	2.98 (1.98)	1.15 (0.79)	1.31 (0.83)
		L	17	3.11 (2.26)	1.20 (0.88)	
	≥ 20 yrs	R	4	7.94 (8.74)	2.46 (2.46)	2.94 (2.09)
		L	5	6.05 (2.87)	2.10 (1.13)	
Secondary Progressive	Total	R	31	7.62 (5.20)	2.75 (1.84)	3.04 (1.86)
		L	31	7.13 (4.64)	2.54 (1.52)	
	0-9 yrs	R	6	6.76 (3.79)	2.62 (1.51)	2.72 (1.53)
		L	6	5.72 (2.70)	2.21 (1.08)	
	10-19 yrs	R	12	6.07 (1.80)	2.26 (0.69)	2.40 (0.69)
		L	12	5.55 (1.80)	2.08 (0.74)	
	≥ 20 yrs	R	13	9.45 (7.23)	3.27 (2.56)	3.78 (2.49)
		L	13	9.24 (6.29)	3.13 (2.04)	
Primary Progressive	Total	R	23	5.57 (3.30)	2.00 (1.20)	2.18 (1.12)
		L	23	5.24 (2.71)	1.87 (0.94)	
	0-9 yrs	R	13	4.73 (2.95)	1.80 (1.16)	1.98 (1.04)
		L	13	4.38 (1.76)	1.65 (0.67)	
	10-19 yrs	R	7	8.36 (2.68)	2.88 (0.94)	2.98 (1.04)
		L	7	7.63 (3.27)	2.61 (1.13)	
	≥ 20 yrs	R	3	2.68 (1.27)	0.81 (0.34)	1.16 (0.12)
		L	3	3.39 (0.81)	1.04 (0.21)	

Vibration values are mean (standard deviation) vibration units. Vibration units are the amplitude of vibration (proportional to the square of applied voltage). Vibration Norm are the normalized mean vibration threshold/standard deviation). Normalized= subject's raw value/control value (calculated for age and side). yrs= years; R= right; L= left; n= number of subjects; Norm.= normalized; Vib.=vibration. Worse Vib. Norm are the normalized mean sensory thresholds (standard deviation) for the more sensory impaired side.

Table 2B

Ankle dorsiflexion and hip flexion strength values in individuals with multiple sclerosis

