Cognitive Impairment Has a Strong Relation to Nonsomatic Symptoms of Depression in Relapsing–Remitting Multiple Sclerosis

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Abstract

It is unclear how cognitive impairment in multiple sclerosis (MS) is influenced by physical disability, fatigue, and depression. Our aim was to identify the strongest clinical predictors for cognitive impairment in relapsing-remitting MS (RRMS) patients. The clinical risk factors included in the analysis were physical disability (EDSS), fatigue (FSS), the somatic and nonsomatic components of depression (BDI), disease progression rate [Multiple Sclerosis Severity Score (MSSS)], and psychotropic medication. Cognitive impairment had a prevalence of 30.5% in patients affecting preferentially attention, executive functions, processing speed and visual perception/organization. MSSS was not associated with cognitive impairment, depression, or fatigue. In regression models, cognitive performance was best predicted by the nonsomatic symptoms of depression alone or in combination with physical disability. Exclusion of patients with any psychotropic medication did not influence the results. Our results underscore the importance of evaluating depressive symptoms when suspecting cognitive impairment in patients with RRMS.

Keywords: Multiple sclerosis; Neuropsychological assessment; Depression; Physical disability; Fatigue; Psychotropic medication

Introduction

Cognitive impairment in multiple sclerosis (MS) is frequent, affecting up to 65% of MS patients in cross-sectional studies (Amato, Zipoli, & Portaccio, 2006; Rao, Leo, Bernardin, & Unverzagt, 1991). It is detectable at all stages of the disease, including a clinically isolated syndrome suggestive of MS (CIS) (Khalil et al., 2011). In relapsing–remitting MS (RRMS), the prevalence of cognitive dysfunction is estimated to be 22% (Patti et al., 2009) and 40% (Potagas et al., 2008). Severity and prevalence of cognitive impairment is influenced by the clinical subtype of the disease, where patients with progressive forms of MS tend to perform worse than patients with RRMS (Huijbregts, Kalkers, de Sonneville, de Groot, & Polman, 2006). Reduced performance has been demonstrated in several cognitive domains including information processing speed, attention, executive functions, and long-term memory (Chiaravalloti & DeLuca, 2008). Impaired information processing speed, in classic clinical terminology “bradyphrenia”, is a prominent neuropsychological deficit in MS (Bergendal, Fredrikson, & Almkvist, 2007; Langdon, 2011). Essential verbal skills are usually preserved (Rao et al., 1991), whereas verbal fluency is commonly affected (Prakash, Snook, Lewis, Motl, & Kramer, 2008). Once cognitive dysfunction has developed, it is likely to persist (Bagert, Camplair, & Bourdette, 2002) and to continue to worsen, although the rate of progression may be slow or vary (Amato et al., 2006). However, cognitive decline in MS seldom reaches the severity observed in dementia (Cook, 2001). Furthermore, self-perception of cognitive performance in MS patients is unreliable and not predictive of objective cognitive functioning (Julian, Merluzzi, & Mohr, 2007; Middleton, Denney, Lynch, & Parmenter, 2006), stressing the need of formal testing.
A consistent finding in previous studies is that there is a weak or no correlation between the duration of MS and cognitive impairment (Chiaravalloti & DeLuca, 2008; Lynch, Parmenter, & Denney, 2005; Patti et al., 2009; Rao et al., 1991). However, several studies find a modest or moderate association between cognitive performance and physical disability (Beatty, Goodkin, Hertsgaard, & Monson, 1990; Lynch et al., 2005; Patti et al., 2009). The relationship between depression in MS and cognitive impairment is still not clear (Chiaravalloti & DeLuca, 2008), but an association has been demonstrated in adequately powered studies (Arnett, Barwick, & Beeney, 2008) and primarily between depression and the cognitive domains of information processing speed and executive functions (Feinstein, 2006; Siegert & Abernethy, 2005). Fatigue is a common problem in MS patients; however, no clear association has been found between cognitive impairment and self-reported fatigue (Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009). The need for a deeper understanding of MS-associated cognitive disturbances is stressed by the detrimental effects on many activities of daily life such as physical independence, employment, coping, medication adherence, symptom management, rehabilitation potential, and driving safety (Langdon, 2011).

