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# Quantitative measures detect sensory and motor impairments in multiple sclerosis

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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 relapsing-remitting MS, 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 (i.e., EDSS), but they had improved sensitivity, as they detected impairments in up to 32% of MS subjects with normal sensory and pyramidal FSS.
*Conclusions:* Sensory and motor deficits in MS 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.


## 1. 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 controls, 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

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impairments in a heterogeneous group of MS patients and that they are more precise than their respective sensory and pyramidal functional system scores (FSS) 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 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.

## 2. Methods

### 2.1. 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° 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 sensation 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 h in MS subjects to determine the effects of day to day variability. For the quantitative methods, three examiners (J.W., J.K., and S.N.) were trained and tested by one experienced tester (K.M.Z.) to use the same testing technique.

### 2.2. 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 sensorimotor data.

### 2.3. Statistical analysis

Statistical analyses were completed using Stata 10 (StataCorp LP, College Station, TX) 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

**Table 1**
Characteristics of individuals with multiple sclerosis.

| MS type | Disease duration (years) | Gender | Age (years) | Disease duration (years) | EDSS | Median EDSS |
|---|---|---|---|---|---|---|
| Relapsing-remitting | Total | 65/26 | 38.5 (10.7) | 6.9 (6.4) | 2.6 (1.6) | 2.5 |
| | 0–9 | 47/22 | 36.0 (9.5) | 4.0 (2.8) | 2.3 (1.4) | 2.0 |
| | 10–19 | 15/2 | 43.2 (9.5) | 13.2 (2.4) | 3.1 (1.8) | 3.0 |
| | ≥20 | 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 | 3/3 | 46.7 (4.8) | 5.5 (2.4) | 4.1 (1.6) | 3.8 |
| | 10–19 | 7/5 | 49.0 (7.0) | 15.3 (2.9) | 5.6 (1.4) | 6.0 |
| | ≥20 | 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 | 6/7 | 47.5 (8.2) | 5.0 (2.7) | 4.5 (1.6) | 4.0 |
| | 10–19 | 4/3 | 55.1 (6.5) | 15.0 (2.9) | 6.6 (0.9) | 6.5 |
| | ≥20 | 2/1 | 61.0 (8.7) | 32.3 (10.7) | 4.8 (2.0) | 6.0 |

Values are mean (standard deviation); Gender = number of female/male subjects; EDSS = Expanded Disability Status Scale.