
Volume 31, Issue 2, March/April 2010
ISSN 0891-4222
ELSEVIER
Research in Developmental Disabilities

Research in Developmental Disabilities 31 (2010) 577–586

Contents lists available at ScienceDirect

Research in Developmental Disabilities

Evaluating functional decline in patients with Multiple Sclerosis

Sara Rosenblum *, Patrice L. (Tamar) Weiss

Department of Occupational Therapy, Faculty of Social Welfare & Health Sciences, University of Haifa, Haifa, Israel

ARTICLE INFO

Article history:
Received 17 November 2009
Accepted 8 December 2009

Keywords:
Fatigue
Personal activities of daily living
Handwriting

ABSTRACT

Multiple Sclerosis (MS) is a disease with a wide-ranging impact on functional status. The aim of the study was to examine the added value of simultaneously evaluating fatigue, personal ADL and handwriting performance as indicators for functional decline among patients with MS. Participants were 50 outpatients with MS and 26 matched healthy controls. Data collection instruments included a disability status scale, the Fatigue Severity Scale (FSS), and the Physical Self-Maintenance Scale (PSMS). Handwriting performance was evaluated by objective computerized measures of the handwriting process (ComPET). Significant differences were found between patients with MS and control subjects in their fatigue level, their PSMS score and In-air time per stroke while writing. The FSS together with specific PSMS items and handwriting measures achieved correct classification of 87.7% of the participants. These results are the first step towards demonstrating the added value of evaluating body function outcomes (fatigue) together with activity performance (handwriting and ADL) to document functional decline among patients with MS. These results may contribute to the development of practical intervention strategies targeted at improving performance abilities among patients with MS.

Multiple Sclerosis (MS) is a complex disease of the central nervous system (CNS) affecting predominantly the white matter, with secondary damage to the gray matter (Brassington & Marsh, 1998), and one of the most common causes of chronic neurological disability among young adults in the western world (McDonnell & Hawkins, 2001). It is characterized by a progressive functional decline although the course and clinical manifestations of the disease vary considerably from one patient to another (Brassington & Marsh, 1998). The varied features of patients with MS regarding their cognitive, motor ADL performance and fatigue have been described in the literature. Nevertheless, there is still a need to determine how to best characterize the *functional, every day decline* in abilities for this population using a standardized and feasible method (Pompeii, Moon, & McCrory, 2005).

Cognitive impairments and extreme fatigue are the two symptoms most commonly found in patients with MS, both lead to severe disability (Finlayson, Denend, & Hudson, 2004). Cognitive dysfunction affects 40–65% of patients with MS from all the disease phenotypes and can have a great functional impact (Amato, Zipoli, & Portaccio, 2008). For example, the commonly found deterioration in memory, complex attention, information processing speed, and executive functions is typically associated with a significant decline in the performance of activities of daily living (Bobholz & Rao, 2003). Similarly, 53–92% of patients with MS mentioned fatigue as the major factor leading to limitations in their social and occupational responsibilities (Branas, Jordan, Fry-Smith, Burls, & Hyde, 2000; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) and thus disrupts their general well being (Provinciali, Ceravolo, Bartolini, Logullo, & Danni, 1999).

* Corresponding author. Tel.: +972 4 8240474; fax: +972 4 8249753.
E-mail address: rosens@research.haifa.ac.il (S. Rosenblum).

0891-4222/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ridd.2009.12.008

In most studies of patients with MS, fatigue was measured using a *self-report scale* which indeed reflects the participant's subjective feelings regarding his fatigue (Krupp & Christodoulou, 2007), while the Fatigue Severity Scale (FSS) (Krupp et al., 1989) has been shown to be one of the most discriminative scales (Flachenecker et al., 2002).

Performance-based assessments were implemented in studies which focused more specifically on outcomes related to muscle, or motor performance (e.g. Djaldetti, Ziv, Achiron, & Melamed, 1996; Schwid et al., 1999) or on mental or cognitive fatigue, e.g., Kujala, Portin, Reconsuo, & Ruutiainen, 1995). The performance by patients with MS in both physical (e.g., Djaldetti et al., 1996; Schwid et al., 1999), and cognitive tasks that required continuous effort (e.g., Johnson, Gudrun, DeLuca, Korn, & Natelson, 1997; Krupp & Elkins, 2000) declined late in the testing session in comparison to controls who did not.

However, despite the meaningful contribution of the above-mentioned studies to our understanding of the features of fatigue by patients with MS, the tasks that were requested were not representative of activities performed in every day life. Their relevance to actual daily performance ability is therefore uncertain. There do not appear to be any previous studies in which a fatigue self-report scale was combined with a performance-based evaluation of a specific daily activity.

Documentation of the features of *every day performance* is achieved with ADL scales. The impact of MS on the performance of ADL is typically graded using scales ranging from *dependence* to *independence* or on how much assistance is required for performance on personal ADL (e.g., walking, descending stairs, eating, dressing, toileting, bathing, and grooming) or on Instrumental ADL (e.g., communication, shopping, and domestic activities) (e.g., Inarsson, Gottberg, Fredrikson, Koch, & Widen Holmqvist, 2006; Mansson & Lexell, 2004; McDonnell & Hawkins, 2001; Midgard, Riise, & Nyland, 1996). Patients with moderate to severe MS are less able to perform personal ADL and I-ADL (Mansson & Lexell, 2004), and approximately one-third of patients are dependent and need assistance in varied domains of activities (e.g., McDonnell & Hawkins, 2001; Midgard et al., 1996). However, the tools used in these studies are limited to certain basic activities and do not include very frequent and essential activities for adults such as handwriting (Dixon, Kurzman, & Friesen, 1993). The method of grading is crude and does not facilitate description of the occurrence of small changes in the performance of various daily activities including deterioration that may result from cognitive deficits or fatigue (Candpolit, Riise, Myhr, & Nyland, 1999; Sharrack & Hughes, 1996). Furthermore, most scales are subjective, completed by self-report or by a caregiver or clinician who observed the client performance. It is important to determine whether the limitations of ADL evaluation tools is whether some percentage of the two-thirds of patients with MS who represent the mild to moderate MS population and who, to date, were not identified as having ADL deficits, do have a functional decline that the currently available tools are simply not sensitive enough to detect. Moreover, information that may contribute to early diagnosis of MS is not readily available (Inarsson et al., 2006).

