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Multiple sclerosis : how cognitive performance relates to quality of life, depression, and perception of deficits

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Multiple Sclerosis:

How Cognitive Performance Relates to Quality of Life, Depression, and Perception of Deficits

By

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CERTIFICATE OF APPROVAL

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This is to certify that the Master's thesis of

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List of Abbreviations

BDI	Beck Depression Inventory
COWAT	Controlled Oral Word Association Test
CVLT-II	California Verbal Learning Test II
DKEFS	Delis-Kaplan Executive Function System Sorting Test
EDSS	Expanded Disability Status Scale
MCS	Mental Component Summary
MS	Multiple Sclerosis
MSNQ-I	Multiple Sclerosis Neuropsychological Questionnaire – Informant
MNPI	Modified Neuropsychiatric Inventory
PASAT	Paced Auditory Serial Addition Test
PCS	Physical Component Summary
PDQ	Perceived Deficits Questionnaire
SDMT	Symbol Digit Modalities Test
SF-36	Short Form 36
Stroop	Victoria Stroop Test

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Abstract

Introduction: Cognitive impairment is common in multiple sclerosis (MS). The negative consequences of cognitive impairment on daily activities makes early detection important, but subjective cognitive complaints may be attributed to depression. In this study we sought to add to current understanding of cognitive impairment in MS by examining its relationship to quality of life, depression, self-perception of deficits, and caregiver perception of deficits. We also closely examined the relationship between subjectively reported, caregiver reported, and objectively measured cognitive impairment in MS.

Methods: A neuropsychological battery of tests, measures of mental and physical quality of life (the mental [MCS] and physical [PCS] composite scores of the Short Form-36), the Perceived Deficits Questionnaire (PDQ), and the Beck Depression Inventory (BDI) were administered to 119 MS patients participating in a clinical trial. The Multiple Sclerosis Neuropsychological Questionnaire-Informant (MSNQ-I) and the Modified Neuropsychiatric Inventory (MNPI) were administered to 112 caregivers as measures of caregiver perceived cognitive impairment. We also examined data from two other clinical trials, which used some of the above measures, to validate the results, adding 179 patients to the study.

Findings: Cognitive impairment in the domains of auditory information processing speed and concept formation was associated with lower mental quality of life, but physical disability was associated with both cognition and mental quality of life and confounded the relationship. Cognitive impairment was not related to mild or moderate depression. Caregivers' perceptions of patients' cognitive deficits reflected objective cognitive impairment in the domains of auditory information processing speed and verbal association fluency, but caregivers' perceptions were also influenced by patients' physical disability and depressive symptoms. Patients' self-perceptions of cognitive deficits were not reflective of their actual cognitive disability, and their self-perceptions of cognitive ability strongly correlated with depression. Results regarding patient and caregiver agreement on the degree of cognitive impairment were inconclusive. Interesting gender differences in the above results were noted: for men, but not for women, lower mental quality of life was strongly associated with physical disability and verbal function was strongly associated with perceived cognitive deficits.

Conclusion: Those MS patients with cognitive impairment have a lower quality of life, reaffirming the importance of attending to cognitive function in the clinic. MS patients who self-report cognitive impairment are more likely to have depression than objective cognitive decline, and while caregivers' perceptions of cognitive impairment are associated with objective cognitive deficits, caregivers' perceptions are also influenced by patients' physical disability and depression. Depression should be ruled out when patients report cognitive difficulties, and brief objective cognitive screening tests should be incorporated into clinical practice to detect early cognitive decline in MS.

Introduction

Multiple sclerosis (MS) is a common and often disabling complex demyelinating disease with a relatively unpredictable course. MS causes physical impairment, resulting in a variety of problems, most notably impairment in ambulation, and those who develop MS before the age of 20 tend to suffer from visual dysfunction and sensory problems. The most frequent symptoms are fatigue, spasticity, bladder dysfunction, and ataxia, followed closely by pain, depression, and loss of cognitive function (Stuke 2009). Cognitive impairment cannot be reliably predicted on the basis of physical impairment, disease duration, or disease course (Amato 1995). Understanding of cognitive dysfunction in multiple sclerosis is vital for physicians treating patients who report neuropsychological symptoms.

Quality of Life and Cognitive Dysfunction in Multiple Sclerosis

Health-related quality of life is of critical importance in the care of patients with multiple sclerosis (MS). A review by Benito-Leon et al. (Benito-Leon 2003) pointed out several features of MS that particularly contribute to poor quality of life. These are: 1) MS is a disease with a long list of possible deficits, encompassing a broad range of neurologic and neuropsychiatric functions. Symptoms of MS include motor and sensory disturbances, sphincter problems, sexual dysfunction, cognitive impairment, mood disorder, psychosis, limited mobility, and fatigue. 2) Because people with MS often are diagnosed as young adults, MS greatly affects the development and course of their lives as they try to anticipate their future disability. 3) Given MS's unpredictable course, this anticipation is often unsuccessful, and patients have difficulty maintaining a sense of control over their disease. 4) There is no possibility of cure. 5) Current treatments are imperfect, carry some risk, and are sometimes inaccessible because of inequities in health care provision.

Patients with MS report lower health-related quality of life than healthy controls (McCabe 2002). They also have a notably lower health-related quality of life than patients with other chronic diseases, such as rheumatoid arthritis, inflammatory bowel disease, and psychosis (Rudick 1992; Chopra 2008). MS patients have worse health-related quality of life scores than the general population with respect to physical

functioning, vitality, and general health (Pittock 2004).

Cognitive dysfunction in MS has repeatedly been found to be associated with lower health-related quality of life on various measures (Mitchell 2010). The estimated prevalence of cognitive dysfunction in the multiple sclerosis population is 45% to 65% (Rao 1995). Short-term memory, sustained attention, and verbal fluency are the most frequently impaired cognitive domains (Rao, 1991b). Impairments in executive function, conceptual reasoning, recognition memory, and auditory or visual span can also occur, while language, long-term memory and knowledge of prior events are generally spared (Bagert 2002). MS patients with cognitive dysfunction have fewer social interactions, more sexual dysfunction, greater difficulty with household tasks, and higher unemployment than those with normal cognition (Rao 1991a). Once cognitive impairment develops it usually persists and increases in severity (Amato 2001). Impairment in mental function (including cognitive, emotional, and sleep functions) has been found to be the Multiple Sclerosis Impact Profile (MSIP) domain most closely related to decreased health-related quality of life, much more so than limitations in basic movement activity (Wynia 2008).

The current study used a battery of cognitive tests designed to capture those areas of cognitive function which are most commonly impaired in multiple sclerosis (Rao 1991b). The Paced Auditory Serial Addition Test (PASAT), in particular, was recommended by a task force for use in multiple sclerosis clinical trials (Rudick 1997). Based on the literature, we expected quality of life to be associated with cognitive function as measured by the tests on this battery. Thus, we hypothesized that among subjects with multiple sclerosis and cognitive impairment, **objectively measured cognitive impairment would be associated with decreased quality of life**.

Depression and Cognitive Dysfunction in Multiple Sclerosis

Depression is highly correlated with subjective cognitive complaints in MS patients (Benedict 2004; Julian 2007; Maor 2001; Middleton 2006). Specifically, MS patients suffering from depression overreport their cognitive difficulties (Benedict 2004; Carone 2005), and cognitive complaints often correlate more highly with depressive symptoms than with cognitive performance (Benedict 2004; Bruce & Arnett, 2004; Gold

2003; Maor 2001; Randolph 2004). Bruce and Arnett (2004) found that degree of accuracy in self-assessment of cognitive abilities in MS patients depended on degree of depression in a non-linear fashion: cognitive performance was over-estimated by non-depressed patients, underestimated by mildly depressed patients, and accurately estimated by moderately depressed patients.

While the literature is clear that there is a relationship between depression and self-perception of cognitive function, research examining the association between depression and objective cognitive functioning has been equivocal (Arnett et al., 2008), with some studies finding an association (Marrie 2005; Rosti 2007) and others finding none (Kinsinger 2010; Maor 2001; Gold 2003).

The current study sought to examine the relationship between depression, self-report of cognitive deficits, and objectively measured cognitive deficits. Based on the literature, we expected patient perception of deficits to be more strongly associated with depressive symptoms as measured by the BDI than with objective measurement of cognitive function. However, as our sample size was large and studies with adequate sample sizes generally have reported a positive association between depression and cognitive dysfunction in MS (Arnett 2008), we hypothesized that among subjects with multiple sclerosis and cognitive impairment, **objectively measured cognitive impairment would be positively associated with depression**.

