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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.

Table 2A
Great toe vibration sensation in individuals with multiple sclerosis.

MS type	Disease duration (years)	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	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	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	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	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	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	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	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	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	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). 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 3
Ankle dorsiflexion and hip flexion strength values for healthy controls.

Muscle action	Age (years)	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; R = right; L = left; *n* = number of subjects; SD = standard deviation.

less sensitive) for comparative statistics. All reported *p* values are two-tailed and statistically significant if $p<0.05$.

For our study aim 2: to compare 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: to compare 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

Table 2B
Ankle dorsiflexion and hip flexion strength values in individuals with multiple sclerosis.

MS type	Disease duration (years)	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 (0.19)	89	21.0 (5.6)	0.71 (0.17)	0.67 (0.18)
		L	88	21.6 (5.9)	0.72 (0.20)		89	20.5 (5.9)	0.71 (0.19)	
	0–9	R	65	23.3 (5.7)	0.80 (0.19)	0.72 (0.19)	68	21.8 (5.9)	0.74 (0.18)	0.70 (0.19)
		L	67	22.3 (5.9)	0.74 (0.21)		68	21.0 (6.3)	0.73 (0.21)	
	10–19	R	16	21.1 (5.3)	0.74 (0.16)	0.64 (0.18)	16	17.7 (3.0)	0.61 (0.10)	0.59 (0.10)
		L	16	19.0 (5.4)	0.63 (0.19)		16	17.6 (3.5)	0.62 (0.12)	
	≥20	R	5	20.4 (6.5)	0.70 (0.24)	0.66 (0.20)	5	20.3 (3.4)	0.69 (0.09)	0.69 (0.09)
		L	5	21.8 (5.6)	0.71 (0.18)		5	21.7 (3.6)	0.76 (0.10)	
Secondary progressive	Total	R	29	13.5 (9.2)	0.47 (0.32)	0.38 (0.26)	31	10.2 (8.0)	0.36 (0.35)	0.29 (0.23)
		L	31	15.2 (7.7)	0.51 (0.26)		30	11.0 (6.9)	0.38 (0.23)	
	0–9	R	6	16.2 (11.7)	0.53 (0.37)	0.45 (0.31)	6	14.3 (8.4)	0.47 (0.27)	0.44 (0.25)
		L	6	17.1 (6.2)	0.55 (0.17)		6	15.5 (3.9)	0.53 (0.12)	
	10–19	R	11	13.7 (8.4)	0.47 (0.30)	0.40 (0.27)	12	10.8 (8.5)	0.40 (0.28)	0.33 (0.26)
		L	12	15.5 (7.1)	0.51 (0.25)		11	12.7 (7.1)	0.44 (0.24)	
	≥20	R	12	12.0 (9.1)	0.43 (0.33)	0.34 (0.24)	13	7.8 (7.1)	0.27 (0.24)	0.20 (0.17)
		L	13	14.1 (9.1)	0.48 (0.31)		13	7.5 (6.5)	0.27 (0.23)	
Primary progressive	Total	R	21	18.5 (8.8)	0.62 (0.26)	0.43 (0.30)	22	15.8 (7.7)	0.53 (0.25)	0.42 (0.24)
		L	21	14.7 (10.0)	0.48 (0.32)		22	14.1 (8.4)	0.48 (0.28)	
	0–9	R	13	20.2 (10.0)	0.65 (0.29)	0.51 (0.27)	13	18.9 (6.2)	0.63 (0.19)	0.56 (0.21)
		L	13	19.7 (7.6)	0.64 (0.23)		13	18.9 (7.2)	0.65 (0.23)	
	10–19	R	5	12.6 (4.1)	0.45 (0.15)	0.20 (0.22)	6	8.5 (6.7)	0.29 (0.23)	0.20 (0.16)
		L	5	7.7 (8.8)	0.27 (0.32)		6	6.5 (5.1)	0.23 (0.18)	
	≥20	R	3	20.9 (5.4)	0.75 (0.20)	0.44 (0.45)	3	16.9 (7.0)	0.58 (0.24)	0.30 (0.05)
		L	3	4.2 (7.2)	0.14 (0.24)		3	8.5 (1.5)	0.30 (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). 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 4A
Age-matched vibration sensation differences between MS subtypes and healthy controls.