In that context, Suthers and Seeman (2004) added that a self-report ADL assessment exploring the details of daily living performance should be combined with a performance-based measure of *functioning*, such as the ability to write one's name or a sentence. This type of performance-based evaluation is sensitive to visuo-spatial domains, psychomotor retardation, and information processing speed while supplying quantitative measures of performance. Such a combination would provide clinicians and researchers with much broader information about patients *'body functions'* (cognitive, fatigue) *activity* limitations, and *participation* restrictions, as recommended by the International Classification of Functioning Disability and Health (ICF) (ICF, 2001), and will lead to establishing focused intervention methods and outcome measures.

Handwriting has been selected to be a target performance measure since it is one of the most common daily activities performed by adults in a variety of leisure and vocational settings (Dixon et al., 1993). It is a complex human activity that entails an intricate blend of cognitive, kinesthetic, and perceptual-motor components, including visual and kinesthetic perception, motor planning, eye-hand coordination, visual-motor integration, dexterity, and manual skills (Tseng & Cermak, 1993). Thus it reflects both muscle/motor/physical and mental/cognitive fatigue occurs among patients with MS.

Although MS is associated with substantial changes in fine motor skills and handwriting, very little has been reported on the difficulties that patients with this disease experience when writing or on whether their handwriting processes differ from those of the general population (Manikel & Girouard, 2000; Schenk, Walter, & Mai, 2000). Most previous studies were single case reports that characterized deterioration of the written text, such as letter substitutions, omissions, and transpositions (e.g., Baxter & Warrington, 1986) Using a graphological charting system to compare the handwriting of patients with MS to control participants, Wellingham-Jones (1991) found that text written by patients with MS was more irregular and angular and had less fluency, organization and rhythm. Only four previous studies have examined the handwriting process of patients with MS using a computerized system including a digitizer (electronic tablet). Two of these studies focused on MS patients with upper limb tremor (Alusi, Worthington, Glickman, Findley, & Bain, 2000; Erasmus et al., 2001) and the other two included patients with MS at different phases of the disease (Schenk et al., 2000; Longstaff & Heath, 2003). As far as we know, there was no previous study which focused on finding the correlations between fatigue, ADL performance and actual activity performance (handwriting) process measures.

Hence, the aims of the present study were: (1) To evaluate fatigue (FSS) and personal everyday life activities (PSMS) among patients with MS in comparison to controls, (2) to describe the handwriting performance characteristics of patients with MS based on objective measures of the handwriting process, in comparison to controls, (3) to identify the relationships between fatigue, every day life activities and handwriting performance measures in each group (MS versus control participants) and (4) to determine which of the measures will best differentiate between patients with MS and control participants.

1. Methods

1.1. Participants

Outpatients aged 18–70 years with clinically definite and laboratory-supported MS, according to the Poser criteria (Poser et al., 1983), were eligible for the study. MRI data, when available, was used as supportive data according to the McDonald criteria (McDonald et al., 2001). Inclusion criteria for patients with MS was an Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score ≤ 6.5; Mini-Mental State Examination (MMSE) (Werner, Heinik, & Mendel, 1999) score > 28, and a relapse-free history for at least 3 months prior to entry in the study.

Study participants included 50 patients with MS and 26 healthy controls matched for gender, age, and education. The MS group included 40 participants with relapsing-remitting MS (RR-MS) and 10 with relapsing-progressive MS (RP-MS). The inclusion criterion for patients with RR-MS was a history of at least two clearly identified and documented relapses during the 2 years prior to this study. The patients with RP-MS were defined as those who had a period of deterioration, independent of relapses, sustained for at least 6 months, following a period of RR-MS. Details for both patient and control participants are provided in Table 1.

Participants in the control group were obtained by referral from each participant in the MS group. Once they were confirmed to meet the inclusion and exclusion criteria and matching requirements, they completed the MMSE and demographic questionnaire in their homes.

Sixty-seven percent of the participants were female in the patient group and 61% were female in the control group. Age range was 20–68 years. The mean age of the MS group was 40.8 (SD = 10.9) years and of the control group was 37.5 (SD = 12.7) years.

T-test and χ^2 analyses showed that there were no significant differences between the groups for age, gender, hand dominance and years of education.

All participants were free of any history of drug or alcohol abuse or CNS disorder other than MS, and had no severe visual impairment, dominant hand tremor, significant weakness or sensory symptoms or signs that might interfere with the testing. None of the patients with MS had any exacerbation of symptoms (relapse) at the time of testing and had not been treated with corticosteroid therapy 3 months prior to testing. Regarding the frequency of handwriting, all the participants in both groups reported that they performed different writing tasks at least every day or once every few days. Sixty-eight percent of the participants in both groups were employed; 46% of the MS group and 65% in the control group had a full time job.

1.2. Instruments

1.2.1. Fatigue Severity Scale (FSS) – short version (Krupp et al., 1989)

The FSS is a validated tool that assesses the level of fatigue and monitors its change over time or in response to therapeutic interventions. The test is made up of nine questions assessing the general effect of fatigue on daily activities such as

Table 1
Characteristics of the MS and healthy control participants.