Self- and Caregiver-Report of Cognitive Dysfunction in Multiple Sclerosis

Most referrals for cognitive testing are secondary to either patient self-report or caregiver report of cognitive difficulties. The current study addresses the question of which of these is more accurate, and whether patients and caregivers agree. A great deal of previous research has examined the accuracy of MS patients' self-report of their cognitive deficits, with mixed results. Some studies have found patients' subjective cognitive impairment is accurate in that it is significantly associated with objective cognitive impairment (Kinsinger 2010; Marrie 2005; Basso 2008; Benedict 2004), while other research has shown that patients are inaccurate reporters of their own cognitive deficits (Hoogervorst 2001; Maor 2001; Christodoulou 2005; Gold 2003; Beatty 1991). A study by Middleton et al. (2006) using a large sample of 221 MS patients reached both

conclusions, finding that while perceptions of global cognitive functioning were unrelated to objective cognitive performance, patients were reasonably good at estimating how well they performed specifically on the cognitive battery. As we used a self-report measure of global cognitive function, we anticipated that patient self-report would be inaccurate. Therefore, we hypothesized that among subjects with multiple sclerosis and cognitive impairment, **objectively measured cognitive impairment would not be associated with self-report of cognitive impairment**.

As to whether patients or caregivers are better reporters of patient cognitive deficits, conclusions from the literature have run the gamut. There is evidence of caregivers being accurate reporters of patient cognitive deficits (Benedict 2003; Carone 2005; Smith 2010), caregivers and patients being equally accurate in reporting of patients' cognitive difficulties (Randolph 2001), and patients being better than caregivers at rating their cognitive functioning (Smith 2010). We hypothesized that **caregivers' perception of cognitive performance would accurately reflect objective measure of cognitive performance** and that **caregivers' perception and patients' self-report of cognitive performance would not agree.**

Study Overview

In the current study, we examined the relationship between objective and subjective cognitive performance, quality of life, and depression in multiple sclerosis, using baseline data from three randomized double-blind controlled trials examining the effects of memantine and gingko on cognition and ginseng on fatigue in MS. All three studies recruited similar populations of multiple sclerosis patients with similar demographic composition and similar exclusion criteria for comorbid neurological or psychiatric conditions. The memantine and gingko studies recruited subjects who were cognitively impaired, while the ginseng study recruited subjects who were fatigued. All three used depression cut-offs to exclude patients with major depression. The three studies utilized similar measures of cognition, quality of life, depression, and self- and caregiver-perception of cognitive function. Therefore many of the same hypotheses were able to be addressed by these three data sets. The outcomes for the three clinical trials are not presented in this paper; the ginkgo and ginseng results are in the process of

publication, and the memantine outcome data has been recently published (Lovera 2010). Rather, the current study is a cross-sectional design using the baseline data from these three trials. As the memantine data set used all of the measures of interest in the current study, it was examined as the main data set, with analyses of the ginkgo, ginseng, or combined data sets serving to confirm or counter findings from the memantine data. As none of the drugs tested in these trials are of significance in this paper, to lessen confusion the memantine data set will be referred to as M, the ginseng data set will be referred to as Gs, and the ginkgo data set will be referred to as Gk.

Hypotheses

Among subjects with multiple sclerosis (MS) and cognitive impairment:

1. *Objectively measured cognitive impairment* is associated with *lower quality of life*.
2. *Objectively measured cognitive impairment* is associated with *increased depression*.
3. *Objectively measured cognitive performance* is positively associated with *caregivers' perception of cognitive performance*.
4. *Objectively measured cognitive performance* is not associated with *self-report of cognitive performance*.
5. *Self-report of cognitive performance* is not associated with *caregivers' perception of cognitive performance*.

Design & Methods

Baseline data was collected during three clinical studies: M, Gg, and Gk. Study entry and exclusion criteria differed somewhat amongst the three studies. All three studies required a diagnosis of multiple sclerosis per McDonald's criteria determined by a physician. The M study required subjects have subjective cognitive complaints and a score on the Paced Auditory Serial Addition Test (PASAT) or the Califronia Verbal Learning Test II (CVLT-II) (long delay free recall or total recall) worse than 1 standard deviation (SD) below the mean from appropriate age- and education-adjusted norms. Similarly, the Gk study required subjects to score at or below 1 SD on one of the cognitive tests to be included in the study. The Gs study did not have a cognitive inclusion criteria but did require a complaint of fatigue that had been persistent for at

least two months and a Fatigue Severity Scale score of 4 or greater. All three studies employed cutoffs on the Beck Depression Inventory (BDI) above which patients were excluded from the study, effectively eliminating subjects with clinical depression: the M study used 21 as the BDI cutoff, the Gs study used 31, and the Gk study used 27.

At the beginning of the studies, prior to randomization and drug or placebo administration, patients completed a neuropsychological test battery consisting of all (M study) or some (Gs and Gk studies) of the following six tests (test descriptions based on Lovera 2010 & Hebben 2009):

1. **Paced Auditory Serial Addition Test (PASAT)**: This test is used to assess sustained attention and speed of processing. The subject listens to an audiotape on which sequences of digits are read every 3 seconds. The respondent is required to add the numbers in pairs, to say the answer aloud; and then to add each subsequent number to the number presented just before it, not to the sum of the previous two numbers. That is, the participant adds the first two numbers, provides a response, then adds the third number to the second, the fourth number to the third, and so on. The PASAT requires respondents to hold one digit in working memory while performing a mathematical operation (i.e., addition of two numbers). The total number of correct responses represents the individual's score.

2. **California Verbal Learning Test II (CVLT-II)**: This is a verbal learning and memory test where a list of 16 words belonging to four categories (eg., tools, fruits, insects, clothing) are read to the subject and the subject is asked to repeat them. This procedure is repeated over five trials. A different list of words is then presented and the subject is asked to repeat them. The subject is asked to recall the words from the first list with no cues initially and followed by recalling the words using the categories as cues. After 20 minutes the subject is asked to recall the words freely, using the categories as cues and to recognize the initial words from words that were not in the initial list. For this study the delayed free recall trial was the outcome measure of interest.

3. **Controlled Oral Word Association Test (COWAT):** This test measures verbal fluency. The subject must generate as many words as possible beginning with the letters F, A, and S in 1-minute intervals. This study used the total number of words generated after three trials.

4. **Stroop Color and Word Test (Stroop)**: This measure of cognitive flexibility presents three cards in the following sequence: colored dots, neutral words printed in colors, and color words printed in non-congruent colors. The subject is asked to name as quickly as possible the color of the ink. This study used the difference between the time on the color and the dots conditions as the score for the Stroop.

5. **Symbol Digit Modalities Test (SDMT)**: This is a measure of information processing speed and visual tracking. It is a speeded symbol substitution task. With a reference key at hand, the patient pairs specific numbers with specific geometric figures over a 90-second interval.

6. **Delis-Kaplan Executive Function System Sorting Test (DKEFS)**: This task assesses concept formation and flexibility of thinking. Sets of stimulus cards of varying shapes and colors are sorted into two groups in as many ways as possible. The score is the number of confirmed correct sorts.

During the first visit for the M and Gs studies, the subjects also completed the following:

1. **Short Form 36 (SF-36)** from the MS Quality of Life Inventory: A self-report health-related quality of life instrument. The SF-36 has 36 items divided to eight domains: physical functioning, role physical, bodily pain, general health perception, vitality, social functioning, role emotional, and mental health. For each of the items the patient is asked to assess the amount of time during the past 4 weeks s/he experienced these difficulties on a 6-grade scale ranging from all of the time to none of the time. The two subscales used as outcome measures in the current study are the Mental Component Summary (MCS) and the Physical Component Summary (PCS). Scores on the mental and physical component scores may range from 0 to 100, with higher scores indicating better health-related quality of life.

2. **Perceived Deficit Questionnaire (PDQ)** from the MS Quality of Life Inventory: A self-report of symptoms of psychological impairment. The PDQ items assess difficulties with organization, concentration, and memory over the past month. The PDQ consists of 20 items assessing perceived cognitive problems (e.g., "I lose my train of thought when I am speaking"). Participants are asked to indicate how frequently they experience each of the difficulties on a 5-point sale ranging from 0 (never) to 4

(almost always). Total scores range from 0 to 80, with higher scores representing greater perceived cognitive impairment.

3. **Beck Depression Inventory (BDI):** A frequently used self-report measure of depression. The BDI consists of 21 items rated on a 4-point scale and has a possible score range of 0 to 63, with a higher score indicating more depression (scores above 29 indicate severe depression).

4. **Expanded Disability Status Scale (EDSS):** A frequently used neurologist-rated measure of neurologic impairment and disability. The EDSS is divided into 20 half-points ranging from 0 (normal) to 10 (death due to MS). Below 8.0 the EDSS is based on a neurologic examination, which is focused on eight functional systems (visual, brainstem, pyramidal, sensory, cerebellar, sphincter, cerebral, and "others") and the patient's ability to walk. From 8.0 to 9.5 the EDSS is based on self-care functions (Kurzke 2008).

