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Upper and Lower Extremity Motor Function and Cognitive Impairment in Multiple Sclerosis

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Abstract

Motor impairments and cognitive dysfunction are common in multiple sclerosis (MS). We aimed to delineate the relationship between cognitive capacity and upper and lower motor function in 211 MS patients, and 120 healthy volunteers. Lower and upper motor function were assessed with the Timed 25 Foot Walk (T25FW) and the Nine Hole Peg Test (NHPT) as implemented in the Multiple Sclerosis Functional Composite (MSFC). Subjects also underwent neuropsychological evaluation. Hierarchical linear regression analysis was conducted separately for the MS and healthy groups with the T25FW and NHPT serving as the outcome measures. Cognitive performance indices served as predictors. As expected, healthy subjects performed better than the MS group on all measures. Processing speed and executive function tests were significant predictors of lower and upper motor function in both groups. Correlations were more robust in the MS group, where cognitive tests predicted variability in motor function after controlling for disease duration and physical disability. In conclusion, we find evidence of higher order cognitive control of motor function that appears to be particularly salient in this large and representative MS sample. The findings may have implications for risk assessment and treatment of mobility dysfunction in MS. (*JINS*, 2011, *17*, 643–653)

Keywords: Neurological disorder, Executive function, Memory, Physical disability, Gait, Manual dexterity

INTRODUCTION

Loss of motor function is often the most visible symptom of multiple sclerosis (MS) and the hallmark, clinical feature of the disease. Motor dysfunction occurs most commonly in the lower extremity, but upper extremity weakness and ataxia are also common. Recognizing the presence of concurrent impairments in ambulation and upper extremity function, an international consensus panel included representative measures in the MS Functional Composite (MSFC) to reflect both (a) leg function or ambulation and (b) arm/hand function (Cutter et al., 1999; Fischer, Rudick, Cutter, & Reingold, 1999). This effort culminated in a brief, but more comprehensive assessment of overall neurological disability (Cutter et al., 1999; Fischer, et al., 1999) for clinical trials and outcome research. Indeed, measures of ambulation and upper extremity speed or dexterity continue to serve as primary outcomes in MS clinical research and are prime targets for rehabilitation interventions.

By comparison, cognitive impairment is less common in MS, but it can be equally detrimental when considering impact on quality of life and functional adaptation (Benedict et al., 2005; Rao, Leo, Bernardin, et al., 1991). Neuropsychological assessment typically shows significant deficiency on tests emphasizing mental processing speed and memory, although executive function deficits are also observed with considerable frequency (Beatty & Monson, 1996; Benedict et al., 2006; Rao, Leo, Bernardin, & Unverzagt, 1991). As with motor function, the same international consensus panel included a test of cognitive function in the MSFC (Paced Auditory Serial Addition Test, or PASAT), but it is less frequently included as a primary outcome in clinical research.

There is a growing recognition of inter-relationships among these three domains of clinical status in MS patients. Walking requires higher order information processing especially in individuals with compromised ability due to aging or disease (Yogev-Seligmann, Hausdorff, & Giladi, 2008). In older adults with a mean age of 72 years, walking speed

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was significantly correlated with measures of executive function such as the Stroop conflict task (Hausdorff, 2005). In a large community-based sample of 926 adults over age 65, walking speed was correlated with a measure of executive control derived from the Trail Making Test (Ble et al., 2005). Similar associations have been reported in patients with traumatic brain injury (Cantin et al., 2007), Parkinson's disease (Yogev et al., 2005), and Alzheimer's disease (Allali et al., 2008), although this literature is scant and we know of no research in large MS samples that focused on the associations among multiple measures of cognition and motor performance.

We (Drake et al., 2010) recently reported on the validity of various forms of the MSFC in 400 MS patients, and found a correlation of $r = .41$ between the timed 25 foot walk (T25FW) and total time to complete the Nine Hole Peg Test (NHPT) (Mathiowetz, Weber, Kashman, & Volland, 1985). In the retrospective analysis of archival MS data by the MSFC consensus panel, this linear relationship was $r = .39$ (Cutter et al., 1999; Fischer et al., 1999).

Understanding the relationship between cognition and functional motor outcomes such as the T25FW and NHPT has implications for concepts pertaining to the neuropsychology of motor function, as well as the development of new risk assessment procedures and rehabilitation treatments in MS. Executive function may be particularly relevant. Patients with impaired attention, working memory, or reasoning capacity may be more prone to errors in the execution of motor-based tasks, and at high risk for accidents (e.g., falls). It is even conceivable that improving executive function capacity in rehabilitation may have secondary effects on motor function. Recognizing the dearth of literature on the topic in MS, a disease which causes marked impairment in both motor and cognitive function, we undertook a retrospective analysis of timed ambulation, arm/hand function, and a comprehensive record of cognitive capacities in MS. We hypothesized that performance on executive function tasks would be significantly correlated with motor performance in MS, after controlling for demographics, disease characteristics such as disease duration, and other cognitive domains.