Characteristics	MS ($n = 50$)	HC ($n = 26$)	*T*-test	
			T	*p*
Age (years), mean ± SD	40.8 ± 10.9	37.5 ± 12.7	$t(70) = .134$	.18
Education (years), mean ± SD	14.6 ± 2.0	15.4 ± 2.0	$t(73) = 1.45$	1.45
EDSS score, mean ± SD	3.18 ± 1.37	NA		
Duration of MS (years), mean ± SD	6.95 ± 5.30	NA		

Characteristics	MS ($n = 50$)	HC ($n = 26$)	χ^2 test	
			χ^2	*p*
MMSE score (%)				
28	1.9	3.8	$\chi^2(2) = 4.40$	.11
29	9.6	–		
30	86	96.2		
Disease type (%)				
RR	80	NA		
RP	20			
Gender (%)				
Male	33	39		
Female	67	61	$\chi^2(1) = .31$	.57
Hand dominance (%)				
Right	84	86		
Left	14	12	$\chi^2(2) = 3.14$	.20
Mixed	2	2		

Abbreviations: MS, Multiple Sclerosis; HC, healthy controls; MMSE, Mini-Mental State Examination; NA, not applicable; RR, relapsing-remitting; RP, relapsing-progressive.

motivational decrease, prevention of physical functioning and interference with socioeconomic factors during the past week. The questions are rated on a scale from 1 (strongly disagree) to 7 (strongly agree) where higher scores represent more severe levels of fatigue The FSS score is calculated from the mean value of all nine items for a maximum mean score of 7. Scores > 4 are considered to be in the pathological range (Krupp et al., 1989). Krupp et al. (1989) reported that the FSS was internally consistent, clearly differentiated controls from patients with MS and lupus, and could detect clinically predicted changes in fatigue over time.

1.2.2. Physical Self-Maintenance Scale (PSMS; Lawton & Brody, 1969)

The PSMS assesses six personal activities of daily living including toileting, feeding, dressing, grooming, physical ambulation, and bathing using a 5-point Likert scale; a greater mean score signifies greater impairment (Lawton & Brody, 1969). The PSMS may be administered by any health care professional using a variety of informants including the patient, family members or institutional employers (Rubenstein, Schairer, Wieland, & Kane, 1984). High internal reliability ($\alpha = .96$) was reported by the authors (Lawton & Brody, 1969). The scale has been used in varied international survey since it is brief and practical for use. The scale's reliability and validity were previously described (Hokoishi et al., 2001). The internal validity of the scale in the current study was $\alpha = .92$.

1.2.3. ComPET – (previous version knows as POET) – Computerized Penmanship Evaluation Tool

An objective evaluation tool, including digitizing tablet and on-line handwriting data collection and analysis software (Rosenblum, Parush, & Weiss, 2003a; Rosenblum, Parush, & Weiss, 2003b). This unique data collection and analysis program including a suite of on-line, computerized tasks programmed in C++ and implemented via MATLAB software toolkits, was used to administer the stimuli and to collect and analyze the data. The writing tasks were performed on A4 size lined paper (spacing = .5 cm) affixed to the surface of a WACOM Intuos II (407 mm × 417 mm × 36.3 mm) x–y digitizing tablet using a wireless electronic pen with a pressure sensitive, inking tip (model Up 401). The pen size and weight are similar to those of a normal pen (length = 150 mm, circumference = 35 mm, weight = 11 g). Displacement, pressure, and pen tip angle were sampled at 100 Hz via a 90 MHz Pentium laptop computer. Writing tasks include the participant's signature and the copying of a short paragraph. The rational for the selection of these items was that both of them are commonly occurring functional tasks that have relevance for the participant. Signing one's signature is more familiar and is hence executed almost automatically. Copying a short paragraph is somewhat more complex and lengthy and would thus reflect every day performance during prolonged tasks that entail perceptual-motor components and integration.

The system samples temporal, spatial and pressure data. The outcome measures, based on previous study results and the known characteristics of patients with MS, included On-paper and In-air time (i.e., the time while writing in which the pen is not in contact with the paper in seconds) for the whole task or for each stroke, mean stroke width and length in millimeters, and mean pressure and mean standard deviation of pressure in non-scaled units from 0 to 1024. This computerized system enables dynamic handwriting evaluation; previous studies established the ComPET's discriminate validity between control group and groups of participants with varied pathologies (e.g., Rosenblum et al., 2003b; Werner, Rosenblum, Bar-On, Heinik, & Korczyn, 2006) as well as between age groups (Rosenblum & Werner, 2006) Concurrent validity was also established (Rosenblum, Weiss, & Parush, 2004).

1.3. Procedure

Approval for the study was obtained from the Institutional Review Boards of the Lady Davis Carmel Medical Center and the University of Haifa both located in Haifa, Israel. Participants, randomly recruited at the MS clinic, performed the experiment under similar environmental conditions in a quiet room, over two 30-min sessions. During the first session the socio-demographic questionnaire, data from the EDSS (Kurtzke, 1983), the MMSE (Werner et al., 1999), FSS – short version (Krupp et al., 1989), and the subjective report regarding handwriting functional skills were gathered. Participants were also interviewed regarding their main symptoms. Any individual who scored lower than 28 on the MMSE or higher than 6.5 on the EDSS were excluded from the study (6 out of 56 screened patients were exclude accordingly). During the second session (conducted within 10 days from the first session), the participants filled in the PSMS questionnaire and then they performed the Hebrew handwriting tasks on the digitizer.

1.4. Statistical analysis

Descriptive statistics (means, standard deviation, percentages) and independent sampled T-tests were used to describe the study's participants and main variables (EDSS, FSS, PSMS). T-tests comparing differences in the mean values or standard deviations of the spatial, temporal and pressure variables of the two handwriting tasks between the two groups were calculated. In order to avoid inflation of the probability values due to the use of multiple T-tests, the alpha level for these analyses was adjusted by Bonferoni's method (Rothman & Greenland, 1998).