Additionally, the subjects' primary caregivers, usually their spouses, completed the MSNQ-I and MNPI for the M study and the MSNQ-I for the Gk study:

1. **Multiple Sclerosis Neuropsychological Questionnaire - Informant (MSNQ-I):** A questionnaire given to the primary caregiver that screens for neuropsychological impairment. The MSNQ-I is based on observer-reports and can be completed in less than 5 minutes. It tests 15 items: distractibility, problems listening to others, slowed processing, forgetting appointments, forgetting what is read, forgetting shows or programs, forgetting instructions, needing frequent reminders, failing to follow through on planned activities, failing to answer questions coherently, failing to track two things at once, failing to follow conversations, problems controlling impulses, laughing or crying without cause, and excessive egocentric speech. Each item is rated on a 5-point scale, ranging from 0 (never, or does not occur) to 4 (very often, very disruptive).

2. **Modified Neuropsychiatric Inventory (MNPI):** A questionnaire given to the primary caregiver that screens for behavioral abnormalities. It assesses 10 neuropsychiatric domains, including delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor activity such as pacing and stereotyped behaviors. NPI scores are based on behaviors present in the past

month. Each behavior is evaluated by using a standardized script read by the examiner. The symptom is then scored by the caregiver, using operationalized criteria for frequency and severity. For the purposes of this study, the frequency scores for each domain were analyzed separately, and symptom severity was omitted due to missing data.

Tables 1.1 and 1.2 summarize the basic characteristics of all measures used in the study, and Table 2 shows which measures were available in each of the three data sets. The primary analysis was conducted using the M data set, and where overlapping data from the Gs and Gk data sets were available, secondary analysis was conducted with the Gs data, Gk data, and combinations (eg, M+Gs, M+Gk) of the data sets.

Table 1.1: Characteristics of Neurocognitive Tests

	Measure of:	Score Range:	Score Direction:	Subscores:
Paced Auditory Serial Addition Test (PASAT)	Cognitive function: auditory information processing speed, flexibility, and calculation ability	0-60	Lower scores indicate worsening auditory information processing speed, flexibility, and calculation ability	None
California Verbal Learning Test II (CVLT-II)	Cognitive function: verbal memory	0-16	Lower scores indicate lower verbal memory	Many; this study will use the long-delay free recall as the primary score.
Controlled Oral Word Association Test (COWAT)	Cognitive function: spontaneous production of words under restricted search conditions (verbal association fluency)	No limit; mean varies with age and education level, from 36.5±9.9 to 40.1±10.5	Lower scores indicate lower verbal association fluency	None
Victoria Stroop Test (Stroop)	Cognitive control: assesses the ease with which a person can maintain a goal in mind and suppress a habitual response in favor of a less familiar one	No limit; score is speed to complete task	Higher scores indicate worsening cognitive control	Many different scoring methods for dots, words, colors, and combinations of these; this study will use the difference between the time on the color and the dots conditions.
Symbol Digit Modalities Test (SDMT)	Cognitive function: divided attention, visual scanning, tracking, and motor speed	0-110	Lower scores, 1-1.5 SD below the mean, indicate cerebral dysfunction	None
Delis-Kaplan Executive Function System (DKEFS) Sorting Test	Cognitive function: problem-solving, verbal and nonverbal concept formation, and flexibility of thinking on a conceptual task	No limit; score is number of confirmed correct sorts.	Lower scores indicate worsening performance	None

Table 1.2: Characteristics of Questionnaires and Other Measures

	Measure of:	Score Range:	Score Direction:	Subscores:
Beck Depression Inventory (BDI)	Severity of self-reported depression	0-63	0-13: minimal 14-19: mild 20-28: moderate 29-63: severe	None
Multiple Sclerosis Quality of Life Inventory, Short Form 36 (SF-36)	Health-related quality of life	0-100 for each component summary	0: lowest level of functioning 100: highest level of functioning	Mental Component summary (MCS) & Physical Component summary (PCS)
Perceived Deficits Questionnaire (PDQ)	Patient's perception of cognitive difficulties	0-80	0: no deficits perceived 80: most deficits perceived	None
Multiple Sclerosis Neuropsychological Questionnaire – Informant (MSNQ-I)	Caregiver's perception of patient's cognitive difficulties	0-60	Scores >22 indicate higher risk of neuropsychological impairment	None
Modified Neuropsychiatric Inventory (MNPI)	Caregiver's perception of patient's neuropsychiatric symptoms	0-144	Higher scores indicate worsening neuropsychiatric disturbances	12 behavioral domain subscores
Expanded Disability Status Scale (EDSS)	Physical Disability	0-10	0: no disability 10: death from MS	None

Statistical Analysis

Demographics & Baseline Information: Mean scores and standard deviations on each of the measures used in each data set were calculated. Demographic information was also calculated for each data set separately.

Hypothesis 1: Among subjects with MS and cognitive impairment, *objectively measured cognitive impairment* is associated with *lower quality of life*. Quality of life was measured by two scales: the Mental Component Summary (MCS) and the Physical Component Summary (PCS). The mental and physical component summary scores may range from 0 to 100, with higher scores indicating better health-related quality of life.

Using the M data, a correlation matrix was generated relating the neuropsychological tests (PASAT, CVLT, COWAT, Stroop, SDMT, and D-KEFS sorting task) and the quality of life test (SF-36). Linear regression models were fit with the M data set using the neuropsychological tests as independent variables and the SF-36 MCS & PCS as dependent variables. Linear regression was repeated with the potential confounders of age, sex, EDSS score, and ethnicity individually added to the model. The above analyses were repeated with the Gs data alone (with only PASAT and Stroop as objective measures of cognitive performance), and then with the Gs data added to the M data. For all multivariate data analyses, subjects with data missing on any of the measures involved in the analysis were excluded.

Hypothesis 2: Among subjects with MS and cognitive impairment, *objectively measured cognitive impairment* is associated with *increased depression*. Using the M data, a correlation matrix was generated relating the neuropsychological tests (PASAT, CVLT, COWAT, Stroop, SDMT, and D-KEFS sorting task) and the BDI. Linear regression models were fit with the M data set using the neuropsychological tests as independent variables and the BDI as the dependent variable. Linear regression were performed as above with the potential confounders of age, sex, EDSS score, and ethnicity added individually to the model. These analyses were repeated with the Gs data alone (with only PASAT and Stroop as objective measures of cognitive performance), then with the Gs data added to the M data. The above analyses were repeated with the Gk data, using the BDI-II to measure depression, and the PASAT, CVLT-II, and COWAT as the neuropsychological tests.

Hypothesis 3: For patients with multiple sclerosis and cognitive impairment, *objective measure of cognitive performance* is associated with *caregivers' perception* of the patients' cognitive deficits. Using the M data, a correlation matrix was generated relating the neuropsychological tests (PASAT, CVLT, COWAT, Stroop, SDMT, and D-KEFS sorting task) and measures of caregivers' perception of patient deficits (MSNQ-I and the 12 domains of the MNPI). Linear regression was conducted with the M data set using the neuropsychological tests as independent variables and the MSNQ-I as dependent variable. This same regression was repeated with each behavioral domain of the MNPI as the dependent variable. Linear regression was performed with the potential

confounders of age, sex, EDSS score (a measure of disability), and ethnicity individually added to the model. The above processes were repeated using the Gk data alone (with PASAT, CVLT-II, COWAT, and Stroop as independent variables and the MSNQ-I as the dependent variable), and then with the Gk data added to the M data.

Hypothesis 4: For patients with multiple sclerosis and cognitive impairment, *objective measurement of cognitive performance* is not associated with *self-report of cognitive performance*. Using the M data, a correlation matrix was generated relating the neuropsychological tests (PASAT, CVLT, COWAT, Stroop, SDMT, and DKEFS sorting task) and the measure of self-reported deficits (PDQ). Linear regression was conducted with the M data set using the neuropsychological tests as independent variables and PDQ as dependent variable, and then with the potential confounders of age, sex, EDSS score (a measure of disability), and ethnicity added to the model. The above analyses were repeated with the Gk data alone (with PASAT, CVLT-II, COWAT, and Stroop as independent variables and the PDQ as the dependent variable), and then with the Gk data added to the M data.

Hypothesis 5: For patients with multiple sclerosis and cognitive impairment, *self-report of cognitive performance* is not associated with *caregivers' perception* of the patients' cognitive deficits. Using the M data, a correlation matrix was generated relating the PDQ to the MSNQ-I and the MNPI. This correlation was repeated with the Gk data, using the PDQ and the MSNQ-I, and again with the M and Gk data together.

Summary: All statistical analyses were computed using Stata 11. A value $p<0.05$ was considered statistically significant. Pearson's r was used for all correlations. Linearity of relationships between variables was checked using scatterplots. For all linear regressions in hypotheses 1 through 4, forward and backward selection were first conducted with the cognitive tests as the independent variables to create an initial model, followed by adding each potential confounder individually to the model to check for confounding. Linear regression models were evaluated using the adjusted R-squared, the size and direction of the coefficients, and the statistical significance of the individual predictors in the models.