METHODS

Participants

We studied retrospectively 211 patients with clinically definite MS or clinically isolated syndrome (Polman et al., 2005) followed at the Jacobs Neurological Institute (JNI) in Buffalo, New York. The data were collected using methods approved by the Health Sciences Institutional Review Board (IRB) at SUNY Buffalo. Patients were excluded from the study if any of the following criteria were met: (a) past history of medical or psychiatric disorder that could substantially influence cognitive function or have a lasting impact on brain integrity, including but not limited to craniocerebral trauma with greater than 5-min loss of consciousness, alcohol or drug dependence, and learning disability; (b) current major depression or alcohol/substance abuse as identified by in house standard interview based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; APA, 2000) criteria; (c) neurological impairment that might interfere with cognitive testing; (d) MS relapse or acute corticosteroid treatment within six weeks of testing. Mean ($\pm SD$) age was 44.9 ± 10.0 years. The MS sample was 79.1% female and 92.3% Caucasian. Patients had completed on average 14.4 ± 2.2 years of education before participation.

All patients were characterized according to their current disease course (Lublin & Reingold, 1996) as follows: relapsing-remitting ($n = 172$ or 81%), secondary-progressive ($n = 26$), relapsing progressive ($n = 4$), primary progressive ($n = 5$), and CIS ($n = 4$). The Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) is an ordinal scale of neurological disability designed specifically for MS patients. There is a strong emphasis on physical functioning, particularly ambulation. EDSS within 6 months of testing was obtained by a treating neurologist. The mean EDSS was 2.8 ± 1.6 and the median was 2.5 (range, 0–7.0), reflecting mild to moderate disability. The mean disease duration was 9.6 ± 7.9 years (range, 0–38).

The patients were compared to a demographically matched sample of 120 healthy volunteers with the following demographic characteristics: age $43.9 + 9.8$ years, education $14.9 + 2.0$ years, 73.3% female, 95.0% Caucasian. These subjects were recruited during the course of prior MS research and were selected for demographic parameters approximating our MS population. Exclusion criteria for these subjects were any medical condition that might conceivably compromise neuropsychological or neurological capacity, including developmental disorder. There were no significant patient/normal differences on demographic features by analysis of variance (ANOVA) and χ^2 test.

Measures

All participants underwent neuropsychological testing using the Minimal Assessment of Cognitive Function in MS (MACFIMS). This consensus battery (Benedict et al., 2002) was validated in large prospective MS samples (Benedict et al., 2006; Parmenter, Testa, Schretlen, Weinstock-Guttman, & Benedict, 2010; Strober et al., 2009), and the reliability of the component tests is well established in the various test manuals and in prospective research (Benedict, 2005). The specific tests are as follows: Controlled Oral Word Association Test (COWAT) (Benton, Sivan, Hamsher, Varney, & Spreen, 1994), Judgment of Line Orientation Test (JLO) (Benton et al., 1994), California Verbal Learning Test, second edition (CVLT2) (Delis, Kramer, Kaplan, & Ober, 2000), Brief Visuospatial Memory Test-Revised (BVMTR) (Benedict, 1997), Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977), Symbol Digit Modalities Test (SDMT) (Smith, 1982), and the Delis-Kaplan Executive Function System Sorting Test (DKEFS) (Delis, Kaplan, & Kramer, 2001). In addition to acceptable psychometric standards, the MACFIMS tests show good correlation with a range of brain MRI variables in MS samples

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(Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2009; Benedict et al., 2008; Houtchens et al., 2007; Tekok-Kilic et al., 2007).