MS Type	Disease Duration	Side	Ankle Dorsiflexion				Hip Flexion			
			n	Force	Force Norm.	Worse Force Norm.	n	Force	Force Norm.	Worse Force Norm.
Relapsing-Remitting	Total	R	86	22.7 (5.7)	0.79 (0.19)	0.70	89	21.0 (5.6)	0.71 (0.17)	0.67
		L	88	21.6 (5.9)	0.72 (0.20)	(0.19)	89	20.5 (5.9)	0.71 (0.19)	(0.18)
	0-9 yrs	R	65	23.3 (5.7)	0.80 (0.19)	0.72	68	21.8 (5.9)	0.74 (0.18)	0.70
		L	67	22.3 (5.9)	0.74 (0.21)	(0.19)	68	21.0 (6.3)	0.73 (0.21)	(0.19)
	10-19 yrs	R	16	21.1 (5.3)	0.74 (0.16)	0.64	16	17.7 (3.0)	0.61 (0.10)	0.59
		L	16	19.0 (5.4)	0.63 (0.19)	(0.18)	16	17.6 (3.5)	0.62 (0.12)	(0.10)
	≥ 20 yrs	R	5	20.4 (6.5)	0.70 (0.24)	0.66	5	20.3 (3.4)	0.69 (0.09)	0.69
		L	5	21.8 (5.6)	0.71 (0.18)	(0.20)	5	21.7 (3.6)	0.76 (0.10)	(0.09)
Secondary Progressive	Total	R	29	13.5 (9.2)	0.47 (0.32)	0.38	31	10.2 (8.0)	0.36 (0.35)	0.29
		L	31	15.2 (7.7)	0.51 (0.26)	(0.26)	30	11.0 (6.9)	0.38 (0.23)	(0.23)
	0-9 yrs	R	6	16.2 (11.7)	0.53 (0.37)	0.45	6	14.3 (8.4)	0.47 (0.27)	0.44
		L	6	17.1 (6.2)	0.55 (0.17)	(0.31)	6	15.5 (3.9)	0.53 (0.12)	(0.25)
	10-19 yrs	R	11	13.7 (8.4)	0.47 (0.30)	0.40	12	10.8 (8.5)	0.40 (0.28)	0.33
		L	12	15.5 (7.1)	0.51 (0.25)	(0.27)	11	12.7 (7.1)	0.44 (0.24)	(0.26)
	≥ 20 yrs	R	12	12.0 (9.1)	0.43 (0.33)	0.34	13	7.8 (7.1)	0.27 (0.24)	0.20
		L	13	14.1 (9.1)	0.48 (0.31)	(0.24)	13	7.5 (6.5)	0.27 (0.23)	(0.17)
Primary Progressive	Total	R	21	18.5 (8.8)	0.62 (0.26)	0.43	22	15.8 (7.7)	0.53 (0.25)	0.42
		L	21	14.7 (10.0)	0.48 (0.32)	(0.30)	22	14.1 (8.4)	0.48 (0.28)	(0.24)
	0-9 yrs	R	13	20.2 (10.0)	0.65 (0.29)	0.51	13	18.9 (6.2)	0.63 (0.19)	0.56
		L	13	19.7 (7.6)	0.64 (0.23)	(0.27)	13	18.9 (7.2)	0.65 (0.23)	(0.21)
	10-19 yrs	R	5	12.6 (4.1)	0.45 (0.15)	0.20	6	8.5 (6.7)	0.29 (0.23)	0.20
		L	5	7.7 (8.8)	0.27 (0.32)	(0.22)	6	6.5 (5.1)	0.23 (0.18)	(0.16)
	≥ 20 yrs	R	3	20.9 (5.4)	0.75 (0.20)	0.44	3	16.9 (7.0)	0.58 (0.24)	0.30
		L	3	4.2 (7.2)	0.14 (0.24)	(0.45)	3	8.5 (1.5)	0.30 (0.05)	(0.05)

Force values are mean (standard deviation). Force= kilograms. Force Norm are the normalized mean force values (standard deviation). Normalized= subject's raw strength value/control value (calculated for gender, age, and side). yrs.= years; R= right; L=left; n= number of subjects; Norm.= normalized. Worse Force Norm. are the normalized mean force values (standard deviation) for the weakest side.

Table 3

Ankle dorsiflexion and hip flexion strength values for healthy controls

Muscle Action	Age-yr	Side	n	Male force	SD	n	Female force	SD
Ankle DF	20-29	R	5	30.98	4.05	5	28.71	4.02
		L	5	27.94	4.93	5	26.67	7.43
	30-39	R	7	32.21	3.96	8	31.41	4.39
		L	7	30.45	7.56	8	31.18	3.80
	40-49	R	5	34.38	5.08	5	26.90	3.37
		L	5	33.20	6.11	5	25.17	4.19
	50-59	R	5	27.62	3.59	8	26.08	5.06
		L	5	26.49	2.79	8	25.54	4.83
	60-69	R	5	27.90	2.87	5	24.90	4.24
		L	5	30.07	4.63	5	24.81	3.60
Hip Flexion	20-29	R	5	30.12	3.23	5	25.40	3.11
		L	5	28.58	2.95	5	24.00	4.06
	30-39	R	7	32.89	4.39	8	24.38	4.09
		L	7	31.95	5.80	8	24.33	3.31
	40-49	R	5	31.57	5.88	5	21.41	5.42
		L	5	30.48	4.73	5	21.09	4.66
	50-59	R	5	29.21	2.82	8	18.62	3.72
		L	5	29.08	2.84	8	18.28	4.20
	60-69	R	5	28.80	4.88	5	17.51	4.03
		L	5	28.21	3.35	5	16.28	3.63

Force is reported in kilograms; DF= dorsiflexion; yrs= years; R=right; L=left; n= number of subjects; SD= standard deviation.