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

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

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.

3. Results

3.1. Study population

In the cohort of 145 MS subjects, there was a mean age of 43.6 ± 11.9 years (mean ± 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).

3.2. 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).

Table 4B
MS subtypes quantitative strength measures Z-score deviation from healthy controls.

Muscle action	Subtype	Gender	Age group (years)	Mean diff.	C.I. 95%	*z*	*p*-value
Ankle DF	RRMS	Females	20–29	−18.71	[−31.26, −6.16]	−2.91	<0.01
	RRMS	Females	30–39	−30.50	[−38.06, −22.94]	−4.16	<0.001
	RRMS	Females	40–49	−13.65	[−23.44, −3.86]	−2.42	0.02
	RRMS	Females	50–59	−17.29	[−28.28, −6.30]	−2.67	<0.01
	RRMS	Males	20–29	−10.09	[−24.76, 4.58]	−2.41	0.02
	RRMS	Males	30–39	−24.57	[−41.73, −7.41]	−2.49	0.01
	RRMS	Males	40–49	−20.86	[−36.43, −5.29]	−2.52	0.01
	SPMS	Females	50–59	−32.25	[−46.37, −18.13]	−3.31	<0.001
	SPMS	Females	60–69	−30.30	[−42.06, −18.54]	−2.61	<0.01
	SPMS	Males	40–49	−49.80	[−83.58, −16.02]	−2.41	0.02
	SPMS	Males	50–59	−33.30	[−57.55, −9.05]	−2.62	<0.01
	PPMS	Females	50–59	−28.05	[−40.79, −15.31]	−2.55	0.01
	PPMS	Males	40–49	−39.67	[−64.99, −14.35]	−2.61	<0.01
	PPMS	Males	50–59	−33.60	[−68.02, 0.82]	−2.21	0.03
Hip flexion	RRMS	Females	20–29	−10.70	[−19.68, −1.72]	−1.95	0.05
	RRMS	Females	30–39	−17.46	[−24.78, −10.14]	−3.66	<0.001
	RRMS	Females	40–49	−8.33	[−23.65, 6.99]	−0.89	0.37
	RRMS	Females	50–59	−4.90	[−12.30, 2.50]	−0.98	0.33
	RRMS	Males	20–29	−5.84	[−21.08, 9.40]	−1.04	0.30
	RRMS	Males	30–39	−23.64	[−46.28, −1.00]	−2.49	0.01
	RRMS	Males	40–49	−14.20	[−29.79, 1.39]	−1.87	0.06
	SPMS	Females	50–59	−22.89	[−33.93, −11.85]	−3.27	<0.01
	SPMS	Females	60–69	−28.80	[−39.28, −18.32]	−2.61	<0.01
	SPMS	Males	40–49	−52.60	[−81.91, −23.29]	−2.64	<0.01
	SPMS	Males	50–59	−39.40	[−60.66, −18.14]	−2.61	<0.01
	PPMS	Females	50–59	−14.21	[−23.64, −4.78]	−2.13	0.03
	PPMS	Males	40–49	−28.78	[−50.44, −7.12]	−2.10	0.04
	PPMS	Males	50–59	−42.70	[−64.36, −21.04]	−2.61	<0.01

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

3.3. Differences among MS subtypes

Fig. 1A–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 ($p>0.05$).