The specific procedures for each test have been described in the aforementioned publications. In brief, Rao's adaptations (Rao, 1991) of the PASAT and SDMT were used to assess mental processing speed and working memory. The PASAT included 60 trials presented at an inter-stimulus intervals of 3 s. The 3-s version is a component of the MS Functional Composite (MSFC), a clinical outcome measure composed of quantitative measures of leg, arm/hand, and cognitive function (Cutter et al., 1999; Fischer et al., 1999). The dependent measure was the number of correct responses from each of the two trials. Following Rao, we used only the oral response version of the SDMT. For memory, the CVLT2 and BVMTR required the unaided recall of word-lists and abstract visual designs, respectively. While these memory tests include multiple measures assessing, for example, delayed recall and recognition memory, to reduce the number of independent measures in regression models we used only the total learning measures, that is, the total number of items recalled over all immediate learning trials. Generative word fluency was assessed with the COWAT, which required subjects to generate as many words as possible beginning with a designated letter of the alphabet. The JLO presented line angles and the subject's task was to match the unlabeled lines with a model below. Finally, the DKEFS Sorting Test was administered to evaluate higher executive function. Patients were asked to sort cards into two groups and to describe each sorting principle verbally. The dependent measures were the number of Correct Sorts and the verbal Description Score gathered from the free sorting condition.

Depression was assessed using the Beck Depression Inventory–Fast Screen (BDIFS) (Beck, Steer, & Brown, 2000). The BDI-FS is a seven-item, self-report measure of depression frequently used in medical populations and validated in MS (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003).

The motor tasks from the Multiple Sclerosis Functional Composite (MSFC), developed by the National Multiple Sclerosis Society (NMSS) Clinical Outcomes Assessment Task Force (Cutter et al., 1999; Fischer et al., 1999; Rudick et al., 2001), were also administered. The MSFC combines quantitative measures of upper extremity, lower extremity, and cognitive function into a single composite. The MSFC is widely recognized for its robust psychometric properties, standardized administration, and continuous scoring, which improve measurement characteristics over the customary EDSS (Cohen et al., 2001; Hobart et al., 2004). The motor tasks for the MSFC are the T25FW and the NHPT. The T25FW consisted of the participant walking 25 feet as quickly but as safely as possible. The task was repeated and the mean time (in seconds) taken to complete the T25FW was recorded. The NHPT (Mathiowetz et al., 1985) required that the participant move each of nine pegs into one of nine holes on a peg-board using only one hand and picking up only one peg at a time, followed by removal of all the pegs. The task was administered twice with each hand and the average time taken to complete the task was recorded.

Procedures

The human data included in this manuscript were obtained in compliance with regulations of the SUNY Buffalo IRB. Subjects were evaluated in an outpatient clinical setting housed within an urban hospital in the eastern USA. A trained technician or graduate student, under the supervision of a board-certified neuropsychologist, administered all tests. Board-certified neurologist clinicians reported the EDSS scores. A trained student blind to clinical data and presentation was responsible for entering data into an SPSS database accounting for all of the NP variables.

Analysis Plan

Distributional and descriptive statistics were used to inspect the data for deviation from normality. As the motor tasks were positively skewed in the MS group, for the regression analysis (see below) we transformed the data using the LOG transformation. The LOG transformed measures were used for all statistical analyses, although we report the raw score mean values in the tables.

Between-group effects comparing MS versus healthy volunteers groups were examined using univariate ANOVA and χ^2 tests with effect sizes for mean differences based on Cohen's d (Cohen & Cohen, 1983). We did not adjust for demographic differences because the samples were closely matched in these domains. Bivariate linear relationships were examined with the Pearson product-moment coefficient.

The general hypothesis testing approach used hierarchical regression analysis. To reduce the variables to the smallest possible set, the NHPT dominant and non-dominant hand values were averaged for the NHPT dependent variable. In each model, tests for multicolinearity (variance inflation factor) were examined and were within the acceptable range. We did note that the distributions on the dependent variables had more dispersion in MS, as would be expected (Figures 1 and 2), and hence the LOG transformation. In each analysis, one of the motor outcomes was regressed on three sets of independent variables: (a) demographics and depression, (b) non-executive neuropsychological tests, (c) executive function tests. We began by predicting motor task scores with demographics (age, education, sex, race) and depression as measured by the BDIFS. Significant predictors were carried forward to the next step in the hierarchical regression process which included two sub-analyses. In Model A, the non-executive tests (COWAT, JLO, CVLT2, BVMTR) were entered in Step 2 followed by the executive tests in Step 3 (SDMT, PASAT, DKEFS). The change in R^2 provided the incremental variance accounted for by each set of cognitive tests. Then, in Model B, the sequence of neuropsychological predictors was reversed, with executive tests entered in Step 2 and non-executive tests in Step 3. If our hypothesis was correct, the executive tests should contribute significant incremental variance in both analyses, but the non-executive