The objective of the present study was to identify the strongest clinical predictors for cognitive impairment in RRMS patients. The cognitive performance was studied in a cross section of patients and healthy control subjects, and the effect of potentially interrelated disease variables on the cognitive performance was separated in regression models. Specifically, we wanted to answer the following questions:

- Is cognitive impairment more related to the speed of disease progression than physical disability? The Multiple Sclerosis Severity Score (MSSS) (Roxburgh et al., 2005) incorporates measures of disease duration and physical disability and has, to our knowledge, neither been studied with respect to its association with symptoms of fatigue and depression, nor with cognitive performance.
- Is cognitive impairment more associated with the nonsomatic component of depression than with the somatic component? Most previous studies of depression and cognitive function in MS have not made this distinction.
- Which disease-related variable is the strongest predictor of cognitive impairment in RRMS? Depression, physical disability, and fatigue are known to be inter-related in MS and may all influence cognitive function.
- Is psychotropic medication a confounding factor in the assessment of cognitive performance in patients with RRMS? CNS-active pharmacological therapy is common among MS patients, but its effect on cognitive function is frequently overlooked. Both positive effects (e.g., by treatment of depression) and negative adverse effects may be present.

Materials and methods

Subjects

Patients (n = 74) with a diagnosis of MS according to the McDonald criteria (Polman et al., 2005) attending the MS clinic of the Department of Neurology at the Karolinska University Hospital in Stockholm (Solna) were recruited between April 2006 and May 2011. All patients were diagnosed as RRMS which was validated against their clinical records and the Swedish Multiple Sclerosis Registry (http://www.msreg.net). Exclusion criteria were other chronic neurological or systemic disease that could affect cognition, psychiatric disorders other than depression, and substance abuse. Furthermore, patients with physical disability of such an extent or nature (poor vision or arm and hand function) that it could interfere with cognitive testing procedures were excluded. Subjects were clinically stable at inclusion with a minimum of 4 weeks from a previous relapse or cortisone treatment. Two patients were later excluded: one due to previously unrecognized alcohol abuse and the other due to poor adherence to instructions during the neuropsychological tests. All subjects were recruited by one of the authors (M.S.). Demographic and clinical data were obtained from the medical records, the Swedish Multiple Sclerosis Registry and from an interview. Data included age, sex, body length, body mass index (BMI), years of education, first language, duration of MS and, if present, current disease modulatory treatment (DMT) and other ongoing medication.

Healthy control subjects (n = 89) were recruited randomly by the aid of the Swedish population registry. Only subjects born in Sweden were included to avoid the influence of poor knowledge of Swedish on the results of the neuropsychological tests. Exclusion criteria were disease or previous trauma or ongoing medication that might affect the brain or the nervous system, premature birth, and substance abuse. All subjects were informed about the nature and purpose of the study before consenting to participate. The protocol was approved by the regional ethics committee (Regionala etikprövningsnämnden i Stockholm).
The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

**Clinical Instruments**

Physical disability was assessed by the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The assessment was performed by one of the authors (M.S.) in 64 patients usually on the same day as the neuropsychological testing. The remaining eight had an assessment done by a neurologist during a regular visit shortly prior to study inclusion and testing, and the score was collected from their medical records. MSSS was used for assessment of disease severity. The algorithm is applicable for patients with a disease duration between 1 and 30 years. One patient in our study population had a disease duration of <1 year (6 months) and could not be scored with MSSS.

Symptoms of depression were assessed by the Beck Depression Inventory (BDI) (Beck, Steer, & Garbin, 1988). BDI is a widely used self-report measure of depressive symptoms and has been validated for MS patients and is recommended for use in populations with MS (Arnett et al., 2005). As some items in BDI are likely to overlap with MS-related physical symptoms (Johnson, DeLuca, & Natelson, 1996; Mohr et al., 1997), we separated the full-length score (BDI) into the nonsomatic component (items 1–13), BDI-NS, and the somatic component (items 14–21), BDI-S (Aikens et al., 1999; Plumb & Holland, 1977). Assessment of fatigue was done by the Fatigue Severity Scale (FSS) which is the scale most widely used for assessing fatigue in MS, showing high reliability, validity, and internal consistency (Krupp, Larocca, Muirnash, & Steinberg, 1989).

**Neuropsychological Tests and Cognitive Domain Function**

The neuropsychological tests were administered by the same investigator (M.S.) in all healthy control subjects and in 50 of the included patients, and by another (L.M.) in the remaining 22 patients. All tests were given in Swedish and were administered according to the standard protocols. The individual test scores were grouped into cognitive domains as indicated subsequently. Several tests measure more than one cognitive ability and were thus included in more than one cognitive domain. The global score included all tests. The following tests were administered and the session time was approximately 55 min:

- **Controlled Oral Word Association Test (COWAT)** from the Delis–Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001). Domains: verbal ability, executive functions, processing speed.
- **The Color-Word Interference Test (CWIT)** from D-KEFS (Delis et al., 2001). CWIT consists of four sub-tests (Condition 1–4): Color Naming, Word Reading, Inhibition and Inhibition/ Switching. Domains: attention (CWIT Condition 1 and 2), executive functions (CWIT Condition 1, 2, 3, and 4).
- **The Trail Making Test (TMT)** from D-KEFS (Delis et al., 2001). TMT consists of five sub-tests (Condition 1–5): Visual Scanning, Number Sequencing, Letter Sequencing, Number-Letter Sequencing and Motor Speed. Domains: attention (TMT Condition 1, 2, 3, and 5), executive functions (TMT Condition 1, 2, 3, 4, and 5).
- **The Digit Span Test (DST)** from WAIS-III (Wechsler, 1997). Domains: attention (DST Forward, Backward and Total), executive functions (DST Backward).
- **The Digit Symbol Coding Test (DSCT)** from WAIS-III (Wechsler, 1997). Domains: visual perception/organization, processing speed.
- **The Symbol Search Test (SST)** from WAIS-III (Wechsler, 1997). Domains: visual perception/organization, processing speed.
- **Vocabulary Test (SRB:1)** (Dureman & Sälde, 1959; Psykologiförlaget, 1971). Domain: verbal ability.

There was an interrater variability between the two test administrators in two of the 18 cognitive measures (Vocabulary and TMT-5), but there was no significant interrater variability in the domain scores. Tests and test order were the same for all participants with the following exceptions. Seventeen of the patients were administered two additional tests (additional 15 min) as...
they were also included in a longitudinal study. One of these tests [Swedish Lexical Decision Test (Almkvist, Advleen, Henning, & Tallberg, 2007)] was added as the last in the session and the other [Rey Auditory Verbal Learning Test (Schmidt, 1996)] was inserted at position 2 in the test order, and the recall-part of the same test at position 6 in the otherwise identical test order. The healthy control subjects were given seven additional tests intended for other studies. As a result the test session was longer for the healthy controls (approximately 110 min). None of the tests analyzed in this study was given earlier to the control subjects during the test session than for the patients, and any decline in performance due to long session-time would have a negative influence on the outcome for the control subjects only. All patients and healthy control subjects were tested in a distraction free and quiet environment.

Patients on natalizumab therapy (n = 26) had previously been exposed to one neuropsychological test (Symbol Digit Modalities Test, SDMT) as part of their clinical protocol at the start of treatment and every 6 months thereafter. This test resembles DSCT to some extent. However, a cross-test practice effect seems unlikely because SDMT in repeated testing exhibits only minimal practice effects (Benedict et al., 2008). Of the nine included neuropsychological tests, three are composed of several subtests resulting in a total of 18 cognitive scores in the test battery.

Statistics

Values of each cognitive test were normalized (z-scored) in order to adjust for normal effects of age, sex and education (years in school and higher education). In this way the tests scores obtained the same weight and the cognitive domain scores could be calculated from the mean scores of the included tests. First a linear regression model of the effect of age on the test score was calculated in the healthy controls separately for men and women. The residuals were used to study the effect of education in a second linear regression model and a final set of residuals was obtained. The regression lines obtained in the healthy control group for each test score were used on the patient data to adjust for the effect of age separately for men and women and education, and the final residuals were obtained for each subject and test. Z-scores were calculated by dividing the final residuals with the standard deviation (SD) of the final residuals in the healthy controls.

Missing data existed in four test scores for one patient (TMT condition 1–4). Five patients and one control subject did not have Swedish as their first language, and their results on verbal tests (Vocabulary and COWAT) were therefore excluded. Missing or excluded data were replaced with the mean value for each score in patients and controls, respectively. Differences in means between groups were tested using t-test. Correlations were studied with ranked data (Spearman’s correlation) because normal distribution of variables was not consistently satisfied. Multiple regression analysis was performed with robust linear regression. A value of p < .05 was considered significant. Calculations were performed with Matlab 7.10.0 with Statistics Toolbox.

Results

Demographic and Clinical Properties of the Patients and the Controls

The demographic and clinical characteristics of patients and healthy control subjects are summarized in Table 1. Patients and control subjects had similar age, education, body length and BMI. Body length and BDI were included in the analysis because both factors may influence cognitive performance in healthy subjects (Teasdale, Owen, & Sorensen, 1991; Teasdale, Sorensen, & Stunkard, 1992; Tuvemo, Jonsson, & Persson, 1999) and in patients with diabetes (Brismar et al., 2007). In the patient group, the proportion of women (71%) was slightly (n.s.) higher than in the controls (57%). The mean disease duration was 9.3 years and the mean EDSS was low (2.7). The majority of patients (75%) was mildly disabled (EDSS ≤3.5) and only two patients had EDSS ≥6.0. Disease severity (MSSS) had a mean of 4.1. A majority of the patients was receiving DMTs, natalizumab being the most frequent treatment (36%) and interferon-beta (IFNb) the second most frequent (33%). A few patients (8%) were on unknown DMT (or placebo) due to participation in randomized controlled trials.