3.4. 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) was 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:

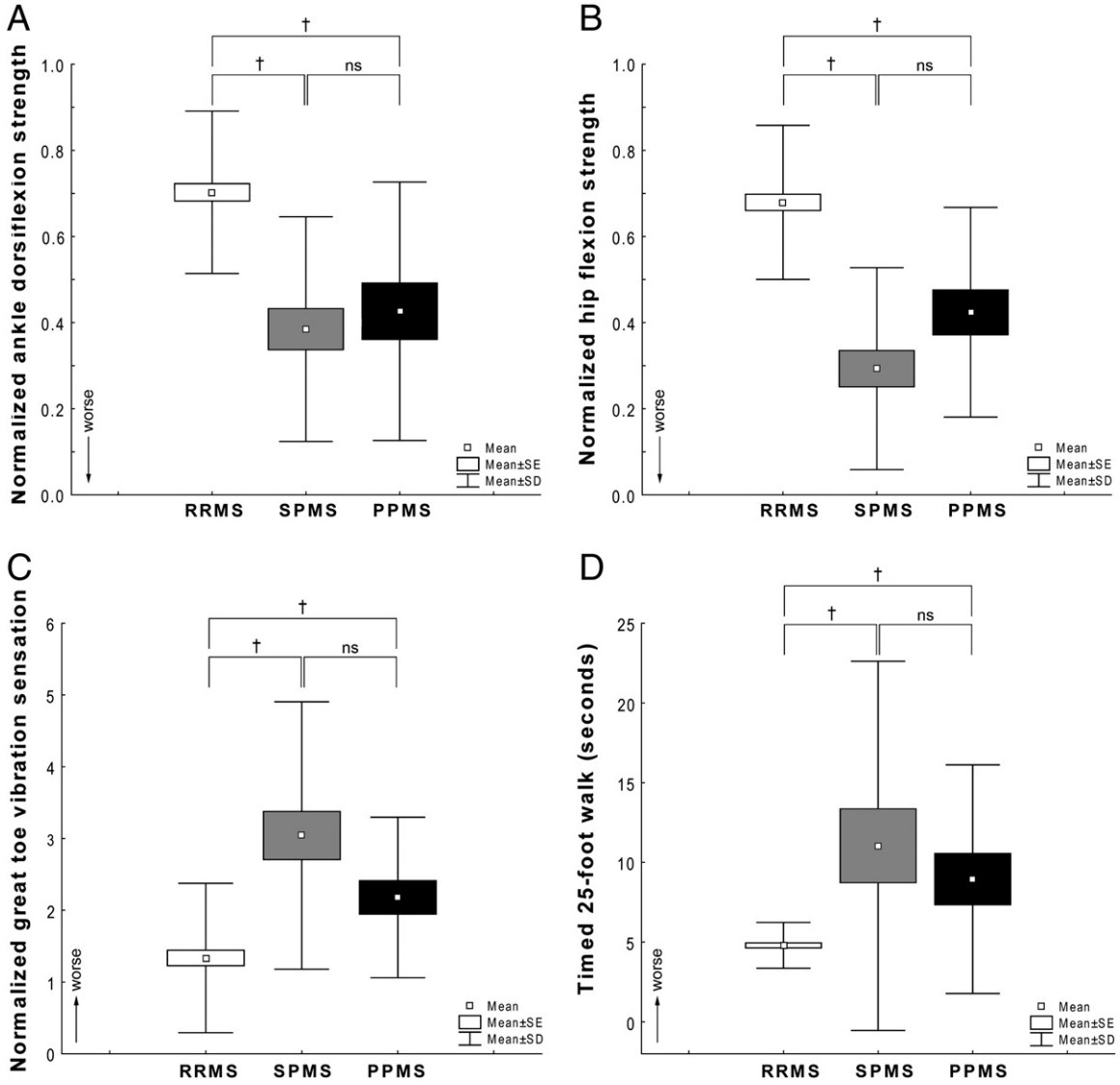

Fig. 1. Box plots showing group means of disease impairment for RRMS, SPMS, and PPMS groups. (A) Normalized ankle dorsiflexion strength, (B) Normalized hip flexion strength, (C) Normalized great toe vibration sensation, and (D) T25FW in individuals with multiple sclerosis (MS). RRMS = relapsing-remitting MS; SPMS = secondary progressive MS; PPMS = primary progressive MS; ns = not significant; † $p \leq 0.0001$.