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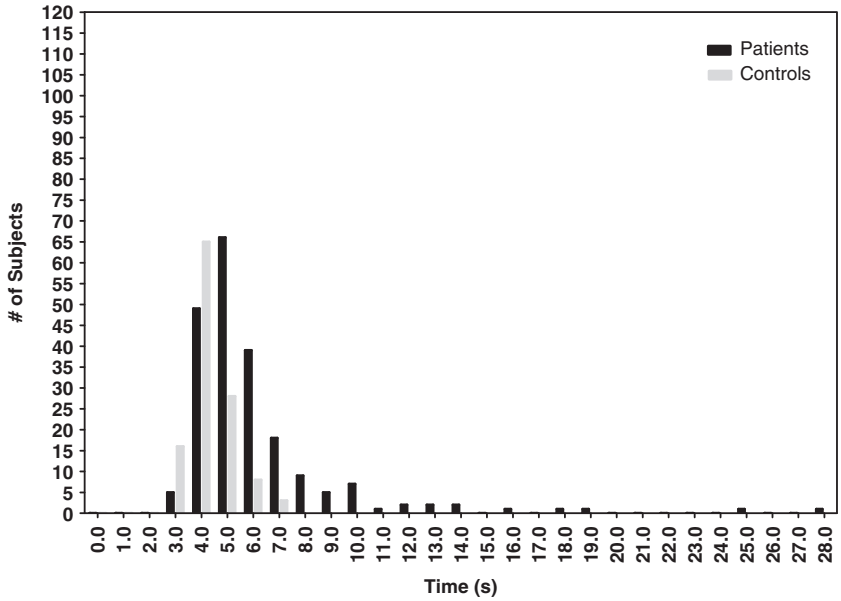

Fig. 1. Frequency distribution for the Timed 25 Foot Walk, in seconds, for normal control and multiple sclerosis patients segregated.

tests should not contribute significant incremental variance after accounting for the executive tests in Model B. There were four basic analyses, predicting T25FW and NHPT, in both healthy and MS groups. Then the same approach was repeated for the MS group, only disease features (EDSS, course, disease duration) were added in Step 1, ahead of the neuropsychological measures. Finally, to specifically test for the influence of diagnosis on the degree of correlation between cognition and motor function, we calculated an interaction (Dx $\times$ performance) term and included it in *post hoc*, stepwise regression models predicting the motor outcomes.

For the between-group and univariate correlations, a conservative p value of $p < .01$ was used to designate statistical significance. For the regression models, we used the conventional $p < .05$ threshold for identifying significant IVs for each model. Throughout, we reported Cohen's d and R^2 effect size descriptors to enable the reader to judge the meaningfulness of the statistically significant results.

RESULTS

The distributions of the T25FW and NHPT are presented in Figures 1 and 2. These distributions approximated a Gaussian

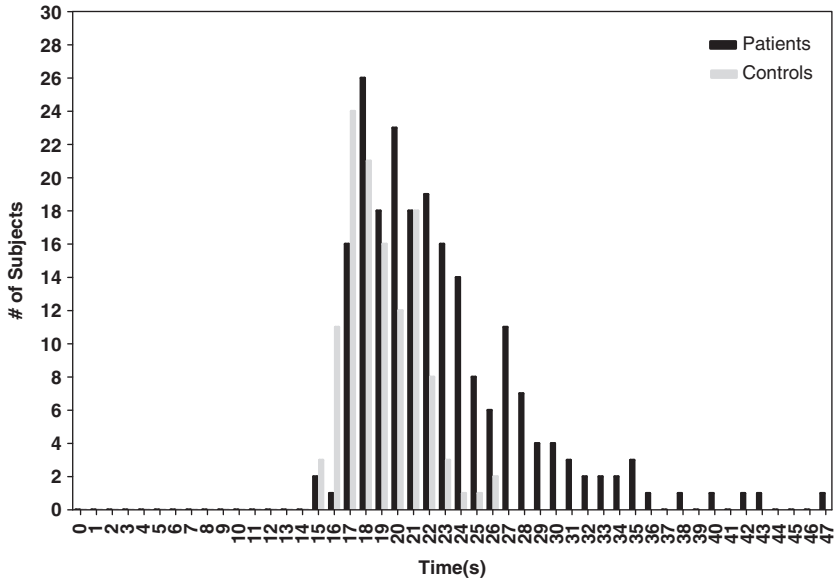

Fig. 2. Frequency distribution for the Nine Hole Peg Test – Average of Dominant and Non-Dominant Hands, in seconds, for normal control and multiple sclerosis patients segregated.