Twenty-five patients had psychotropic medication (one or several drugs) and most frequently antidepressants of selective serotonin (SSRI) or serotonin–norepinephrine re-uptake inhibitor (SNRI) type (n = 12). Other psychotropic medications included analgesics (dextropropoxiphene, codeine, or tramadol, n = 6) or other drugs for neuropathic pain relief such as amitriptyline in low dose (20–50 mg) (n = 3), lamotrigine (n = 1), and gabapentine (n = 2). Other classes of medication were stimulants (modafinil, n = 9), hypnotics (zopiclone, zolpideme, propiomazine, n = 6), spasmyloitics (baclofen, n = 4), and spasmyloitics–anxiolytics (diazepam, n = 3). No control subject was receiving psychotropic medication.
Depression and Fatigue

Patients had more symptoms of depression and fatigue when compared with the control subjects and patients differed more in BDI-S than in BDI-NS (Table 1). Among the patients 31.9% reached BDI $\geq 10$ and five patients (6.9%) had moderate-to-severe depression with BDI $\geq 17$. Fifty-four percent of the patients with BDI $\geq 10$ received treatment with SSRI or SNRI. Fatigue defined as FSS $\geq 5$ (Andreasen, Spliid, Andersen, & Jakobsen, 2010; Tellez et al., 2005) was present in 52.8% of the patients. In the control group, 10% of the subjects had BDI $\geq 10$ and 2% had FSS $\geq 5$.

Cognitive Scores of the Patients

Patients had deficits in cognitive domain functions that were most pronounced in executive functions ($r = 0.92$, $p < .0001$) followed by attention ($r = -0.88$, $p < .0001$), global score ($r = -0.71$, $p < .0001$), processing speed ($r = -0.64$, $p < .0001$), visual perception/organization ($r = -0.49$, $p < .003$), and verbal ability ($r = -0.29$, $p < .04$). Only in the domain of visual memory was there no difference from the control subjects. The percentage of subjects with a domain z-score of less than $-1.5$ was estimated, and in patients it was most common in executive functions (24%), followed by attention (22%), processing speed (21%), global score (17%), visual memory (17%), visual perception/organization (14%) and verbal ability (7%). Some of the control subjects had a deficit in visual memory (7%), verbal ability (3%), and visual perception/organization (2%). Cognitive impairment defined as a z-score of less than $-1.5$ in at least two domains had a prevalence of 30.5% in the RRMS group and 4.5% in the control group.

Correlations Between Clinical Properties and Cognitive Data

Cognition had significant correlations (all negative) with several of the clinical parameters (Fig. 1). EDSS correlated with processing speed ($r = -0.40$) and executive functions ($r = 0.37$), visual perception/organization ($r = 0.33$) and attention ($r = 0.31$), and the global cognitive function ($r = 0.36$) but not with visual memory or verbal ability. FSS showed the same pattern of correlation as EDSS, correlating with processing speed ($r = 0.33$), executive functions ($r = 0.31$), visual perception/organization ($r = 0.27$), attention ($r = 0.25$), and the global score ($r = 0.31$).

Cognitive function had stronger correlation with BDI-NS than with BDI-S. Hence, BDI-NS correlated with processing speed ($r = 0.37$), executive functions ($r = 0.32$), visual perception/organization ($r = 0.32$), attention ($r = 0.29$), and the global score ($r = 0.32$). BDI-S had weak correlation with visual memory, executive functions, visual perception, and organization and processing speed. In the healthy control group, cognitive function did not correlate with BDI-NS, BDI-S, or FSS.