Table 4A

Age-matched vibration sensation differences between MS subtypes and healthy controls

Subtype	Age group	95% CI	p value
RRMS	< 35 yrs	2.15-3.39	<0.0001
RRMS	36-50 yrs	2.61-4.45	<0.0001
RRMS	51-65 yrs	2.78-5.36	<0.001
SPMS	36-50 yrs	5.76-9.48	<0.0001
SPMS	51-65 yrs	5.14-12.08	<0.001
PPMS	36-50 yrs	2.57-7.47	<0.01
PPMS	51-65 yrs	5.14-9.74	<0.001

RRMS=relapsing-remitting MS; SPMS=secondary progressive MS; PPMS=primary progressive MS; yrs=years; CI=confidence interval.

Table 4B

MS subtypes quantitative strength measures Z-score deviation from healthy controls

Muscle Action	Subtype	Gender	Age group	Mean Diff.	C.I. 95%	z	p-value
Ankle DF	RRMS	Females	20-29 yrs	-18.71	[-31.26, -6.16]	-2.91	<0.01
	RRMS	Females	30-39 yrs	-30.50	[-38.06, -22.94]	-4.16	<0.001
	RRMS	Females	40-49 yrs	-13.65	[-23.44, -3.86]	-2.42	0.02
	RRMS	Females	50-59 yrs	-17.29	[-28.28, -6.30]	-2.67	<0.01
	RRMS	Males	20-29 yrs	-10.09	[-24.76, 4.58]	-2.41	0.02
	RRMS	Males	30-39 yrs	-24.57	[-41.73, -7.41]	-2.49	0.01
	RRMS	Males	40-49 yrs	-20.86	[-36.43, -5.29]	-2.52	0.01
	SPMS	Females	50-59 yrs	-32.25	[-46.37, -18.13]	-3.31	<0.001
	SPMS	Females	60-69 yrs	-30.30	[-42.06, -18.54]	-2.61	<0.01
	SPMS	Males	40-49 yrs	-49.80	[-83.58, -16.02]	-2.41	0.02
	SPMS	Males	50-59 yrs	-33.30	[-57.55, -9.05]	-2.62	<0.01
	PPMS	Females	50-59 yrs	-28.05	[-40.79, -15.31]	-2.55	0.01
Hip Flexion	PPMS	Males	40-49 yrs	-39.67	[-64.99, -14.35]	-2.61	<0.01
	PPMS	Males	50-59 yrs	-33.60	[-68.02, 0.82]	-2.21	0.03
	RRMS	Females	20-29 yrs	-10.7	[-19.68, -1.72]	-1.948	0.05
	RRMS	Females	30-39 yrs	-17.46	[-24.78, -10.14]	-3.66	<0.001
	RRMS	Females	40-49 yrs	-8.33	[-23.65, 6.99]	-0.89	0.37
	RRMS	Females	50-59 yrs	-4.90	[-12.30, 2.50]	-0.98	0.33
	RRMS	Males	20-29 yrs	-5.84	[-21.08, 9.40]	-1.04	0.30
	RRMS	Males	30-39 yrs	-23.64	[-46.28, -1.00]	-2.49	0.01
	RRMS	Males	40-49 yrs	-14.20	[-29.79, 1.39]	-1.87	0.06
	SPMS	Females	50-59 yrs	-22.89	[-33.93, -11.85]	-3.27	<0.01
	SPMS	Females	60-69 yrs	-28.80	[-39.28, -18.32]	-2.61	<0.01
	SPMS	Males	40-49 yrs	-52.6	[-81.91, -23.29]	-2.64	<0.01
PPMS	SPMS	Males	50-59 yrs	-39.4	[-60.66, -18.14]	-2.61	<0.01
	PPMS	Females	50-59 yrs	-14.21	[-23.64, -4.78]	-2.13	0.03

DF= dorsiflexion; RRMS=relapsing-remitting MS; SPMS=secondary progressive MS; PPMS=primary progressive MS; yrs=years. Mean Diff=average difference between age and gender matched MS subjects and controls. C.I. 95%= The 95% confidence interval for the mean difference.