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Table 1. MS patients compared to healthy volunteers

	MS		NC			
	Mean	*SD*	Mean	*SD*	*p*	d
Age	46.2	8.9	44.7	9.4	ns	.1
Education	14.2	2.3	14.4	1.7	ns	.0
Sex: male/female, % male	32/88; 27% Male		44/167; 21% Male		ns	
Race/ethnicity: C/A/O, % Caucasian	114/5/1; 95% Cauc		193/14/2; 92% Cauc		ns	
BDI-FS	3.3	3.4	.9	1.4	<.001	.9
COWAT	36.7	10.9	42.6	11.9	<.001	.5
JLO	22.3	5.5	24.1	3.9	<.01	.3
CVLT2 Total Learning	48.8	10.5	55.7	9.3	<.001	.7
BVMT Total Learning	20.9	7.1	26.6	5.5	<.001	.9
PASAT 3.0 ISI	40.0	13.3	46.3	12.1	<.001	.4
SDMT	49.5	13.2	61.4	9.3	<.001	1.0
DKEFS Sorting Correct Sorts	9.4	2.4	10.2	2.3	<.01	.3
DKEFS Sorting Description Score	35.5	10.5	38.6	10.0	<.05	.2

distribution (T25FW Kurtosis 0.72 and Skewness 0.87; NHPT Kurtosis 41.80 and Skewness 5.50), although there was considerable positive skew among MS patients and thus the LOG transformation. MS patients were significantly impaired on both measures by ANOVA (T25FW normal = 4.4 ± 0.9; MS = 6.3 ± 4.1; $p < .001$; NHPT normal = 18.9 ± 2.3; MS = 22.8 ± 5.4; $p < .001$).

As expected, the data replicated earlier work (Benedict et al., 2006; Parmenter, et al. 2010; Strober et al., 2009) showing significant differences on all MACFIMS cognitive tests, favoring the NC group (Table 1). Nearly all p values were <.01, and the effect sizes ranged from d of .2 for DKEFS to 1.0 for SDMT.

Correlations between the motor tasks and the NP measures are presented in Table 2, for both the healthy volunteers and MS group. All of the correlations were in the anticipated direction, with better cognitive performance associated with faster times on the motor tasks. The $p < .01$ threshold for statistical significance identified nine correlation coefficients as statistically significant in the NC group, but there were only two medium (T25FW and DKEFS Description Score −0.40; NHPT and SDMT −0.43) and no large magnitude effects. In the MS group, all of the correlations were statistically significant at $p < .01$. The correlation coefficients were generally larger in magnitude than in the healthy volunteer group, with 8 correlations exceeding .4, and there was one large effect (NHPT-N and SDMT −0.65). Fisher Z test showed significantly greater r values for MS compared to healthy volunteers for CVLT2 and SDMT. This reflects a generally stronger and more consistent association between cognition and motor performance in the MS than normal group.

Regression Analysis in Healthy Volunteers

The regression models predicting the motor tasks in the normal group are presented in Table 3. For T25FW, in the first step, only age was significantly associated (marginally) with motor performance. In Analysis A, significant incremental variance (R^2 change = .10) was associated with the non-executive tests, in step 2 driven mostly by COWAT, and age was no longer significant. Next, in Step 3, adding the executive tests resulted in significant incremental variance over and above that of the non-executive tests (R^2 change = .12; $p = .003$). In contrast, in Model B, whereas significant variance was added by the executive tests in Step 2, there was no significant increase in Step 3 with the non-executive tests (R^2 change = .05; $p = .108$). As can be seen in Table 3, the significant executive function effects were driven by PASAT and DKEFS.

The NHPT model for the healthy volunteer group revealed similar findings except that age, sex and race were included in Step 1, and the executive function effects were driven by SDMT and DKEFS. Again, executive function tests contributed

Table 2. Correlations between motor tasks and NP test measures

	COWAT	JLO	CVLT2	BVMTR	SDMT	PASAT	DKEFS CS	DKEFS DS
Healthy volunteers								
T25FW	−.20	−.15	.03	−.21	−.17	−.26	−.35	−.40
NHPT	−.25	−.01	−.14	−.30	−.43	−.24	−.32	−.33
Multiple sclerosis								
T25FW	−.25	−.21	−.47*	−.39	−.48*	−.36	−.42	−.38
NHPT	−.27	−.20	−.47*	−.45	−.65*	−.41	−.43	−.35

Note. For NC correlations, $p < .01$ applies to all r values greater than .23. For MS correlations, $p < .01$ applies to all r values greater than .19.
*Signifies a significant difference in r values between group by Fisher Z test.