### Table 1. Demographic and clinical data of study population

<table>
<thead>
<tr>
<th></th>
<th>Patients ($n = 72$)</th>
<th>Controls ($n = 89$)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 37.9, Min 22, Max 61, SD 10.0</td>
<td>Mean 38.2, Min 21, Max 60, SD 11.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>71%</td>
<td>57%</td>
<td>n.s. (.08)</td>
</tr>
<tr>
<td>Body length (cm)</td>
<td>172, Min 153, Max 198, SD 9.8</td>
<td>173, Min 157, Max 193, SD 8.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI</td>
<td>24.5, Min 16.7, Max 35.9, SD 4.3</td>
<td>24.1, Min 18.1, Max 35.1, SD 3.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Education (years)</td>
<td>Mean 13.8, Min 8, Max 21, SD 2.8</td>
<td>Mean 14.1, Min 9, Max 21, SD 2.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>BDI total (range 0–63)</td>
<td>8.8, Min 0, Max 44, SD 7.3</td>
<td>4.0, Min 0, Max 21, SD 4.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BDI-NS (range 0–39)</td>
<td>4.7, Min 0, Max 30, SD 4.8</td>
<td>2.3, Min 0, Max 15, SD 2.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BDI-S (range 0–24)</td>
<td>4.2, Min 0, Max 14, SD 3.0</td>
<td>1.7, Min 0, Max 8, SD 1.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>FSS (range 1–7)</td>
<td>3.9, Min 1, Max 7, SD 1.8</td>
<td>2.6, Min 1, Max 5.7, SD 1.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Psychotropic medication (%)</td>
<td>35%</td>
<td>0%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9.3, Min 0.5, Max 31, SD 6.5</td>
<td>0, Min 1, Max 30, SD 1</td>
<td>n.s.</td>
</tr>
<tr>
<td>EDSS (range 0–10)</td>
<td>Mean 2.7, Min 0, Max 7.5, SD 1.5</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>MSSI (range 0.01–9.99)</td>
<td>4.1, Min 0.5, Max 9.1, SD 2.2</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Natalizumab (%)a</td>
<td>36%</td>
<td>n.s. (.08)</td>
<td></td>
</tr>
<tr>
<td>Interferon beta (%)a</td>
<td>33%</td>
<td>n.s. (.08)</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate (%)a</td>
<td>8</td>
<td>n.s. (.08)</td>
<td></td>
</tr>
<tr>
<td>Unknown (clinical trial) (%)a</td>
<td>8</td>
<td>n.s. (.08)</td>
<td></td>
</tr>
<tr>
<td>No immunomodulating treatment (%)a</td>
<td>14</td>
<td>n.s. (.08)</td>
<td></td>
</tr>
</tbody>
</table>

Note: *The ongoing disease treatment is indicated and the number of patients is given in %.
Disease duration had weak correlation with the domains of executive functions and processing speed, but not with the other four cognitive domains or with global function. Notably, MSSS showed only a weak correlation with visual perception/organization and not with function in other domains or with the global score. Although the normal effects of age, sex, and education were adjusted for in the statistical analysis, there was a weak correlation between age and processing speed in the patients. There was no correlation between any disease variable and the domain of verbal ability. Sex, education, body length, and BMI had no correlation with cognitive performance in patients and were not included in Fig. 1. Only variables that had significant effect on the global score were considered to be significant in order to avoid errors due to repeated comparisons (six cognitive domains). Accordingly, age, disease duration, and MSSS had no significant effect on cognitive function.

Patients on psychotropic medication \( (n = 25) \) differed from those without psychotropic medication in age (mean 45 vs. 34 years, \( p < .0001 \)), education (mean 12.6 vs. 14.4 years, \( p < .008 \)), BDI (mean 12.2 vs. 7.0, \( p < .003 \)), and FSS (mean 4.8 vs. 3.4, \( p < .001 \)). The cognitive domain scores were lower for patients on psychotropic medication than for those without, but this difference was only significant for processing speed \( (p < .03) \). Patients on amitriptyline or diazepam \( (n = 6) \), with potentially a stronger effect on cognitive function than other psychotropic medication (see Discussion), did not differ in clinical characteristics or cognitive function relative to patients without psychotropic medication.

Correlations Between Demographic and Clinical Properties

Many of the variables that correlated with cognitive performance were intercorrelated (Fig. 2). EDSS had a strong positive correlation with age, disease duration, MSSS, FSS, and BDI-NS \( (p < .0001 \) or \( p < .001 \)). FSS was strongly correlated with EDSS, BDI-NS, and BDI-S (all with \( p < .0001 \)) and more weakly with age and disease duration. BDI-NS and BDI-S were strongly correlated. BDI scores did not correlate with age and only BDI-NS had weak correlation with the disease duration. MSSS did not correlate with FSS or BDI. A small negative correlation was present between MSSS and disease duration, reflecting that among patients with equal EDSS those with shorter disease duration attain higher MSSS values. There was a similar strong correlation between BDI-NS and BDI-S \( (p < .0001) \) in the control group (not illustrated), and also between fatigue and BDI-NS \( (p < .0001) \) and BDI-S \( (p < .001) \).