As a secondary analysis we investigated the early functional decline associated with MS by comparing the MS group to controls on each the PSMS items using Man Whitney tests (as previously done by Jefferson et al., 2008). Significance was set at $\alpha = .05$ for this analysis.

Pearson correlation coefficients were calculated to examine relationships between the PSMS and the handwriting process measures who differentiate between groups (air time per stroke writing name and paragraph copying task and on paper time while paragraph copying). Spearman correlations were done in order to examine relationships between the PSMS and handwriting process measures (ComPET) that were found as differentiators between groups.

Finally, a discriminate analysis was conducted in order to determine which variables; objective handwriting performance measures (ComPET), PSMS and FSS measures were the best predictors of group membership (i.e., MS versus control).

2. Results

2.1. Fatigue Severity Scale (FSS)

Significant differences were found between the groups for the (FSS) – short version – score (MS: 4.97 ± 1.74; controls: 2.82 ± (1.03); $t(70) = 5.44$, $p < .001$). Among the participants with MS, the mean score of 35% of the participants was between 1 and 4, 15% between 4 and 5, 15% between 5 and 6 and 35% above 6.

2.2. Personal activities of daily living performance – Physical Self-Maintenance Scale (PSMS)

Significant differences were found between the groups for the PSMS final score (MS: 1.23 ± .49; controls: 1.04 ± .20; $t(70) = 2.33$, $p = .023$).

As presented on Table 2, the Mann-Whitney analysis for the PSMS items demonstrated significant differences between the groups in two prolonged functional items: bathing ($Z = -2.31$, $p = .020$) and physical ambulation ($Z = -3.16$, $p = .002$).

2.3. Handwriting performance

The paragraph copying task as performed by a representative patient with MS (panel B) and by a participant from the healthy control group (panel C) is shown in Fig. 1. The target paragraph as presented on the computer screen is shown in panel A. The thicker lines represent the actual trajectory of the writer's pen when in contact with the writing surface and the

Table 2
A comparison between the groups for each item of the *Physical Self-Maintenance Scale (PSMS) items*.

Item	MS group $n = 50$		HC group $n = 26$		Z	p
	Mean	SD	Mean	SD		
Toileting	1.12	.44	1.00	.00	−1.46	.144
Feeding	1.08	.35	1.00	.00	−1.28	.200
Dressing	1.23	.63	1.16	.80	−1.31	.190
Grooming	1.12	.44	1.00	.00	−1.46	.144
Physical ambulation						
Bathing	1.31	.69	1.00	.00	−2.31	.020

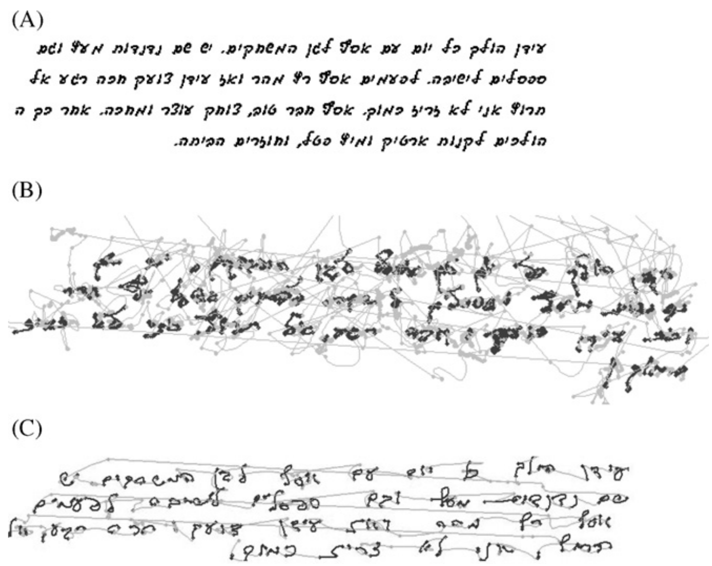

Fig. 1. (A) The paragraph copying task as presented on the computer screen. (B) A paragraph copying task written by a patient with MS. (C) A paragraph copying task written by a participant from the healthy control group.

thinner lines show the In-air trajectory, i.e., when the pen was above the writing surface. There was considerably more correction of mistakes and the letters were a less rounded and smooth when written by the patient with MS. Furthermore, an examination of the extent of the thin line trajectories reveals that the amount of time spent In-air by the patient was considerably greater than that by the participant from the control group; the transitions between letters and words are more direct within the typical writing sample and much more complex within the sample from the patient with MS. We chose these examples since they illustrate the above-mentioned phenomena which are characteristic of patients with MS and not seen in the control group. These differences exceed those due to personal writing style. In the following section, statistical tests are used to determine which measures differ significantly between the two groups.

Temporal, spatial and pressure measures were analyzed for the name writing and whole paragraph copying tasks for subjects of both groups. The means and standard deviations for these measures are presented in Table 3. The SDs for each of the measures in both groups were high, showing individual variation in handwriting performance.

For both tasks, patients with MS required more On-paper and In-air time. There was no clear difference regarding stroke width and height nor for the mean pressure measures. In contrast, the SD of the pressure exerted by the patients with MS was higher in both tasks. Significant differences were found between the groups (even when using the Bonferoni adjusted alpha of .008) for In-air time per stroke measure for the name writing task ($t(104) = 4.13$, $p = .001$) and for both In-air time ($t(104) = 4.06$, $p = .001$) and On-paper time ($t(104) = 3.68$, $p = .001$) for the paragraph copying task.