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.

3.5. 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.

Table 5
Correlations between impairment measures, within MS subtypes.

	n	*r*	*t*	*p*-value
Total cohort variables				
T25FW and EDSS	130	0.72	11.67	<0.0001
W ADF and EDSS	138	−0.53	−7.31	<0.0001
W HF and EDSS	141	−0.62	−9.22	<0.0001
W GT and EDSS	144	0.65	10.16	<0.0001
NT25FW and W ADF	127	−0.43	−5.29	<0.0001
NT25FW and W HF	130	−0.52	−6.93	<0.0001
NT25FW and W GT	130	0.39	4.80	<0.0001
W ADF and W HF	139	0.71	11.62	<0.0001
W ADF and W GT	139	−0.28	−3.45	<0.001
W HF and W GT	142	−0.34	−4.31	<0.0001
RRMS variables				
T25FW and EDSS	85	0.52	5.60	<0.0001
W ADF and EDSS	87	−0.21	−1.97	0.05
W HF and EDSS	88	−0.31	−2.98	0.004
W GT and EDSS	90	0.54	6.01	<0.0001
NT25FW and W ADF	84	−0.16	−1.47	0.15
NT25FW and W HF	85	−0.28	−2.63	0.01
NT25FW and W GT	85	0.26	2.47	0.02
W ADF and W HF	88	0.55	6.07	<0.0001
W ADF and W GT	88	0.03	0.27	0.79
W HF and W GT	89	−0.03	−0.29	0.78
SPMS variables				
T25FW and EDSS	25	0.71	4.83	<0.0001
W ADF and EDSS	30	−0.59	−3.90	0.0005
W HF and EDSS	31	−0.75	−6.16	<0.0001
W GT and EDSS	31	0.07	0.37	0.71
NT25FW and W ADF	24	−0.53	−2.91	0.008
NT25FW and W HF	25	−0.56	−3.28	0.003
NT25FW and W GT	25	−0.01	−0.04	0.97
W ADF and W HF	30	0.68	4.86	<0.0001
W ADF and W GT	30	0.09	0.48	0.64
W HF and W GT	31	−0.01	−0.08	0.94
PPMS variables				
T25FW and EDSS	20	0.78	5.32	<0.0001
W ADF and EDSS	21	−0.47	−2.31	0.03
W HF and EDSS	22	−0.58	−3.17	0.005
W GT and EDSS	23	0.34	1.67	0.11
NT25FW and W ADF	19	−0.36	−1.61	0.13
NT25FW and W HF	20	−0.63	−3.46	0.003
NT25FW and W GT	20	<0.01	0.01	0.99
W ADF and W HF	21	0.74	4.80	0.0001
W ADF and W GT	21	−0.14	−0.63	0.54
W HF and 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.

3.6. 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 was the most significant predictor 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.

3.7. 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 was the most significant predictor 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).

3.8. 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) $N = 21$; and 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) $N = 22$ and 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) $N = 18$; and hip flexion, ICC = 0.95 (1.28 kg, 0.21 kg) $N = 20$.