Results

Demographics:

Baseline characteristics of subjects, outlined in Table 3, revealed that the three studies recruited subjects with a similar age mean and range, similar lack of ethnic diversity with >95% Caucasians comprising the subject pool, and a similar distribution of MS types with the majority from each study having relapsing-remitting MS. Mean scores and standard deviations on measures in each of the three studies can be seen in Table 2. Mean EDSS (physical disability) and BDI (depressive symptoms) scores were comparable for each study, although all three studies had different BDI cutoffs: 21 for M, 27 for Gk, and 30 for Gs. The samples differed the most on gender distribution, with the Gk data set having only 55% women, the M data set having 78% women, and the Gs data set comprising 91% women. As can be seen in Table 2, the subjects in the Gs study performed considerably better on the PASAT (41.9 ± 12.1) than did the subjects in the Gk study (25.9 ± 9.1). This might be explained by the Gk study requiring cognitive dysfunction as an entry requirement, while the Gs study did not require cognitive dysfunction for study enrollment. Otherwise the three data sets did not differ considerably in their scores on any of the measures used in the study.

Table 2: Descriptive Statistics for Baseline Measures for the three studies used in the current investigation

	M Study N=119 Mean±SD(range)	Gs Study N=54 Mean±SD(range)	Gk Study N=125 Mean±SD(range)
Beck Depression Inventory (BDI)	BDI-I** N=119 8.8 ± 5.2 (0-21)	BDI-I** N=53 9.3 ± 6.7 (0-30)	BDI-II** N=122 9.7 ± 6.7 (0-27)
Multiple Sclerosis Quality of Life Inventory, Short Form 36 (SF-36)	N=86 PCS: 36 ± 12 (18-61) MCS: 45 ± 6.2 (27-57)	N=44 PCS: 36 ± 8.2 (18-54) MCS: 50 ± 9.1 (29-64)	
Perceived Deficits Questionnaire (PDQ)	N=116 41 ± 13 (6-69)		N=120 38 ± 13 (4-71)
Multiple Sclerosis Neuropsychological Questionnaire – Informant (MSNQ-I)	N=103 28 ± 13 (0-50)		N=72 27 ± 12 (1-52)
Modified Neuropsychiatric Inventory (MNPI)	N=112 12 separate domain frequency scores		
Paced Auditory Serial Addition Test (PASAT**)**	N=118 33 ± 13 (0-60)	N=51 42 ± 12 (7-59)	N=120 26 ± 9.1 (5-56)
California Verbal Learning Test II (CVLT-II) *	N=119 7.7 ± 3.6 (0-16) (raw scores)	N=30 53 ± 6.9 (41-67) (t-scores)	N=121 9.0 ± 3.6 (0-16) (raw scores)
Controlled Oral Word Association Test (COWAT)	N=119 32 ± 12 (0-66)		N=125 32 ± 12 (0-59)
Stroop Color and Word Test (Stroop)	N=119 13 ± 15 (-53-52)	N=54 12 ± 8.0 (-4.8-36.7)	N=125 17 ± 12 (-16-45)
Symbol Digit Modalities Test (SDMT)	N=119 39 ± 13 (7-67)		
Delis-Kaplan Executive Function System (DKEFS) sorting test	N=119 3.7 ± 1.8 (0-8)		

* CVLT-II is not comparable across data sets, as t-scores were used for the Gs data set while raw scores were used for the M and Gk data sets.

** Two different versions of the BDI were used: the BDI-I for M and Gs, and the BDI-II for Gk.

Table 3: Demographics of subjects participating in the M, Gs, and Gk studies

Variable, units	M Data (n=119)	Gs Data (n=54)	Gk Data (n=125)*
Mean Age ± SD (range)	51 ± 7.9 (29-65)	47 ± 10 (25-67)	52 ± 9.1 (24-65)
Female / Male	93 (78%) / 24 (20%)	49 (91%) / 5 (9.3%)	67 (55%) / 55 (45%)
Race			
Caucasian	113 (95%)	52 (96%)	116 (95%)
African-American	2 (1.7%)	1 (1.2%)	2 (1.7%)
Other	1 (0.84%)	1 (1.2%)	3 (2.5%)
Hispanic	3 (2.5%)	n/a	1 (0.80%)
MS Clinical Course			
Relapsing-remitting	75 (63%)	42 (78%)	79 (65%)
Primary Progressive	26 (22%)	3 (5.6%)	9 (7.4%)
Secondary Progress.	18 (15%)	9 (17%)	33 (27%)
Duration of MS	13 ± 8.4 (0-41)	10 ± 8.6 (1-30)	20 ± 12 (1-47)
Mean EDSS ± SD (range)	4.4 ± 2.0 (0-8)	3.2 ± 1.8 (0-7)	4.1 ± 1.9 (0-7.5)
Mean BDI ± SD (range)	8.8 ± 5.2 (0-21)	9.3 ± 6.7 (0-30)	9.7 ± 6.7 (0-27)

* Three subjects in the Gk data set were missing demographic information.

Hypothesis 1:

Mental Component Summary:

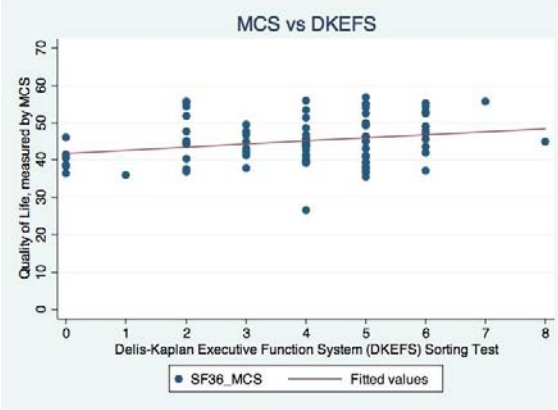
In the M data set, the DKEFS was the only cognitive test associated with quality of life as measured by the MCS ($r=0.24$, $p=0.03$), as can be seen in Figure 1. The correlation was positive, indicating that higher cognitive performance on the DKEFS was associated with better quality of life.

Figure 1:

Correlations of Cognitive Tests with Mental Component Summary (MCS)

Data: M

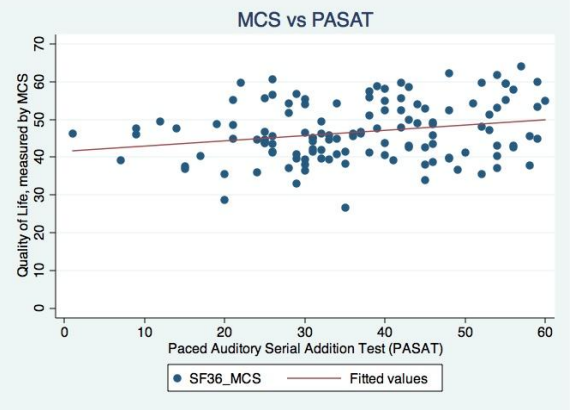
MCS vs. DKEFS



r=0.24, p=0.03*

Data: M + Gs

MCS vs. PASAT



r=0.24, p=0.007*

As can be seen in Table 4, unadjusted regression coefficients (beta, or β) revealed a significant association between the MCS and the DKEFS (β=0.85, p=0.029). The MCS was also significantly associated with the EDSS, a measure of physical disability (β=-0.87, p=0.011), indicating that a worse level of physical disability was associated with poorer quality of life. The MCS was also associated with sex (β=-3.5, p=0.034). As females were the referent, the -3.46 coefficient for sex indicated that males had decreased overall MCS as compared to females. When the association between the DKEFS and MCS was adjusted by both EDSS score and gender, the magnitude of the association decreased and was no longer statistically significant (β=0.68, p=0.07).

Table 4: Linear Regression Models with MCS as Outcome

Unadjusted

Independent Variable	M Data β(95% CI)	Gs Data β(95% CI)	M + Gs Data β(95% CI)
PASAT	0.035 (-0.073, 0.14)	0.20 (-0.046, 0.45)	0.14 (0.039, 0.24)*
CVLT-II	0.096 (-0.32, 0.51)	-0.18 (-0.76, 0.41)	N/A **
COWAT	-0.0072 (-0.13, 0.12)		
Stroop	-0.018 (-0.11, 0.069)	-0.095 (-0.44, 0.25)	-0.030 (-0.13, 0.071)
SDMT	0.040 (-0.065, 0.15)		
DKEFS	0.85 (0.090, 1.6)*		
EDSS	-0.87 (-1.5, -0.20)*	-0.27 (-1.8, 1.3)	-1.0 (-1.6, -0.35)*
Sex (M vs F)	-3.5 (-6.7, -0.28)*	4.4 (-6.6, 15)	-3.3 (-6.9, 0.27)

Adjusted by EDSS & Gender

Independent Variable	M Data β(95% CI)	Gs Data β(95% CI)	M + Gs Data β(95% CI)
PASAT	0.020 (-0.086, 0.13)	0.21 (-0.038, 0.47)	0.12 (0.0036, 0.21)*
CVLT-II	-0.081 (-0.50, 0.34)	-0.26 (-0.89, 0.38)	N/A**
COWAT	-0.030 (-0.15, 0.088)		
Stroop	-0.0084 (-0.093, 0.076)	-0.10 (-0.46, 0.25)	-0.023 (-0.12, 0.075)
SDMT	0.010 (-0.099, 0.12)		
DKEFS	0.068 (-0.063, 1.4)		

β = regression coefficient, CI = confidence interval

**=$p<0.05$*

** CVLT-II is not comparable across data sets, as t-scores were used for the Gs data set while raw scores were used for the M and Gk data sets.