2.4. Correlational analysis between FSS and PSMS mean scores

To examine the relationships between the FSS and PSMS mean scores in each group (MS versus controls), Pearson's correlation coefficients were calculated. No significant correlations were found between those scores among the control group. Significant moderate correlation was found between the FSS and PSMS mean scores for the MS group ($r = .345$, $p = .022$).

2.5. Correlational analysis between FSS means score, PSMS, and handwriting process measures (ComPET)

To examine the relationships between FSS mean score, the PSMS and handwriting process measures (ComPET) which were shown to differ significantly between the groups in prior statistical testing (see Tables 2 and 3 and results description above), Spearman's correlation coefficient was calculated for each group. No significant correlations were found among the control participants while a significant moderate correlation was found between the FSS mean score and the time on paper per stroke while paragraph copying ($r = .388$, $p = .012$). No significant correlations were found among the control participants while significant moderate correlations were found among the MS groups between the PSMS items: 'physical ambulation' and 'bathing' with the mean stroke duration on paper while writing name ($r = .51$, $p < .001$; $r = .47$, $p = .001$) and while paragraph copying ($p = .43$ and .005; $r = .390$, $p = .011$).

2.6. Discriminate analysis

In order to assess the relative importance of the different variables in differentiating between patient with MS and control participants, a discriminant analysis was performed using the independent variables which were shown to differ significantly between the groups in prior statistical testing, including FSS score, handwriting measures (In-air time for the name writing task, In-air and On-paper time for the paragraph copying task), and PSMS measures (bathing and physical ambulation). One discriminate function was found for group classification of all participants (Wilks' Lambda = .48, $p < .001$).

Table 3
A comparison between the groups for the measures of writing name task, with open eyes.

Measure	MS group $n = 50$		HC group $n = 26$		$T(74)$	p
	Mean	SD	Mean	SD		
Name writing task						
On-paper time per stroke (s)	.23	.12	.18	.07	2.62	.01
In-air time per stroke (s)	.26	.27	.10	.03	4.13	<.001
Mean stroke width (mm)	2.89	1.94	2.97	1.68	.24	n.s
Mean stroke height (mm)	4.51	2.52	4.06	1.82	1.04	n.s
Mean Pressure (non-scaled units 0–1024)	709.29	161.62	699.29	131.76	.24	n.s
Pressure SD	175.22	32.92	164.15	22.63	2.09	.04
Paragraph copying task						
On-paper time (s)	33.33	14.91	25.18	6.10	3.68	<.001
In-air time per (s)	58.16	42.57	32.26	18.37	4.06	<.001
Mean stroke width (mm)	2.71	1.78	2.27	.64	1.68	n.s
Mean stroke height (mm)	4.01	2.57	3.47	.85	1.46	n.s
Mean Pressure (non-scaled units 0–1024)	716.79	148.44	719.24	125.30	.09	n.s
Pressure SD	175.00	27.40	165.02	18.12	2.19	.03

Table 4
The discriminant analysis structure matrix.

	Function 1
Fatigue Severity Scale (FSS) mean score	.738
Stroke duration in air – name writing (ComPET)	.276
Physical ambulation (PSMS scale)	.267
Stroke duration in air – paragraph writing (ComPET)	.214
Writing a shopping list (SRHQ)	.206
Stroke duration on paper – paragraph writing (ComPET)	.194
Bathing (PSMS scale)	.191
Writing a paragraph (SRHQ)	.187
Writing a sentence (SRHQ)	.169
Writing a phone number (SRHQ)	.118

As shown in Table 4, the variables which made the greatest contribution to group membership were the FSS mean final score (.77), the stroke duration in air while name writing (.30), physical ambulation (.29) and stroke duration in air while paragraph writing (.23). The values of the other measures are presented in Table 4. Based on this one function, 89.8% of the total sample was correctly grouped (85% of the MS group and 100% of the control group). A Kappa value of .78 ($p < .001$) was calculated demonstrating that the group classification did not occur by chance.

3. Discussion

The aim of this study was to increase our awareness of fatigue and functional impairments as manifested in personal activities of daily life and handwriting activity performance of patients with MS. The results of this integrated analysis were based on both self-report and objective measures of performance and appear to have important clinical relevance.

In accordance with previous study results (e.g., Bakshi et al., 2000; Bergamaschi, Romani, Versino, Poli, & Cosi, 1997), the participants with MS reported excessive fatigue, as indicated by their FSS mean score, in comparison to control participants. However, increased fatigue in itself is not sufficient to determine functional status and designate functional decline (Pompeii et al., 2005).

It is clear from the literature that using ecologically valid evaluation tools which focus on performance is of utmost importance for evaluation of patients with MS (Higginson, Arnett, & Voss, 2000). The results of the current study indicate that the PSMS is a short, practical tool, suitable for this purpose. Significant differences were found between the groups for the PSMS mean final score and, more specifically, for the 'physical ambulation' and 'bathing' items. The significant correlations which were found among the MS group between the FSS and both the PSMS mean final score and 'on paper' time while paragraph writing are indicative of the relationships between fatigue and performance abilities.

The far-reaching implications of fatigue on different aspects of quality of life in patients with MS have previously been discussed (Olsson, Lexell, & Soderberg, 2005; Packer, Sauriol, & Brouwer, 1994). The results of the current study demonstrate the relationship between fatigue and handwriting performance via an objective measure. This support for the FSS is important in view of the findings that fatigue and ambulation are the symptoms most frequently reported as reasons that people with MS discontinue work (Brassington & Marsh, 1998).