Multiple Regression Analysis

Multiple regression analysis was performed to separate the effects of discrete but interrelated clinical variables (Table 2). Only clinical variables that had effect on the global cognitive score were included. Independent variables were EDSS, FSS, BDI-NS, BDI-S, and BDI (total). BDI-NS had stronger effect on performance than other clinical variables in all domains except verbal ability (which had no significant predictor). Notably, BDI-NS was a stronger predictor than BDI (total) and BDI-S. The strongest association was between BDI-NS and executive functions \( (p < .0001, \text{adjusted } r^2 = .223) \) and visual
perception/organization \( (p < .0001, \text{adjusted } r^2 = .198) \). EDSS and FSS had significant relation to function in four domains and the global score, and were stronger predictors than BDI-S. Depression is strongly related to and may be secondary to the level of disability \( (\text{Chwastiak et al., 2002}) \). The effect of a second predictor was therefore tested when EDSS had been forced into the model (Table 3). Inclusion of BDI-NS as the second predictor had significant effect on function in four domains and on the global score, and resulted in higher adjusted \( r^2 \) values for visual perception/organization \((0.221)\) and processing speed \((0.221)\). BDI-S or BDI (total) as the second predictor had weaker effect than BDI-NS, and FSS was not significant in any domain. A model with FSS + second predictor (not shown) resulted in lower adjusted \( r^2 \) values than the previous model, and lower adjusted \( r^2 \) values than BDI-NS as the single predictor except for the effect on the processing speed. FSS was not a significant second predictor in models including BDI-NS.

The regression analysis was repeated after exclusion of 25 patients on any psychotropic medication. This gave very similar results. BDI-NS was the strongest predictor of performance in attention \((p < .0004, \text{adjusted } r^2 = .246)\), executive functions \((p < .002, \text{adjusted } r^2 = .241)\), and global score \((p < .0002, \text{adjusted } r^2 = .288)\), and the model EDSS + BDI-NS resulted in the highest adjusted \( r^2 \) values in domains of visual perception/organization \((.256)\) and processing speed \((.178)\).

### Discussion

In the present study, regression models were applied to separate the effect of different disease variables on cognitive function in RRMS. The main finding was that cognitive impairment is best predicted by the nonsomatic symptoms of depression alone or in combination with physical disability. Disease duration and disease progression rate (MSSS) were not significant
predictors. Psychotropic medication was common among patients but had a small or negligible contribution to the cognitive impairment.

The study population consisted of patients with RRMS attending a university clinic. A majority of the patients was receiving DMT and the most frequent DMT was natalizumab followed by IFNb. The patients were not randomized and the majority was mildly disabled with low EDSS (mean 2.7) and short disease duration when compared with a cross section of the MS population in the same residential area (Gottberg, Einarsson, Fredrikson, von Koch, & Holmqvist, 2007). With EDSS ≤3.5, a patient may have moderate disability in one or more neurological function systems but is fully ambulatory. The sex distribution in our patient sample (71% women) was similar to that of the entire MS population in Sweden (Ahlgren, Öden, & Lycke, 2011).

Approximately 30% of patients with RRMS were cognitively impaired, defined as a deficit of more than 1.5 SD in two or several tested domains. Executive functions, attention, and processing speed were the most commonly affected domains. Previous studies have similarly identified these domains and also memory to be preferentially affected in MS (Arnett & Strober, 2011; Chiaravalloti & DeLuca, 2008; Prakash et al., 2008). Memory is a complex cognitive domain that is not uniformly affected in MS (Arnett & Strober, 2011) and in our study this function was examined with only one test. Also a number of control subjects (n = 6) had memory z-score of less than −1.5, indicating that the data in the healthy control group were skewed in this domain. These factors may explain why patients did not differ significantly from controls, and that a relatively large number of healthy control subjects (4.5%) had cognitive impairment defined as a deficit of more than 1.5 SD in two or several tested domains.

The prevalence of depression with BDI ≥10 (32%) was less than that found in a population-based study of MS patients in Stockholm County (40%) (Gottberg et al., 2007). Depression has equal prevalence among MS subtypes (Chwastiak et al., 2002; Gottberg et al., 2007) but it is strongly related to the level of physical disability, being six times more common in subjects with EDSS 7.0–9.5 when compared with those with EDSS <4.0 (Chwastiak et al., 2002). The reason for the lower prevalence in the present study may therefore be that the patients had lower EDSS than the general MS population.

It has been suggested that cognitive deterioration appears mainly at higher levels of depression and that inclusion of MS patients with mild depression leads to failure in detecting a relationship with cognitive impairment (Demaree, Gaudino, & DeLuca, 2003; Feinstein, 2006; Siegert & Abernethy, 2005). However, our data indicate that even relatively mild symptoms of depression are associated with cognitive impairment. A clear association between depressed mood and cognition has been demonstrated in depressed but physically healthy individuals (Shenal, Harrison, & Demaree, 2003) and most data indicate a similar association in people with MS (Arnett et al., 2008). However, the large COGIMUS study of RRMS (Patti et al., 2009) did not find such a relationship. The reason could be that patients had a very mild physical disability and short duration of disease. Furthermore, patients with major depression were excluded and the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967) was used, which is more influenced by MS-related physical symptoms than the BDI (Moran & Mohr, 2005).