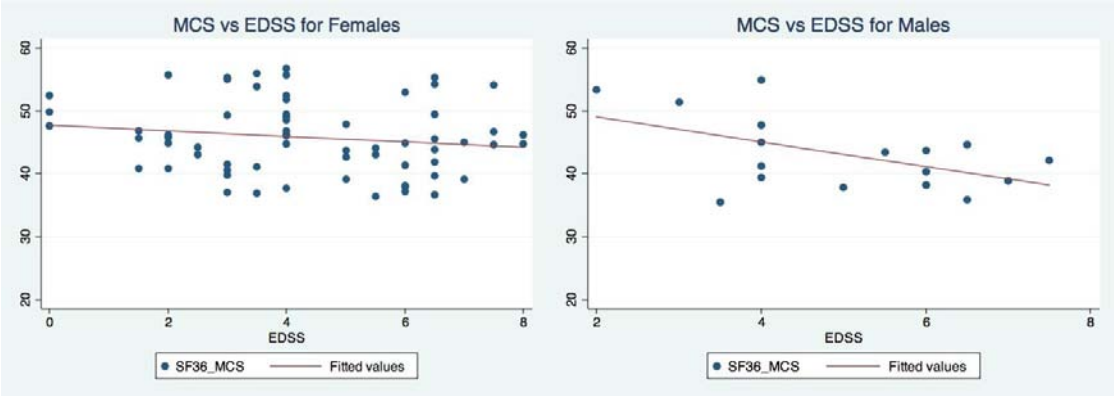
Multiple regression using both forward selection and backward elimination variable selection strategies yielded a model with only the DKEFS. The EDSS score was a confounder of the relationship between the DKEFS and the MCS, as it was associated with the MCS (r=-0.28, p=0.01). Adding the EDSS slightly lowered the magnitude of coefficient for the DKEFS, from 0.85 to 0.79, but did not change its significance. Adding gender to the model lowered the coefficient for DKEFS from 0.85 to 0.73, and removed its statistical significance by raising its p-value from 0.03 to 0.06. Gender slightly altered the association between the MCS and the DKEFS and dramatically altered the association between the MCS and the EDSS (see Figure 2). This can be partially explained by the slight gender difference in MCS scores: the mean for females was 46 ± 5.7, while for males it was 42 ± 6.9, and this difference was statistically significant (t-test yields $p<0.05$). The best model included the DKEFS, EDSS, gender, and an interaction term of EDSS*gender. Removing an outlier with a very low MCS score of 26 increased the

significance of every independent variable in the model, and the final model with the outlier removed is shown in Table 5.

Figure 2: Gender in Relationships between MCS, EDSS, and DKEFS

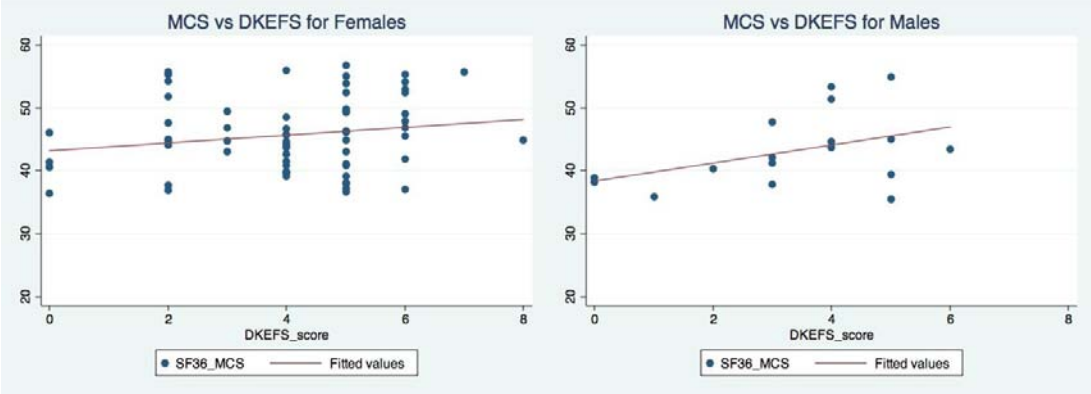
Data: M, outlier removed

MCS vs. EDSS, by gender



Females: r=-0.15, p=0.22 Males: r=-0.52, p=0.032*

MCS vs. DKEFS, by gender



Females: r=0.18, p=0.15 Males: r=0.43, p=0.085

Table 5:
Multiple Regression Models showing Relationship of Cognitive Tests to MCS
Dependent variable: MCS
Data set: M, with outlier removed
Adjusted R-squared: 0.0938

Independent Variable	Coefficient	95% Confidence Interval	P-value
DKEFS	0.63	-0.11, 1.4	0.092
Sex (M vs F)	3.8	-6.3, 14	0.46
EDSS	-0.45	-1.1, 0.24	0.20
EDSS*Sex (M vs F)	-1.1	-3.1, 0.83	0.25

Data set: M & Gs
Adjusted R-squared: 0.0856

Independent Variable	Coefficient	95% Confidence Interval	P-value
PASAT	0.11	0.0028, 0.21	0.044
EDSS	-0.83	-1.5, -0.16	0.016

The Gs data set confirmed the finding that the MCS was not associated with the PASAT, CVLT-II, or the Stroop. As the DKEFS was not available in the Gs data set, analysis of the Gs data could neither confirm nor negate the findings in the M data. However, in the combined M and Gs data sets, unlike in either data set alone, the MCS was correlated with the PASAT ($r=0.24$, $p=0.007$), as can be seen in Figure 1. The association and direction were consistent with the positive nonsignificant associations seen in both the M and Gs data sets separately, indicating that the association is genuine but required a larger number of subjects to reach statistical significance. In multiple regression, the PASAT was significant with both forward selection and backward elimination. The relationship between the PASAT and the MCS was confounded by level of physical disability, as measured by the EDSS, which was itself significantly associated with the MCS ($r=-0.26$, $p=0.003$). None of the other demographic variables, including gender, were significant confounders. The final model, which includes the PASAT and the EDSS, can be seen in Table 5.

In sum, quality of life as measured by the mental component summary (MCS) is positively associated with cognitive function as measured by scores on the Delis-Kaplan Executive Function System Sorting Task (DKEFS) and the Paced Auditory Serial Addition Test (PASAT). This means that higher quality of life is associated with higher

cognitive function, specifically in the domains of auditory information processing speed, flexibility, calculation ability, problem solving, and concept formation. The relationship between quality of life and cognitive function is confounded by physical disability as measured by the EDSS: physical disability is associated with both lower quality of life and with lower cognitive function.

Physical Component Summary:

In the M data set, none of the cognitive tests correlated with quality of life as measured by the PCS, and as can be seen in Table 6 no unadjusted associations were statistically significant.

In multiple regression, using backward elimination, the PASAT, SDMT, and Stroop were associated with the PCS. Of these, the PASAT and the Stroop were positively correlated with each other ($r=0.19$, $p=0.04$) and the PASAT and SDMT were also correlated ($r=0.54$, $p<0.0001$), therefore the model suffered from some collinearity. No outliers or influential observations were identified for the model. When gender was added to the model, the PASAT became more statistically significant, but its coefficient did not change in direction or magnitude, and scatter plots of the relationship between the PCS and the PASAT were similar for both genders. Therefore, gender was not a confounder in the relationship between the PCS and the PASAT, Stroop, and SDMT. There was no confounding effect for age, EDSS score, or ethnicity. The final model for the relationship between cognitive tests and the PCS is shown in Table 7.