Indeed the Mann-Whitney analysis of the PSMS items indicated significant differences for the physical ambulation and bathing items. Functional ambulation abilities were previously mentioned as impaired among patients with MS (e.g., Maureen, Kathleen, & Magliozzi, 1986). Maureen et al. (1986) found strong linear relationships between reports by participants with MS regarding their functional ambulation abilities and temporal-distance gait measures. Results of the current study demonstrated significant correlations between the participant's report about their functional ambulation and bathing abilities and temporal measures of writing on paper. In this case, an objective temporal measure supports the participants' subjective assessment of their abilities. It seems that their slowness in performance is particularly evident in their ambulation, bathing, and also in handwriting performance abilities. Thus, performance measures of handwriting activity add objective value to the ADL self-report results.

When the participant's handwriting performance was evaluated with the computerized system, significant differences were found between the groups for the In-air time measure on both handwriting tasks, namely, writing one's own name which is presumably more familiar and automatic, and the paragraph copying task which is more complex and lengthy. Furthermore, on the paragraph copying task, significant differences were also found for On-paper time. These findings show that the computerized system is indeed sensitive to temporal deficits in the performance of people with MS.

In our previous study, we showed that the In-air time measure differentiated between people with different degrees of cognitive impairment, including those with Mild Cognitive Impairments (MCI), those with Alzheimer's disease, and a control group of elderly people (Werner et al., 2006). Similarly, handwriting performance requires specific cognitive components that have been reported to be impaired among people with MS, including attention, information processing speed, working memory, planning and organization in space and time (Andrade et al., 1999; Brassington & Marsh, 1998; Wallin, Wilken, & Kane, 2006).

Further studies with larger samples combining additional neuropsychological evaluations focused on cognitive aspects are required in order to examine the hypothesis that the In-air measure is indeed indicative of cognitive decline previously described among patients with MS as an influential factor on their every day performance (Birnboim & Miller, 2004; Goverover et al., 2005; Wallin et al., 2006).

There are additional benefits to the use of handwriting performance measures with a tool that is sensitive to ADL. The significant correlations that were found between the handwriting activity measures (time per stroke on paper while paragraph copying) and the PSMS items (physical ambulation and bathing) indicate that combining the data accumulated by patients' subjective reports about their ADL performance with objective measures of functional activity may lead to a greater understanding of the unique performance characteristics among patients with MS and thus improve evaluation and intervention methods. For example, it was found that In-air time differentiated between the controls and the participants with MS during both the short (name writing) and long (paragraph copying) handwriting tasks. This fact indicates that people with MS need more time for activity performance, not only while performing a task (in this case, while forming letters on a paper) but also between segments of the task (in this case, while progressing from one segment to the next, i.e., In-air time). Moreover, in addition to requiring more time between the task's segments (In-air time) in a short and familiar task (name writing), they also required more time for the performance itself (On-paper time) in a more complex and lengthy task (paragraph copying). The computerized system, with its graphic representations of the handwriting process (as shown in Fig. 1), provides the participant with visual evidence of the functional limitations produced by MS. This is an important first step towards developing strategies to deal with the patient's day-to-day challenges.

It is clear that fatigue is an important measure based on its greatest contribution to group membership (.74). Furthermore, based on the current study results it is sufficient to give the participant two tasks to write on a digitizer (own name and paragraph) and to pose two questions about physical personal ADL performance (physical ambulation and bathing). Combining this self-report with a subjective report about handwriting (the every day tasks of writing a phone number, shopping list, sentence and paragraph) and to the objective tasks of actually writing his name and paragraph appear sufficient to characterize functional decline.

Furthermore, given the general agreement that the level of ADL performance influences quality of life and participation (Brassington & Marsh, 1998; Goverover et al., 2005; McDonnell & Hawkins, 2001) it appears that a short, practical and sensitive daily living assessment tool (PSMS), combined with a sensitive test of a complex perceptual-motor performance activity (i.e., handwriting), is very useful. Such tools may be used to determine the level of functioning and ability to work (Pompeii et al., 2005) or drive (Schultheis, Edward, & DeLuca, 2001) as well as the need for rehabilitation programs (Paltamaa, Sarasoja, Wikström & Mälkiä, 2006) In addition, they can be employed to measure the outcome of therapeutic interventions (Bloom et al., 2006; Morris et al., 2006) including the evaluation of various pharmacological options for the management of MS symptoms, such as fatigue, tremor, motor dysfunction, and depression. (e.g., Caligiuri, Teulings, Filoteo, & Song, 2006).

The findings of the current study should be regarded as preliminary and still need to be confirmed in regard to their validity, reliability and sensitivity in future studies with larger cohorts of patients. However, taken together, the findings suggest that the computer-based analysis of handwriting performance may be used as an objective, simple, quick and relatively inexpensive method for evaluating the kinematics of handwriting movements. This instrument appears to be a promising assessment tool when used together with an ADL test for purposes of screening and diagnosis among patients with MS.

Acknowledgements

The authors would like to thank Ariel Miller, MD, PhD from the Department of Neurology, Carmel Medical Center, Haifa 34362, Israel, for his valuable contribution to patient selection and diagnosis. The authors are grateful to the Israeli Science Foundation (Academia) for financial support. We also thank and appreciate Liat Lachter for her assistance with the research process.

References

Alusi, S. H., Worthington, J., Glickman, S., Findley, L. J., & Bain, P. G. (2000). Evaluation of three different ways of assessing tremor in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 68*, 756–760.

Amato, M. P., Zipoli, V., & Portaccio, E. (2008). Cognitive changes in multiple sclerosis. *Expert Review of Neurotherapeutics, 8*, 1585–1596.

Andrade, V. M., Bueno, O. F. A., Oliveira, M. G. M., Oliveira, A. S. B., Oliveira, E. M. L., & Miranda, M. C. (1999). Cognitive profile of patients with relapsing remitting multiple sclerosis. *Arquivos de Neuro-Psiquiatria, 57*, 775–783.

Bakshi, R., Shaikh, Z. A., Miletich, R. S., Czarnecki, D., Dmochowski, J., Henschel, K., et al. (2000). Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Multiple Sclerosis, 6*, 181–185.