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Table 3. Regression models for healthy volunteers

Healthy controls		Significant IVs	Beta weights	R^2	R^2 Change	p
T25FW Model A	Step 1	Age	.14	.02	.02	=.130
	Step 2	COWAT	−.21	.12	.10	=.016
	Step 3	CVLT2	.22	.24	.12	=.003
		PASAT	−.23			
		DKEFS-DS	−.32			
T25FW Model B	Step 1	Age	.14	.02	.02	=.130
	Step 2	DKEFS-DS	−.30	.18	.16	<.001
	Step 3	PASAT	−.23	.23	.05	=.108
		DKEFS-DS	−.32			
		CVLT2	.22			
NHPT Model A	Step 1	Age	.21	.24	.24	=.013
		Sex	−.36			
		Race	.33			
	Step 2	Sex	−.31	.29	.05	=.090
		Race	.29			
		BVMTR	−.21			
	Step 3	Sex	−.31	.39	.10	=.002
		Race	.25			
		SDMT	−.30			
		DEKEFS-DS	−.30			
NHPT Model B	Step 1	Age	.21	.24	.24	=.013
		Sex	−.36			
		Race	.33			
	Step 2	Sex	−.32	.38	.14	<.001
		Race	.25			
		SDMT	−.33			
		DEKEFS-DS	−.33			
	Step 3	Sex	−.32	.39	.01	=.717
		Race	.25			
		SDMT	−.30			
		DEKEFS-DS	−.30			

significant incremental variance after accounting for non-executive tests in Model A (R^2 change = .10; p = .002), but the converse was not found (R^2 change = .01; p = .717).

Regression Analysis in MS Patients

Model A found that age, education and BDIFS were significantly associated with the T25FW (Table 4). Significant incremental variance was then accounted for by non-executive tests in Step 2 (R^2 change = .12; $p < .001$), and, executive function tests in Step 3 (R^2 change = .07; $p < .001$). The effects were driven mainly by CVLT2 and SDMT. When the order was reversed in Model B, significant variance was only found in Step 2, for the executive function tests (R^2 change = .17; $p < .001$).

Similar findings occurred for NHPT, where only executive function tests accounted for significant variance in Model B. The executive function effects were again driven mainly by SDMT.

As expected, the motor tasks were significantly correlated with EDSS (r for T25FW = .47; for NHPT = .49; p values <.001). Correlations with disease duration were more marginally significant but in the expected direction with longer disease associated with longer times to complete the tasks (r for T25FW = .17; p = .013; NHPT = .28; $p < .001$).

The MS models accounting for disease features in Step 1 revealed similar results as in Table 4. As can be seen in Table 5, EDSS was retained after Step 1, accounting for a large portion of the variance (beta weights .46 for T25FW and .34 for NHPT). Again, the incremental variance in the final Step 3 was significant for the executive function tests in Model A, but not the non-executive tests in Model B. SDMT accounted for the most variance among the neuropsychological test predictors.

Regression Analysis Interaction Effects

Tables 3 and 4 suggest that there is more variance accounted by cognitive tests in the MS than healthy volunteer models

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Table 4. Regression models for multiple sclerosis patients

Multiple sclerosis I		Significant IVs	Beta weights	R^2	R^2 Change	p
T25FW Model A	Step 1	Age	.35	.21	.21	<.001
		Education	−.15			
		BDIFS	.25			
	Step 2	Age	.24	.33	.12	<.001
		BDIFS	.16			
		CVLT2	−.29			
	Step 3	Age	.15	.40	.07	<.001
		BDIFS	.12			
		CVLT2	−.20			
		SDMT	−.26			
T25FW Model B	Step 1	Age	.35	.21	.21	<.001
		Education	−.15			
		BDIFS	.25			
	Step 2	Age	.16	.38	.17	<.001
		BDIFS	.15			
		SDMT	−.30			
	Step 3	Age	.15	.40	.02	=.087
		BDIFS	.12			
		SDMT	−.26			
		CVLT2	−.20			
NHPT Model A	Step 1	Age	.41	.23	.23	<.001
		Education	−.19			
		BDIFS	.15			
	Step 2	Age	.28	.35	.12	<.001
		CVLT2	−.24			
		BVMTR	−.17			
	Step 3	Age	.14	.50	.15	<.001
		SDMT	−.53			
NHPT Model B	Step 1	Age	.41	.23	.23	<.001
		Education	−.19			
		BDIFS	.15			
	Step 2	Age	−.17	.49	.26	<.001
		SDMT	−.51			
	Step 3	Age	.14	.50	.15	=.138
		SDMT	−.53			