Table 6: Linear Regression Models with PCS as Outcome
Unadjusted

Independent Variable	M Data β(95% CI)	Gs Data β(95% CI)	M + Gs Data β(95% CI)
PASAT	0.13 (-0.072, 0.34)	-0.11 (-0.34, 0.11)	0.051 (-0.096, 0.20)
CVLT-II	-0.23 (-1.0, 0.58)	0.24 (-0.22, 0.70)	N/A**
COWAT	0.093 (-0.14, 0.33)		
Stroop	-0.16 (-0.33, 0.0066)	0.36 (0.072, 0.65)*	-0.094 (-0.24, 0.047)
SDMT	-0.088 (-0.29, 0.12)		
DKEFS	-0.50 (-2.0, 1.0)		
EDSS	-0.027 (-1.4, 1.3)	-1.6 (-2.9, -0.33)*	-0.44 (-1.4, 0.50)
Sex (M vs F)	1.3 (-5.0, 7.7)	-7.2 (-16, 2.5)	-0.026 (-5.1, 5.1)

Adjusted by EDSS & Gender

Independent Variable	M Data β(95% CI)	Gs Data β(95% CI)	M + Gs Data β(95% CI)
PASAT	0.13 (-0.083, 0.35)	-0.15 (-0.36, 0.063)	0.029 (-0.12, 0.18)
CVLT-II	-0.16 (-1.0, 0.71)	0.14 (-0.36, 0.64)	N/A**
COWAT	0.087 (-0.16, 0.33)		
Stroop	-0.16 (-0.33, 0.0067)	0.32 (0.039, 0.60)*	-0.092 (-0.23, 0.050)
SDMT	-0.074 (-0.30, 0.15)		
DKEFS	-0.47 (-2.0, 1.1)		

β = regression coefficient, CI = confidence interval
**=p<0.05*
** CVLT-II is not comparable across data sets, as t-scores were used for the Gs data set while raw scores were used for the M and Gk data sets.

Table 7:
Multiple Regression Model showing Relationship of Cognitive Tests to PCS
Data set: M
Dependent variable: PCS
Adjusted R-squared: 0.0634

Independent Variable	Coefficient	95% Confidence Interval	P-value
PASAT	0.28	0.028, 0.53	0.030
SDMT	-0.23	-0.48, 0.025	0.077
Stroop	-0.15	-0.32, 0.019	0.081

The Gs data set did not support the findings in the M data set. While in the M data the Stroop was negatively, and nonsignificantly, associated with the PCS, the correlation was positive and significant (r=0.36, p=0.016) in the Gs data set. In multiple regression with forward selection and backward elimination, the Stroop was found to be associated with the PCS (β=0.31, p=0.11), but the association was weak (adjusted

R-squared = 0.071).

Also, while in the M data set physical disability as measured by the EDSS was not associated with the PCS, the PCS and EDSS were negatively associated (β=-1.6, p=0.015) in the Gs data set. Higher scores on the EDSS indicated worsening physical disability, while higher scores on the PCS indicated better quality of life, therefore the negative direction of this association is as expected: in the Gs data, better quality of life was associated with less physical disability.

Combining the Gs and M data sets also did not support the findings in the M data set alone. In the combined data set, the PCS was not associated with either the PASAT or the Stroop.

In sum, in the M data set, quality of life as measured by the Physical Component summary (PCS) of the Short Form 36 (SF-36) was found to be associated with the Paced Auditory Serial Addition Test (PASAT), the Symbol Digit Modalities Test (SDMT), and the Stroop. However, these findings were not confirmed by the Gs data set or by adding the Gs data to the M data, especially with regards to the Stroop whose coefficient is negative in the M data and positive in the Gs data. Interestingly, physical disability as measured by the EDSS was not associated with quality of life as measured by the Physical Component summary in the M data, but was strongly associated in the Gs data. Therefore, a likely conclusion from this data analysis is that quality of life as measured by the PCS was not consistently associated with cognitive dysfunction. Another possibility is that the data sets have differing results due to the differences in recruitment of subjects; that is, patients who were fatigued were recruited for the Gs study while patients who were cognitively impaired were recruited for the M study. The patients in the Gs data set had lower levels of physical disability as measured by the EDSS and performed markedly better on the PASAT than those in the M data set. Therefore another conclusion might be that for a patient population where all have cognitive dysfunction, physical quality of life is associated with cognitive dysfunction, while for a patient population where some have cognitive dysfunction and others do not, physical quality of life and cognitive dysfunction are not associated.

Hypothesis 2:

We hypothesized that among subjects with multiple sclerosis and cognitive impairment, objectively measured cognitive performance would correlate with depressive symptoms as measured by the Beck Depression Inventory (BDI).

In the M data set, the BDI did not correlate with any cognitive test. Multiple regression showed CVLT-II's association with the BDI was borderline significant, with a coefficient of 0.310 (95% CI: -0.027, 0.65; p=0.07). This one-variable model was both weak and nonsignificant (adjusted R-squared=0.03, prob>F = 0.07).

The Gs, Gk, and combined data sets all supported the findings of the M data set, as can be seen in Table 8. As all three data sets had BDI cutoffs to eliminate clinically depressed patients, these findings cannot be used to conclude that depression is not associated with cognitive deficits. Rather, these findings showed that within the range of mild to moderate depression, scores on cognitive tests were not affected by mood symptoms.

Table 8: Linear Regression Models showing Relationship of Cognitive Tests to BDI
Outcome: BDI

Independent Variable	**M Data β(95% CI)**	**Gs Data β(95% CI)**	**M + Gs Data β(95% CI)**	**Gk Data β(95% CI)**
PASAT	0.0026 (-0.069, 0.074)	0.0012 (-0.16, 0.16)	0.0063 (-0.058, 0.070)	-0.038 (-0.17, 0.096)
CVLT-II	0.20 (-0.068, 0.46)	0.047 (-0.32, 0.41)	N/A**	-0.12 (-0.45, 0.22)
COWAT	0.032 (-0.044, 0.11)			.023 (-0.091, 0.14)
Stroop	0.024 (-0.038, 0.085)	0.025 (-0.21, 0.26)	0.024 (-0.040, 0.087)	-0.018 (-0.12, 0.08)
SDMT	0.032 (-0.044, 0.11)			
DKEFS	-0.025 (-0.15, 0.099)			

β = regression coefficient, CI = confidence interval
**=p<0.05*
** CVLT-II is not comparable across data sets, as t-scores were used for the Gs data set while raw scores were used for the M and Gk data sets.

Hypothesis 3:

We hypothesized that among subjects with multiple sclerosis and cognitive impairment, objective measures of cognitive performance would positively correlate with caregivers' (mostly spouses) perception of the patients' cognitive deficits. Caregivers' perception of patients' cognitive deficits was measured by the Multiple Sclerosis Neuropsychological Questionnaire – Informant (MSNQ) and by the Modified Neuropsychiatric Inventory (MNPI).

In the M data set, for patients with both multiple sclerosis and cognitive impairment, two objective measures of cognitive performance – the PASAT ($r=-0.35$, $p<0.001$) and the CVLT-II ($r=-0.20$, $p=0.05$) – significantly correlated with the MSNQ, although simple linear regressions revealed only the PASAT to be significant ($\beta=-0.33$, $p<0.001$), as can be seen in Table 9. With multiple regression using forward selection and backward elimination, the best model included the PASAT. The EDSS was a confounder, as it lowered the PASAT's coefficient from -0.33 to -0.28 and was significantly associated with both the MSNQ-I($r=0.26$, $p<0.01$) and the PASAT ($r=-0.21$, $p=0.022$). In other words, caregivers' perceptions accurately reflected patients' performance on the PASAT, but not on any other cognitive test, and their perceptions were also significantly influenced by the patient's level of physical disability. Age and sex were not confounders in the relationship between the MSNQ-I and the PASAT.

Table 9:
Linear Regressions Models showing Relationship of Cognitive Tests to MSNQ
Outcome: MSNQ-I
Unadjusted

Independent Variable	**M Data β(95% CI)**	**Gk Data β(95% CI)**	**M + Gk Data β(95% CI)**
PASAT	-0.33 (-0.51, -0.15)*	-0.33 (-0.67, 0.0030)	-0.26 (-0.41, -0.11)*
CVLT-II	-0.70 (-1.4, 0.0063)	-0.63 (-1.4, 0.12)	-0.68 (-1.2, -0.19)*
COWAT	-0.15 (-0.36, 0.062)	-0.16 (-0.45, 0.12)	-0.16 (-0.33, 0.0084)
Stroop	-0.12 (-0.27, 0.037)	.022 (-0.23, 0.27)	-0.085 (-0.21, 0.042)
SDMT	-0.17 (-0.36, 0.028)		
DKEFS	-0.035 (-0.34, 0.27)		
EDSS	1.6 (.42, 2.8)*		
Sex (M vs F)	2.0 (-4.1, 8.1)		

Adjusted by EDSS & Gender

Independent Variable	**M Data β(95% CI)**
PASAT	-0.30 (-0.49, -0.11)*
CVLT-II	-0.58 (-1.3, 0.18)
COWAT	-0.14 (-0.34, 0.071)
Stroop	-0.11 (-0.26, 0.036)
SDMT	-0.11 (-0.32, 0.11)
DKEFS	-0.057 (-0.36, 0.25)

*β = regression coefficient, CI = confidence interval, *=p<0.05*
Note: Gk cognitive data was not able to be adjusted by EDSS and gender, as Gk demographics information was de-identified.