The original BDI (Beck, Steer, & Garbin, 1988) was used in the present study as well as in several of the above-mentioned studies (Demaree, Gaudino, & DeLuca, 2003; Gottberg et al., 2007; Moran & Mohr, 2005). Some items have been modified in another version of BDI (Beck-DI-II) (Beck, Steer, & Brown, 1996). The correlation between the original BDI and BDI-II is high (0.93), but it should be noted when results from different studies are compared that the average BDI-II score is approximately three points higher than the original score (Beck, Steer, & Brown, 1996).

In the present study, depression was separated into its somatic (BDI-S) and nonsomatic components (BDI-NS) as previously recommended (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003; Mohr et al., 1997). Cognition correlated with both BDI-S and BDI-NS, but BDI-NS had stronger correlation with cognitive function, and in the regression model BDI-NS was a stronger predictor than BDI-S and BDI (total). Previous studies of mixed samples of MS patients with moderate

### Table 3. Effect of EDSS in combination with other clinical variables on cognitive performance in patients

<table>
<thead>
<tr>
<th></th>
<th>EDSS + FSS</th>
<th>EDSS + BDI-NS</th>
<th>EDSS + BDI-S</th>
<th>EDSS + BDI (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p value</td>
<td>Adjusted r²</td>
<td>p value</td>
<td>Adjusted r²</td>
</tr>
<tr>
<td>Memory, visual</td>
<td>n.s.</td>
<td>.002</td>
<td>.120</td>
<td>.016</td>
</tr>
<tr>
<td>Verbal ability</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Attention</td>
<td>.081</td>
<td>.115</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Executive functions</td>
<td>.103</td>
<td>.167</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Visual percep./organization</td>
<td>.083</td>
<td>.221</td>
<td>.016</td>
<td>.141</td>
</tr>
<tr>
<td>Processing speed</td>
<td>.147</td>
<td>.221</td>
<td>n.s.</td>
<td>.154</td>
</tr>
<tr>
<td>Global score</td>
<td>.112</td>
<td>.179</td>
<td>n.s.</td>
<td>.113</td>
</tr>
</tbody>
</table>

Note: Linear regression model (robust fit) was cognitive domain score = constant + EDSS + independent variable. Significance of added independent variable indicated by p values. Indicated in bold are highest adjusted r² of each cognitive domain from comparison of data in Tables 2 and 3.
physical disability (EDSS) have similarly indicated that cognitive impairment has a stronger association with the nonsomatic component than the somatic component of depression (Arnett et al., 1999; Barwick & Arnett, 2011; Beatty, 1998).

Depression in MS is likely to be underdiagnosed and undertreated (Mohr, Hart, Fonareva, & Tasch, 2006) and only 54% of the patients with BDI ≥ 10 in the present study received pharmacological treatment for depression. Though depression in MS can be effectively treated (Koch, Glazenborg, Uyttenboogaart, Mostert, & De Keyser, 2011), it is unclear whether treatment of depression is associated with cognitive improvement (Feinstein, 2006). A recent study, having other primary outcome measures, failed to demonstrate improvement in objective cognitive performance after a 16-week treatment in spite of effects on depression and fatigue (Kinsinger, Lattie, & Mohr, 2010). A reciprocal effect may thus exist between cognitive impairment and depressive symptoms.

Although the level of physical disability was low in the present study population, it had a significant correlation with cognitive performance, and especially with the processing speed. In the regression models, EDSS + BDI-NS gave the best prediction of performance on visual perception/organization and processing speed. An association between cognitive function and physical disability has not been consistently found (Prakash et al., 2008). Our data are in line with the findings of Lynch and colleagues (2005) reporting a correlation of similar magnitude between EDSS and cognitive performance in a large sample of MS patients. Furthermore, tests of information processing speed were most closely associated with EDSS, which concur with the present findings.

Whereas EDSS measures accumulated disability, MSSS instead reflects the rate of worsening. One might expect that a high MSSS score reflecting a more rapid accumulation of physical symptoms would be associated with more fatigue and depression. However, we found no correlation between MSSS and fatigue or depression. MSSS had a weak effect only in one domain (visual perception/organization) and not on the global cognitive score. To our knowledge, this has not been studied previously. Using a different index created by dividing EDSS by disease duration (number of years exceeding 5 years), a significant relationship was found between progression severity and cognitive function (Lynch et al., 2005). Previous studies have consistently reported a weak or no relationship between the disease duration and cognitive test performance in MS (Beatty et al., 1990; Lynch et al., 2005; Rao et al., 1991). Our study showed similar results with only a weak correlation between the disease duration in two cognitive domains and no association with global function. Only disease variables with effects on the global cognitive function were regarded as significant predictors to account for the type 1 error caused by multiple comparisons (six cognitive domains).