(R^2 .40 *vs*. .23 for T25FW and .50 *vs*. .39 for NHPT). A more direct assessment of this difference can be accomplished using a combined stepwise regression approach, with diagnosis nested as an independent variable, and examining for interaction effects between diagnosis and the more frequently significant cognitive predictors. A significant interaction would provide evidence that group status (MS *vs*. normal) influenced the relationship between the cognitive predictors and motor outcomes. For each predictor, we modeled the motor outcome with three blocks: demographics forced entry and retained in Block 1, diagnosis forced entry and retained in Block 2, and the interaction variable in Block 3 (e.g., diagnosis × SDMT) *via* a forward stepwise selection. In the hierarchical regression analysis above, SDMT and DKEFS emerged frequently as statistically significant predictors, and thus we focused this *post hoc* analysis on these predictors. In each model, the interaction term was retained (T25FW-SDMT R^2 change .04; $p < .001$; T25FW-DKEFS R^2 change .03; $p < .001$; NHPT-SDMT R^2 change .02; $p = .009$; NHPT-DKEFS R^2 change .02; $p = .006$).

DISCUSSION

In this large MS sample, we find significant and meaningful associations between motor function in the upper and lower extremities, and cognitive capacity, as measured by conventional neuropsychological tests. Throughout, most of the variance in motor tests was accounted for by neuropsychological measures of executive function, broadly defined as capacity for mental processing speed, working memory, and abstract reasoning. For healthy volunteers, hierarchical regression models retained both SDMT and DKEFS, suggesting

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Table 5. Regression models for multiple sclerosis patients, controlling for neurological variables

Multiple sclerosis II		Significant IVs	Beta weights	R^2	R^2 Change	*p*
T25FW Model A	Step 1	Age	.17	.41	.41	<.001
		BDIFS	.16			
		EDSS	.46			
		Course	.10			
	Step 2	Age	.13	.47	.06	<.001
		EDSS	.41			
		CVLT2	−.20			
	Step 3	EDSS	.36	.50	.03	=.025
		CVLT2	−.16			
		SDMT	−.14			
T25FW Model B	Step 1	Age	.17	.41	.41	<.001
		BDIFS	.16			
		EDSS	.46			
		Course	.10			
	Step 2	EDSS	.36	.49	.08	<.001
		SDMT	−.20			
	Step 3	EDSS	.36	.50	.01	=.203
		SDMT	−.14			
		CVLT2	−.16			
NHPT Model A	Step 1	Age	.25	.36	.36	<.001
		Education	−.16			
		EDSS	.34			
	Step 2	Age	.17	.43	.07	<.001
		EDSS	.28			
		CVLT2	−.17			
	Step 3	EDSS	.17	.54	.11	<.001
		SDMT	−.47			
NHPT Model B	Step 1	Age	.25	.36	.36	<.001
		Education	−.16			
		EDSS	.34			
	Step 2	EDSS	.19	.53	.17	<.001
		SDMT	−.45			
	Step 3	EDSS	.17	.54	.01	=.428
		SDMT	−.47			

that both mental processing speed and higher executive function are independently associated with motor function in healthy persons. The fact that we used an oral response (not written) version of SDMT is particularly noteworthy in this regard. It would be interesting to examine these relationships in an older cohort, as the correlation between mental speed and higher-order reasoning with motor function may be more robust in an aging sample. In our MS sample, SDMT was again retained in models predicting motor function, but a test of auditory/verbal memory also accounted for significant variance. Perhaps, a richer or more variable constellation of cognitive tests is associated with motor function in MS.

Overall, neuropsychological tests accounted for more variance in the motor abilities of MS patients than healthy volunteers. This conclusion is based on three observations. First, bivariate correlations were more often statistically significant and larger in magnitude among MS than in healthy volunteers. The effects were robust in MS patients, even after controlling for demographic variables, depression, EDSS, and disease duration. Second, the generally stronger association was further demonstrated by larger total R^2 values from the MS hierarchical regression models. Third, the greater contribution of cognitive function to motor outcomes in MS was confirmed statistically *via* interaction effects in *post hoc*, stepwise regression models. The greater role for cognition in motor function among MS patients may be explained by cerebral pathology causing impairment in both domains in MS, or merely be due to more variance in the dependent variable in the clinical sample. Certainly replication is needed before we can firmly conclude that there is greater association in MS.