Table 10:
Multiple Regression Models showing Relationship between Cognitive Tests & MSNQ

Outcome: MSNQ-I
Data: M
Adjusted R2 of model: 0.125

Independent Variable	Coefficient	Confidence Interval	p-value
PASAT	-0.28	-0.47, -0.094	0.004
EDSS	1.1	-0.16, 2.3	0.086

Data: Gk
Adjusted R2 of model: 0.065

Independent Variable	Coefficient	Confidence Interval	p-value
PASAT	-0.33	-0.66, -0.0027	0.052
CVLT-II	-0.62	-1.3, 0.11	0.093

Data: M + Gk
Adjusted R2 of model: 0.096

Independent Variable	Coefficient	Confidence Interval	p-value
PASAT	-0.26	-0.41, -0.11	0.001
CVLT-II	-0.68	-1.2, -0.20	0.005

Table 10 shows the final model from the M data for the association of caregivers' perception of patients' deficits, as measured by the MSNQ, with objective measures of cognitive deficits. The model is weak, as the adjusted R-squared is only 0.125, indicating that only 12.5% of the variation in MSNQ-I scores can be explained by PASAT and EDSS scores. The results indicate that caregivers' perceptions were somewhat influenced by the patients' working memory and processing speed, and also by the patients' physical disability level. Overall the findings point to caregivers' reports not accurately reflecting the breadth of cognitive difficulties that patients experience.

The MNPI was divided into its subcomponents: irritability, agitation, anxiety, depression, euphoria, disinhibition, apathy, aberrant motor, delusions, hallucinations, sleep, and appetite. The MSNQ-I interestingly correlated with the following symptoms measured by the MNPI: irritability (r=0.234, p=0.022), anxiety (r=0.25, p=0.013), depression (r=0.24, p=0.017), euphoria (r=0.25, p=0.015), disinhibition (r=0.22, p=0.033), and apathy (r=0.21, p=0.048). The MSNQ-I notably did not correlate with the aberrant motor, delusions, hallucinations, sleep, nor appetite items on the MNPI.

Table 11: Correlations (Pearson's r) between MNPI Subscores & Cognitive Tests M Data

MNPI Subscore	PASAT	CVLT-II	COWAT	Stroop	SDMT	DKEFS
Irritability	-0.024	-0.025	0.027	0.070	-0.16	0.011
Agitation	-0.0076	-0.083	0.056	-0.016	-0.22*	-0.046
Anxiety	0.019	0.045	0.040	0.11	-0.13	0.064
Depression	0.013	0.11	-0.0083	0.0030	-0.076	-0.041
Euphoria	-0.10	0.0047	-0.049	-0.0080	-0.12	0.019
Disinhibition	-0.038	0.067	-0.013	0.17	-0.16	-0.0013
Apathy	-0.14	-0.022	-0.093	-0.039	-0.18	0.076
Aberrant motor	-0.10	-0.0033	-0.0029	-0.078	-0.16	0.0031
Delusions	0.010	-0.036	0.025	0.041	-0.071	-0.12
Hallucinations	0.030	-0.066	-0.097	0.021	-0.10	-0.024
Sleep	0.15	0.17	0.028	0.14	0.071	-0.16
Appetite	-0.070	0.014	-0.060	0.094	-0.091	0.0081

**=p<0.05*

As can be seen in Table 11, very few symptoms as measured by the MNPI were associated with cognitive tests. Agitation on the MNPI was found to be associated with the SDMT (r=-0.22, p=0.019). Apathy was also found to be moderately associated with the SDMT (r=-0.18, p=0.063). No other items on the MNPI were associated with scores on cognitive tests, indicating that the MNPI, like the MSNQ-I, did not accurately reflect patients' objectively measured cognitive deficits.

Like in the M data, the Gk data showed a correlation between the MSNQ-I and the PASAT (r=-0.23, p=0.05). Unlike in the M data, the Gk data showed no correlation between the MSNQ-I and the CVLT-II. In multiple regression with forward selection and backward elimination, the PASAT and the CVLT-II were associated with the MSNQ-I.

Table 10 shows the final model from the Gk data for the association of caregivers' perception of patients' deficits, as measured by the MSNQ, with objective measures of cognitive deficits. The model is weak, as the adjusted R-squared is only 0.133, indicating that only about 13% of the variation in MSNQ-I scores can be explained by PASAT and CVLT-II scores. The results indicate that caregivers' perceptions were somewhat influenced by the patients' working memory and processing speed, and also by the

patients verbal memory. Overall the findings are consistent with the M data in showing that caregivers' reports accurately reflect a subset of patients' cognitive difficulties.

Table 10 also shows the final model from the combined data sets, which reinforces the association of the PASAT with the MSNQ-I and confirms the association between the CVLT-II and the MSNQ-I seen in the Gk data alone. Significant correlations were seen between the MSNQ-I and the PASAT ($r=-0.25$, $p<0.001$) and the MSNQ-I and the CVLT-II ($r=-0.21$, $p=0.0068$). Multiple regression with forward selection and backward elimination showed that the best model included both the PASAT and the CVLT-II.

In sum, caregivers' perceptions of patients' cognitive deficits accurately reflected cognitive deficits as measured by the Paced Auditory Serial Addition Test (PASAT) and the California Verbal Learning Test II (CVLT-II).

Hypothesis 4:

We hypothesized that for patients with multiple sclerosis and cognitive impairment, objective measures of cognitive performance would not be associated with self-perception of deficits.

In the M data set, the PDQ did not significantly correlate with any objective measure of cognitive impairment. None of the objective measures of cognitive performance were significantly associated with the PDQ in simple regression (see Table 12). The PDQ was also not associated with physical disability as measured by the EDSS. The PDQ was, however, highly correlated with the BDI ($r=0.26$, $p<0.01$).

Table 12:
Linear Regression Models showing Relationship between Cognitive Tests and PDQ
Outcome: PDQ
Unadjusted

Independent Variable	M Data β(95% CI)	Gk Data β(95% CI)	M + Gk Data β(95% CI)
PASAT	0.036 (-0.15, 0.22)	-0.26 (-0.51, -0.013)*	-0.022 (-0.16, 0.12)
CVLT-II	0.39 (-0.33, 1.1)	-0.093 (-0.72, 0.54)	0.060 (-0.40, 0.52)
COWAT	-0.016 (-0.21, 0.18)	0.078 (-0.13, 0.29)	0.019 (-0.12, 0.16)
Stroop	0.044 (-0.12, 0.20)	0.048 (-0.15, 0.24)	0.026 (-0.094, 0.15)
SDMT	0.14 (-0.055, 0.34)		
DKEFS	-0.24 (-0.56, 0.076)		
BDI	0.68 (0.21, 1.14)*	0.73 (0.42, 1.0)*	0.68 (0.42, 0.94)*
EDSS	-0.45 (-1.7, 0.79)		

Adjusted by BDI

Independent Variable	M Data β(95% CI)	Gk Data β(95% CI)	M + Gk Data β(95% CI)
PASAT	0.034 (-0.15, 0.22)	-0.24 (-0.47, -0.0086)*	-0.0059 (-0.14, 0.13)
CVLT-II	0.26 (-0.44, 0.96)	-0.012 (-0.59, 0.57)	0.017 (-0.42, 0.46)
COWAT	-0.042 (-0.24, 0.15)	0.062 (-0.13, 0.26)	-0.0041 (-0.14, 0.13)
Stroop	0.030 (-0.12, 0.19)	0.062 (-0.12, 0.24)	0.016 (-0.098, 0.13)
SDMT	0.13 (-0.064, 0.32)		
DKEFS	-0.22 (-0.53, 0.086)		

*β = regression coefficient, CI = confidence interval, *=$p<0.05$*

Age and race were not confounders in the relationship between the PDQ and objective cognitive tests. In other words, neither age nor race changed the either coefficients or the statistical significance of any of the variables in the multiple regression relating PDQ to the cognitive tests. Likewise, the EDSS score was neither a confounder nor an effect modifier in the multiple regression analysis with PDQ as the dependent variable and the cognitive tests as the independent variables.

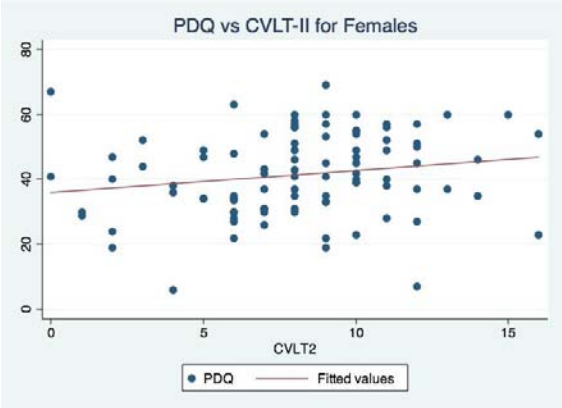
Adding sex to a model containing all of the cognitive tests changed the coefficient for the CVLT-II (from -0.13 to -0.013) and the Stroop (-0.0037 to 0.013). Sex was an effect modifier with regards to the relationship between CVLT-II and PDQ (see Figure 3). In the full model with all cognitive tests included as independent variables, separating the males and the females revealed that CVLT-II was significant for the males (CVLT-II β=-3.2, p=0.025) but not for the females (CVLT-II β=0.50, p=0.26). A model including

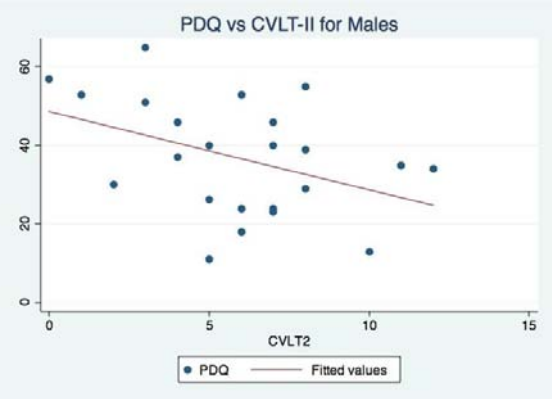
only male subjects, with PDQ as the dependent variable and CVLT-II as the sole independent variable, was significant (Prob>F = 0.05). The model was:
PDQ = 49 -2.0(CVLT-II). In this model, CVLT-II was statistically significant (p=0.05).