4. 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, was stronger, walked more quickly than the progressive groups, and had the lowest EDSS scores. More importantly, our quantitative sensorimotor measures significantly correlated with

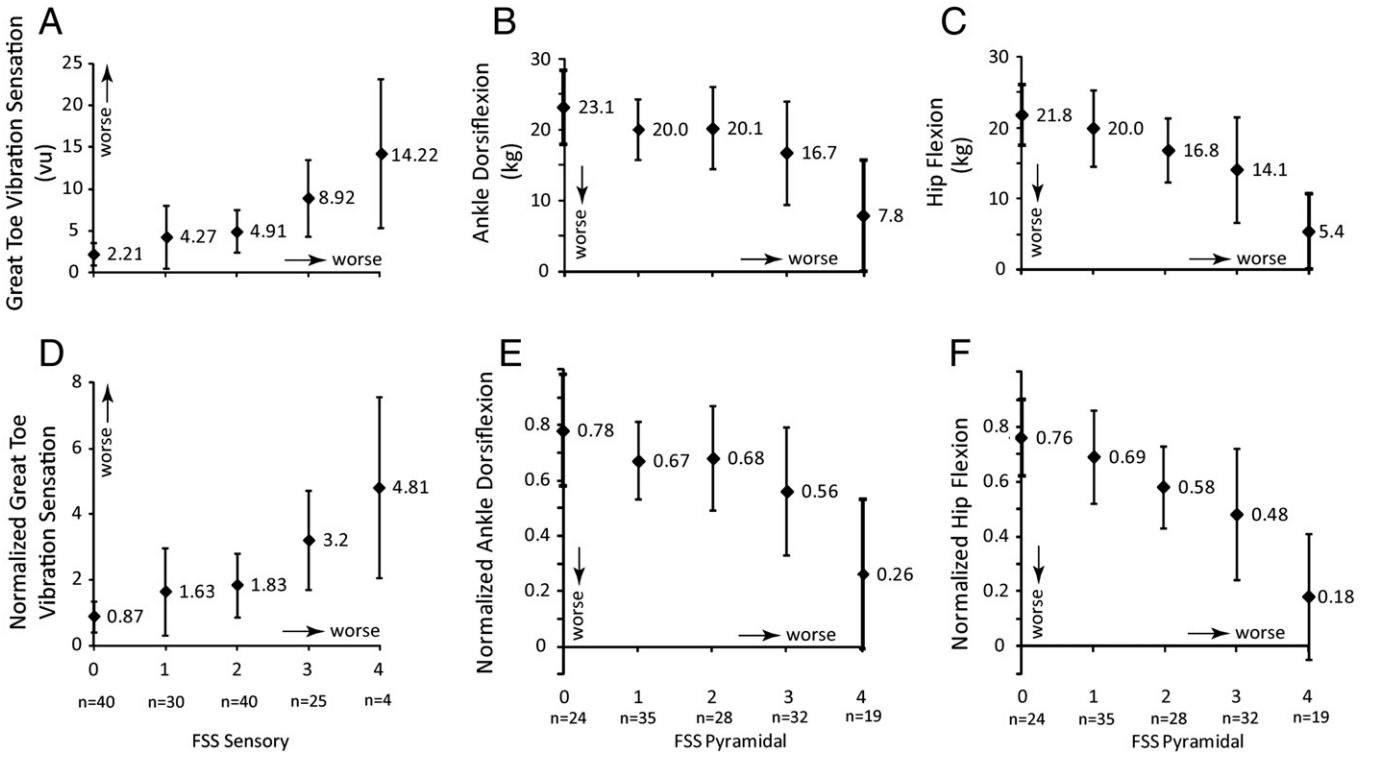

Fig. 2. Plot shows mean values for each MS quantitative sensory and motor measure graphed against the corresponding EDSS functional systems score (FSS). Group means and standard deviations are presented. (A) Raw great toe vibration sensation and sensory FSS, (B) raw ankle dorsiflexion strength and pyramidal 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.

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.

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 and GT vibration	138	0.64	9.82	<0.0001
EDSS and GT vibration	142	0.64	9.97	<0.0001
Pyramidal FSS and ankle DF	139	−0.49	−6.52	<0.0001
EDSS and ankle DF	139	−0.48	−6.32	<0.0001
Pyramidal FSS and hip flexion	139	−0.65	−10.03	<0.0001
EDSS and 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.

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 require examiners to be trained for proper testing technique and assume 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.

4.1. 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.

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