These findings are consistent with previous research revealing that latent factors capturing the domains of executive

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attention and memory are significant predictors of gait speed in non-demented older adults (Holtzer, Verghese, Xue, & Lipton, 2006). While this is admittedly a speculative idea, this association may be attributed, in part, to shared cerebral substrates as suggested by Holtzer et al. (2006) whose work in a large aging sample showed correlation between motor and executive function. In their study, three domains of cognition predicted gait speed. While the neural substrates underlying gait have not been fully delineated (Snijders, van de Warrenburg, Giladi, & Bloem, 2007), structural imaging (Rosano, Aizenstein, Studenski, & Newman, 2007; Rosano, Brach, Studenski, Longstreth, & Newman, 2007), and post-mortem (Whitman, Tang, Lin, & Baloh, 2001) studies suggest that frontal and subcortical regions involved in cognitive processing speed and executive control are related to the spatial (e.g., step length) and temporal (e.g., double support time), aspects of gait. In addition, a recent study showed that the COMT genotype, which is involved in dopamine degradation in the prefrontal cortex and striatum, was differentially linked to both gait speed and executive function (Holtzer et al., 2010). Notably, these are brain regions and systems commonly associated with executive function. The relationship between episodic memory and gait reported herein is harder to explain on a neuroanatomical basis although there is some work suggesting that temporal lobe atrophy is related to poor mobility (Guo et al., 2001), and poor gait is related to memory impairment and increased risk of dementia in aging samples (Verghese, Wang, Lipton, Holtzer, & Xue, 2007). Taken together, there is converging evidence in support of higher order cognitive control of gait in normal and patient populations. Our study extends these findings to MS.

The association between cognitive function and motor performance might also suggest an underlying link between the positive effects of exercise on both motor and cognitive capacity. There is now evidence that aerobic exercise training increases cognitive function in older adults, and the effects are largest for tasks that involve executive control (Colcombe & Kramer, 2003). Some preliminary research suggests an association between aerobic fitness and cognitive function in adults with MS (Prakash et al., 2007), and stronger evidence of a beneficial effect of aerobic exercise training on walking mobility (Snook & Motl, 2009). Future research in rehabilitation may examine the joint effects of aerobic exercise on cognitive function and motor performance in persons with MS. The combined focus on cognitive function and motor performance might even have implications for reducing the risk of falls and perhaps even long-term disability in MS.

Our study also has some more immediate and practical clinical implications. Recent work elsewhere has shown an important relationship between executive function and fall risk in older adults (Holtzer et al., 2007), and our data, while not addressing the same question, would seem to support the notion of the same relationship in MS. We speculate that ambulation capacity as measured by T25FW and cognitive impairment, especially executive dysfunction, could have synergistic effects on fall risk. While failure in the upper extremity is on the surface less dangerous, the same may be true of functional activities requiring hand speed and dexterity (e.g., cooking, using sharp tools or utensils). Future work will examine the utility of screening assessments that include measures of higher executive function, mental speed, as well as motor proficiency.

Our study is limited is several ways, not the least of which is the retrospective, cross-sectional design preventing conclusions about cause and effect relationships between cognition and motor decline. We relied on data collected for other purposes from patients volunteering for research but also seeking clinical evaluation (Duquin, Parmenter, & Benedict, 2008), and some of the patients were taking medication that could conceivably impact cognitive function. The sample had a relatively low EDSS, and while the motor tasks were normally distributed, a greater degree of pathology in motor capacity may have resulted in more generalizable, and robust results. We used gross measures of motor function, rather than more specific measures of spatial (e.g., step width and length) and temporal (double support time, stance time, and step time) gait parameters that can easily be captured with an instrumented walking surface (e.g., GaitMat). We also failed to include important functional outcomes such a fall frequency that have implications for screening (Holtzer et al., 2006, 2007) and treatment in the cognitively impaired MS patient. Finally, the testing of our hypothesis rests on an underlying assumption that the motor defects measured by the T25FW and NHPT are caused by cerebral rather than spinal cord pathology, and assumption which would need verification by both brain and full cord MRI. On the other hand, we did benefit from a large data set with patient and control subjects well matched on demographic characteristics. In addition, our cognitive measures encompassed the full spectrum of cognitive domains frequently compromised in MS and all of the tests have clearly established psychometric validity in this population (Benedict, et al., 2006, 2009; Drake et al., 2010; Parmenter et al., 2007, 2010; Strober et al., 2009).

We conclude that there is a robust correlation between executive function and basic motor functions in MS. Such associations should be examined in a large sample of persons with MS using a more comprehensive battery of motor function assessments along with comprehensive neuropsychological assessment. Future research should consider the neural correlates that underlie the association between motor and cognitive function, and the consequences of the associations (e.g., fall risk) and behavioral approaches for maximizing concurrent improvements in both domains (e.g., exercise training). The present study sets the stage for this more nuanced examination of motor function and cognition in MS.

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