Muscle Action	Subtype	Gender	Age group	Mean Diff.	C.I. 95%	z	p-value
	PPMS	Males	40-49 yrs	-28.78	[-50.44, -7.12]	-2.10	0.04
	PPMS	Males	50-59 yrs	-42.70	[-64.36, -21.04]	-2.61	<0.01

Table 5

Correlations between impairment measures, within MS subtypes

Total Cohort Variables	n	r	t	p-value
T25FW & EDSS	130	0.72	11.67	<0.0001
W ADF & EDSS	138	-0.53	-7.31	<0.0001
W HF & EDSS	141	-0.62	-9.22	<0.0001
W GT & EDSS	144	0.65	10.16	<0.0001
NT25FW & W ADF	127	-0.43	-5.29	<0.0001
NT25FW & W HF	130	-0.52	-6.93	<0.0001
NT25FW & W GT	130	0.39	4.80	<0.0001
W ADF & W HF	139	0.71	11.62	<0.0001
W ADF & W GT	139	-0.28	-3.45	<0.001
W HF & W GT	142	-0.34	-4.31	<0.0001

RRMS Variables	n	r	t	p-value
T25FW & EDSS	85	0.52	5.60	<0.0001
W ADF & EDSS	87	-0.21	-1.97	0.05
W HF & EDSS	88	-0.31	-2.98	0.004
W GT & EDSS	90	0.54	6.01	<0.0001
NT25FW & W ADF	84	-0.16	-1.47	0.15
NT25FW & W HF	85	-0.28	-2.63	0.01
NT25FW & W GT	85	0.26	2.47	0.02
W ADF & W HF	88	0.55	6.07	<0.0001
W ADF & W GT	88	0.03	0.27	0.79
W HF & W GT	89	-0.03	-0.29	0.78

SPMS Variables	n	r	t	p-value
T25FW & EDSS	25	0.71	4.83	<0.0001
W ADF & EDSS	30	-0.59	-3.90	0.0005
W HF & EDSS	31	-0.75	-6.16	<0.0001
W GT & EDSS	31	0.07	0.37	0.71
NT25FW & W ADF	24	-0.53	-2.91	0.008
NT25FW & W HF	25	-0.56	-3.28	0.003
NT25FW & W GT	25	-0.01	-0.04	0.97
W ADF & W HF	30	0.68	4.86	<0.0001
W ADF & W GT	30	0.09	0.48	0.64
W HF & W GT	31	-0.01	-0.08	0.94

PPMS Variables	n	r	t	p-value
T25FW & EDSS	20	0.78	5.32	<0.0001
W ADF & EDSS	21	-0.47	-2.31	0.03
W HF & EDSS	22	-0.58	-3.17	0.005
W GT & EDSS	23	0.34	1.67	0.11

PPMS Variables	n	r	t	p-value
NT25FW & W ADF	19	-0.36	-1.61	0.13
NT25FW & W HF	20	-0.63	-3.46	0.003
NT25FW & W GT	20	<0.01	0.01	0.99
W ADF & W HF	21	0.74	4.80	0.0001
W ADF & W GT	21	-0.14	-0.63	0.54
W HF & W GT	22	-0.05	-0.21	0.83

T25FW=Timed 25-foot walk test; EDSS=Expanded Disability Status Scale; W=worse; ADF=ankle dorsiflexion strength; HF=hip flexion strength; GT=great toe vibration sensation; N=normalized; n=number of subjects; r values were obtained using Spearman test

Table 6

Correlations between MS quantitative sensorimotor measures and their corresponding functional systems score and the EDSS

MS variables	n	r	t	p-value
Sensory FSS & GT vibration	138	0.64	9.82	<0.0001
EDSS & GT vibration	142	0.64	9.97	<0.0001
Pyramidal FSS & Ankle DF	139	-0.49	-6.52	<0.0001
EDSS & Ankle DF	139	-0.48	-6.32	<0.0001
Pyramidal FSS & Hip flexion	139	-0.65	-10.03	<0.0001
EDSS & Hip flexion	139	-0.62	-9.19	<0.0001

FSS= functional system score; GT= great toe; EDSS= Expanded Disability Status Scale; DF= dorsiflexion; n= number of subjects; r values were obtained using Spearman test