Fatigue has been reported to be the most prevalent symptom of MS, affecting up to 92% of the patients (Bol et al., 2009). In the present study population, 53% reached FSS ≥ 5 and the level of fatigue was correlated to cognitive impairment, and most strongly with processing speed, executive functions, and the global score. However, fatigue, disability, and depression were highly intercorrelated as also indicated in several previous studies (Bakshi et al., 2000; Lerdal, Celius, Krupp, & Dahl, 2007; Morrow et al., 2009; Strober & Arnett, 2005) and fatigue was not a significant predictor for cognitive impairment when the effect of BDI-NS or EDSS was included in the regression model. Most previous studies have similarly found that cognitive performance has no consistent relationship with self-reported subjective fatigue in MS when controlling for depression (Andreassen et al., 2010; Bol et al., 2009; Morrow et al., 2009).

CNS-active pharmacological therapy is common among MS patients and frequently overlooked in cognition studies of MS. SSRI was the most common class of medication and the only one that was prescribed for depression. SSRIs are considered to be relatively free from cognitive and psychomotor side effects (Peretti, Judge, & Hindmarch, 2000; Wadsworth, Moss, Simpson, & Smith, 2005). An association between SSRI use and memory impairment has been suggested (Schmitt, Kruizinga, & Riedel, 2001; Wadsworth et al., 2005), but others have reported a beneficial effect of SSRI on memory functions (Harmer, Shelley, Cowen, & Goodwin, 2004; Zobel et al., 2004). Modafinil used for the treatment of fatigue in MS has no conclusive effect on processing speed (Moller et al., 2011). Tricyclic antidepressants and benzodiazepines have well-documented effects on cognitive function (Hindmarch, 2009; Peretti et al., 2000). Other medications (analgectics, hypnotics, lamotrigin, gabapentin, and baclofen) have small or uncertain effect on cognitive function (Arai et al., 2009; O’Neill et al., 2000; Oneill, Hanks, White, Simpson, & Wesnes, 1995; Terzano, Rossi, Pulomba, Smerieri, & Parrino, 2003; Zaccara, Gangemi, & Cincotta, 2008). In the present study, patients on psychotropic medication (most often SSRI/SNRI) had lower function in processing speed when compared with patients without, but did not differ significantly in other cognitive domain scores. However, the comparison is confounded by the fact that patients on psychotropic medication had more depression, fatigue, and physical disability. Patients on tricyclic antidepressants (amitriptyline) or benzodiazepines (diazepam) did not differ from those without psychotropic medication which may be due to the low dose of amitriptyline prescribed for pain relief or the intermittent use of diazepam. Exclusion of patients on any psychotropic medication in the regression model did not alter the finding that BDI-NS or EDSS + BDI-NS were the best predictors of poor cognitive performance. It may be concluded that psychotropic medication was not a confounding factor in the present study. Our finding does not exclude that antidepressive treatment may be beneficial for cognitive performance. This issue should be addressed in a longitudinal study.
The proportion of patients in our sample receiving natalizumab was high. Natalizumab therapy is used mainly as a second-line DMT after failing a first line drug, in this sample mainly IFNb, and these patients represent a group of RRMS patients with a more aggressive disease course. The cognitive scores of patients treated with natalizumab did not significantly differ from patients with other or no treatment, although they had longer disease duration, more physical disability, higher BDI-NS, and FSS. This may be due to a cognition-improving effect of natalizumab therapy (Holmen et al., 2011; Mattioli, Stampatori, & Capra, 2011); however, the cross-sectional design of the present study does not permit conclusions regarding treatment effects.

Conclusions

- Cognitive dysfunction was not related to the rate of disease progression as measured by MSSS, but rather to the accumulated physical disability. MSSS was not related to measures of depression or fatigue.
- A distinction between somatic and nonsomatic components of depressive symptoms is warranted because the nonsomatic component had stronger association with cognitive impairment than the somatic component.
- Although depression was less frequent than fatigue in RRMS, cognitive dysfunction had a stronger association with symptoms of depression than fatigue. Cognitive impairment was best predicted by the nonsomatic symptoms of depression alone or in combination with physical disability.
- There was no confounding effect of psychotropic medication in the present study.

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Conflict of Interest

Fredrik Piehl has a research grant from Biogen Idec and has had travel expenses reimbursed by Sanofi Aventis, Biogen Idec and Novartis; his employer has received payment for lectures and development of educational materials from Biogen Idec, Novartis, and Merck Serono.

The other authors declare no conflict of interest.

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