Baxter, D. M., & Warrington, E. (1986). Ideational agraphia: A single case study. *Journal of Neurology Neurosurgery, and Psychiatry, 49*, 369–374.

Bergamaschi, R., Romani, A., Versino, M., Poli, R., & Cosi, V. (1997). Clinical aspects of fatigue in multiple sclerosis. *Functional Neurology, 12*, 247–251.

Birnboim, S., & Miller, A. (2004). Cognitive strategies application of multiple sclerosis patients. *Multiple Sclerosis, 10*, 67–73.

Bloom, L. F., Lapierre, N. M., Wilson, K. G., Curran, D., DeForge, D. A., & Blackmer, J. (2006). Concordance in goal setting between patients with multiple sclerosis and their rehabilitation team. *American journal of Physical Medicine & Rehabilitation, 85*, 807–813.

Bobholz, J. A., & Rao, S. M. (2003). Cognitive dysfunction in Multiple Sclerosis: A review of recent developments. *Current Opinion in Allergy and Clinical Immunology, 16*, 283–288.

Branas, P., Jordan, R., Fry-Smith, A., Burls, A., & Hyde, C. (2000). Treatments for fatigue in multiple sclerosis: A rapid and systematic review. *Health Technology Assessment, 4*, 1–61.

Brassington, J. C., & Marsh, N. V. (1998). Neuropsychological aspects of multiple sclerosis. *Neuropsychology Review, 8*, 43–77.

Caligiuri, M. P., Teulings, H. L., Filoteo, J. V., & Song, D. (2006). Quantitative measurement of handwriting in the assessment of drug-induced parkinsonism. *Human Movement Science, 25*, 510–522.

Candpolit, M. W. N., Riise, T., Myhr, K. M., & Nyland, H. I. (1999). Quality of life in multiple sclerosis measuring the disease effects more broadly. *Neurology, 53*, 1098.

Dixon, R. A., Kurzman, D., & Friesen, I. C. (1993). Handwriting performance in younger and older adults: Age, familiarity, and practice effects. *Psychology and Aging, 8*, 360–370.

Djaldetti, R., Ziv, I., Achiron, A., & Melamed, E. (1996). Fatigue in multiple sclerosis compared with chronic fatigue syndrome: A quantitative assessment. *Neurology, 46*, 632–635.

Erasmus, L. P., Sarno, S., Albrecht, H., Schweeht, M., Pollmann, W., & Konig, N. (2001). Measurement of ataxic symptoms with a graphic tablet: Standard values in controls and validity in multiple sclerosis patients. *Journal of Neuroscience Methods, 108*, 25–37.

Finlayson, M., Denend, T. V., & Hudson, E. (2004). Aging with multiple sclerosis. *Journal of Neuroscience Nursing, 36*(5), 245–253.

Flachenecker, P., KuÈmpfel, T., Kallmann, B., Gottschalk, M., Grauer, O., Rieckmann, P., et al. (2002). Fatigue in multiple sclerosis: A comparison of different rating scales and correlation to clinical parameters. *Multiple Sclerosis, 8*, 523–526.

Goverover, Y., Kalmar, J., Gaudino-Goering, E., Shawaryn, M., Moore, N. B., Halper, J., et al. (2005). The relation between subjective and objective measures of everyday life activities in persons with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation, 86*, 2303–2308.

Higginson, C., Arnett, P. A., & Voss, W. D. (2000). The ecological validity of clinical tests of memory and attention in multiple sclerosis. *Archives of Clinical Neuropsychology, 115*, 185–204.

Hokoishi, K., Ikeda, M., Maki, M., Nomura, M., Torikawa, S., Fujimoto, N., et al. (2001). Interrater reliability of the Physical Self-Maintenance Scale and the Instrumental Activities of Daily Living Scale in a variety of health professional representatives. *Aging & Mental Health, 5*, 38–40.

Inarsson, U., Gottberg, K., Fredrikson, S., Koch, L. V., & Widen Holmqvist, L. (2006). Activities of daily living and social activities in people with multiple sclerosis in Stockholm. *Clinical Rehabilitation, 20*, 543–551.

Jefferson, A. L., Byerly, L. K., Vanderhill, S., Lambe, S., Wong, S., Ozonoff, A., et al. (2008). Characterization of activities of daily living in individuals with mild cognitive impairment. *The American journal of geriatric psychiatry, 16*, 375–383.

Johnson, S., Gudrun, L., DeLuca, J., Korn, L., & Natelson, B. (1997). The effects of fatigue on neuropsychological performance in patients with chronic fatigue syndrome, multiple sclerosis and depression. *Applied Neuropsychology, 4*, 145–153.

Krupp, L. B., & Christodoulou, C. (2007). Fatigue in multiple sclerosis. *Current Neurology and Neuroscience Reports, 1*, 294–298.

Krupp, L. B., & Elkins, L. E. (2000). Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology, 55*, 934–939.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology, 46*, 1121–1123.

Kujala, P., Portin, R., Reconsuo, A., & Ruutiainen, J. (1995). Attention related performance in two cognitively different subgroups of patients with multiple sclerosis. *Journal of Neurology Neurosurgery, and Psychiatry, 59*, 77–82.

Kurtzke, J. F. (1983). Rating neurological impairment in multiple sclerosis; an expanded disability status scale (EDSS). *Neurology, 33*, 1444–1453.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people; self-maintaining and instrumental activities of daily living. *Gerontologist, 9*, 179–186.

Longstaff, M. G., & Heath, R. A. (2003). The influence of motor system degradation on the control of handwriting movements: A dynamical system analysis. *Human Movement Science, 22*, 91–110.

Manikel, T., & Girouard, P. (2000). Multiple sclerosis and its effect on handwriting. *The Journal of Forensic Document Examination, 13*, 120–130.

Mansson, E., & Lexell, J. (2004). Performance of activities of daily living in multiple sclerosis. *Disability and Rehabilitation, 26*, 576–585.

Maureen, K. H., Kathleen, M. G., & Magliozzi, M. R. (1986). Gait assessment for neurologically impaired patients: Standards for outcome assessment. *Physical Therapy, 66*, 1530–1539.

McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H. P., Lublin, F. D., et al. (2001). Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology, 50*, 121–127.

McDonnell, G. V., & Hawkins, S. A. (2001). An assessment of the spectrum of disability and handicap in a population in multiple sclerosis: A population-based study. *Multiple Sclerosis, 7*, 111–117.

Midgard, R., Riise, T., & Nyland, H. (1996). Impairment, disability and handicap in multiple sclerosis. A cross-sectional study in an incident cohort in Mre and Romsdal County, Norway. *Journal of Neurology, 243*, 337–344.

Morris, M. E., Perry, A., Bilney, B., Curran, A., Dodd, K., Wittwer, J. E., et al. (2006). Outcomes of physical therapy, speech pathology and occupational therapy for people with motor neuron disease: A systematic review. *Journal of Neurologic Rehabilitation, 20*, 424–433.

Olsson, M., Lexell, J., & Soderberg, S. (2005). The meaning of fatigue for women with multiple sclerosis. *Journal of Advanced Nursing, 49*, 7–15.

Packer, T. L., Sauriol, A., & Brouwer, B. (1994). Fatigue secondary to chronic illness: Postpolio syndrome, chronic fatigue syndrome, and multiple sclerosis. *Archives of Physical Medicine and Rehabilitation, 75*, 1122–1126.

Paltamaa, J., Sarasoja, T., Wikström, J., & Mälkiä, E. (2006). Physical functioning in multiple sclerosis: A population-based study in central Finland. *Journal of Rehabilitation Medicine, 38*, 339–345.

Pompeii, L. A., Moon, S. D., & McCrory, D. C. (2005). Measures of physical and cognitive function and work status among individuals with multiple sclerosis: A review of the literature. *Journal of Occupational Rehabilitation, 15*, 69–84.

Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C., et al. (1983). New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Annals of Neurology, 13*, 227–231.

Provinciali, L., Ceravolo, M., Bartolini, M., Logullo, F., & Danni, M. (1999). A multidimensional assessment of multiple sclerosis: Relationships between disability domains. *Acta Neurologica Scandinavica, 100*, 156–162.

Rosenblum, S., Parush, S., & Weiss, P. L. (2003a). Computerized temporal handwriting characteristics of proficient and non-proficient handwriters. *American Journal of Occupational Therapy, 57*, 129–138.

Rosenblum, S., Parush, S., & Weiss, P. L. (2003b). The ''In Air'' phenomenon: Temporal and spatial correlates of the handwriting process. *Perceptual and Motor Skills, 96*, 933–954.

Rosenblum, S., Weiss, P. L., & Parush, S. (2004). Handwriting evaluation for developmental dysgraphia: Process versus product. *Reading and Writing, 17*, 433–458.

Rosenblum, S., & Werner, P. (2006). Assessing the handwriting process in healthy elderly persons using a computerized system. *Aging Clinical and Experimental Research, 18*, 433–439.

Rothman, K., & Greenland, S. (1998). *Modern epidemiology* (2nd ed.). Philadelphia: Lippincott-Raven.

Rubenstein, L. Z., Schairer, C., Wieland, G. D., & Kane, R. (1984). Systematic biases in functional status assessment of elderly adults: Effects of different data sources. *The Journal of Gerontology, 39*, 686–691.

Schenk, T., Walter, E. U., & Mai, N. (2000). Closed and open-loop handwriting performance in patients with multiple sclerosis. *European Journal of Neurology, 7*, 269–279.

Schultheis, M. T., Edward, G. B. S., & DeLuca, J. (2001). The influence of cognitive impairment on driving performance in multiple sclerosis. *Neurology, 56*, 1089–1094.

Schwid, S. R., Thornton, C. A., Pandya, S., Manzur, K. L., Sanjak, M., Petrie, M. D., et al. (1999). Quantitative assessment of motor fatigue and strength in MS. *Neurology, 53*, 743–750.

Sharrack, B., & Hughes, R. A. C. (1996). Clinical scales for multiple sclerosis. *Journal of the Neurological Sciences, 135*, 1–9.

Suthers, K., & Seeman, T. (2004). *The measurement of physical functioning in older adult population. Meeting report 2004* Available at http://www.nia.nih.gov/NR/rolonlyres (accessed 2009).

Tseng, M. H., & Cermak, S. H. (1993). The influence of ergonomic factors and perceptual—Motor abilities on handwriting performance. *American Journal of Occupational Therapy, 47*, 919–926.
Wallin, M. T., Wilken, J. A., & Kane, R. (2006). Cognitive dysfunction in multiple sclerosis: Assessment, imaging, and risk factors. *Journal of Rehabilitation Research and Development, 43*, 63–72.
Wellingham-Jones, P. (1991). Characteristics of handwriting of subjects with multiple sclerosis. *Perceptual and Motor Skills, 73*, 867–879.
Werner, P., Heinik, J., & Mendel, A. (1999). Examining the reliability and validity of the Hebrew version of the Mini-Mental state examination. *Aging Clinical Experimental Research, 11*, 329–334.
Werner, P., Rosenblum, S., Bar-On, G., Heinik, J., & Korczyn, A. (2006). Handwriting process variables discriminating mild Alzheimer's disease and mild cognitive impairment. *Journal of Gerontology, 61*, 228–236.