Figure 3:

Perceived Deficit Questionnaire (PDQ)'s correlation with CVLT-II by gender

M Data



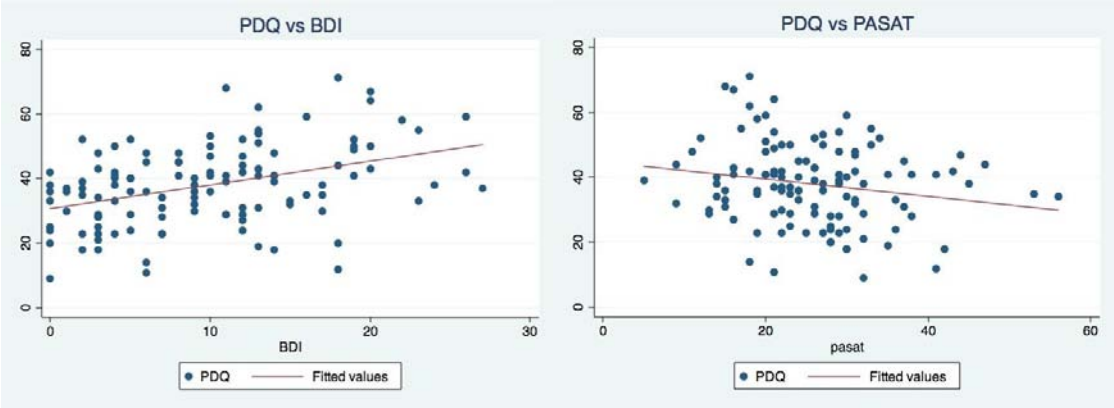


Females: r=0.18, p=0.081 Males: r=-0.41, p=0.054

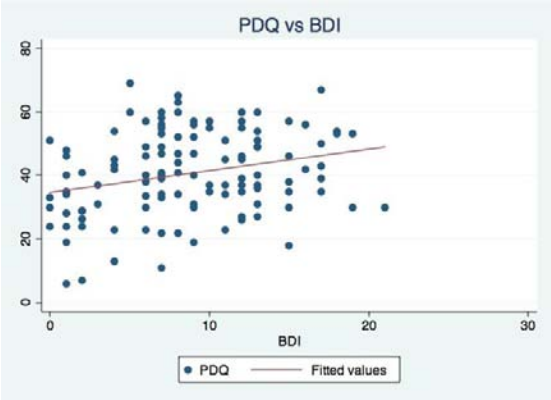
The Gk data showed that the PDQ correlated with the PASAT (r=-0.19, p=0.039), but not with any other objective measures of cognitive performance: not the CVLT-II, the COWAT, nor the Stroop. The PDQ was highly correlated with the BDI (r=0.40, p<.0001). Multiple regression with the Gk data indicated that the PASAT was the only objective measure of cognitive decline that was associated with a patient's perception of his/her cognitive deficits as measured by the PDQ, and this association was very weak (adj R-squared=.036, coeff=-0.26 [95% CI: -0.51, -0.013], p=0.039).

Figure 4: Correlations of BDI and PASAT with Perceived Deficit Questionnaire

Gk Data



M Data



In the M and Gk data sets combined together, the PDQ did not correlate with any cognitive test. However, like in the Gk data set alone, the PDQ correlated with depressive symptoms as measured by the BDI ($r=0.27$, $p<.0001$). Multiple regression with the M & Gk data sets together confirms that the PDQ was not associated with any cognitive test. The PDQ was, however, strongly associated with the BDI (adj R-squared=.096, coeff=.678 [.414, 0.942], $p<.001$). Figure 4 illustrates the strength of the correlations between the PDQ and the BDI and the PDQ and the PASAT.

In sum, patients' perceived deficits as measured by the PDQ are not an accurate reflection of their objective cognitive performance on neuropsychological tests. Rather, even in a population selected with BDI cutoffs to be not clinically depressed, patients' self-perception of their deficits was a reflection of mood symptoms.

Hypothesis 5:

We hypothesized that for patients with multiple sclerosis and cognitive impairment, caregivers' and patients' perceptions of the deficits would disagree. That is, self-perception of deficits would not correlate with caregivers' perception of the patients' cognitive deficits.

Table 13:
Simple Linear Regressions Models showing Relationship of MNPI components to PDQ
Outcome: PDQ

Independent Variable	**M Data β(95% CI)**	**Gk Data β(95% CI)**	**M + Gk Data β(95% CI)**
MSNQ-I	0.18 (-0.016, 0.37)	0.39 (0.16, 0.62)*	0.27 (0.12, 0.41)*
Irritability	0.55 (-1.6, 2.7)		
Agitation	0.75 (-1.6, 3.1)		
Anxiety	1.4 (-0.83, 3.7)		
Depression	2.1 (0.024, 4.2)*		
Euphoria	0.66 (-2.5, 3.8)		
Disinhibition	2.6 (-0.051, 5.2)		
Apathy	0.92 (-1.5, 3.3)		
Aberrant motor	-0.15 (-3.3, 3.0)		
Delusions	0.53 (-3.4, 4.5)		
Hallucinations	3.8 (-0.40, 8.1)		
Sleep	1.8 (-0.35, 3.9)		
Appetite	1.3 (-0.10, 3.6)		

*β = regression coefficient, CI = confidence interval, *=$p<0.05$*

In the M data set the PDQ had a borderline significant correlation with the following items on the MNPI: depression (r=0.19, p=0.048) and disinhibition (r=0.19, p=0.055) (see Table 13).

As seen in Table 14, the PDQ did not correlate significantly with the MSNQ-I in the M data set (r=0.18, p=0.072), but in the Gk data set the PDQ was significantly correlated with the MSNQ-I (r=0.38, p=0.001), and in the Gk and M data sets combined, the PDQ was significantly correlated with the MSNQ-I (r=0.27, p=0.0004).

In the M data set the MSNQ-I was not associated with the BDI (r=0.040, p=0.69), indicating that caregiver assessments of patient function were not a reflection of patient mood symptoms.

Table 14: Correlations of PDQ, MSNQ-I, and BDI

	M	Gk	M + Gk
PDQ vs. MSNQ-I	r=0.18, p=0.072	r=0.38, p=0.0010*	r=0.27, p<0.001*
PDQ vs. BDI	r=0.26, p=0.0050*	r=0.28, p=0.0020*	r=0.27, p<0.0001*
MSNQ-I vs. BDI	r=0.040, p=0.69	r=0.30, p=0.011*	r=0.16, p=0.041*

*r=Pearson's correlation coefficient, *=p<0.05*

In sum, contrary to the hypothesis, caregivers and patients impressions' of patients' cognitive deficits were positively correlated. Caregivers did not appear to be strongly influenced by depressive symptoms in this assessment, as the MSNQ-I did not correlate with the BDI, but patients were influenced by mood as the PDQ did strongly correlate with the BDI.

Discussion

Cognitive Dysfunction & Quality of Life

The findings of the current study support the conclusion that mental quality of life in multiple sclerosis is associated with objective cognitive dysfunction in certain cognitive domains. Quality of life as measured by the Mental Component Summary of the SF-36 was positively associated with the domains of cognitive function measured by the Delis-Kaplan Executive Function System Sorting Task (DKEFS) and the Paced Auditory Serial Addition Test (PASAT). The DKEFS measures concept formation and problem solving. The PASAT measures sustained attention, auditory information processing speed, flexibility, and calculation ability. Sustained attention and memory are frequently impaired in people with multiple sclerosis (Rao 1991b). Previous studies have also found the mental component summary to be associated with cognitive dysfunction as measured by the PASAT (Shawaryn 2002). The current study results are therefore consistent with findings in the literature and indicate that impairment in sustained

attention, memory, concept formation, and problem solving negatively impact patients' quality of life.

It is unclear why the particular cognitive domains measured by the PASAT and the DKEFS were associated with mental quality of life in this study but those cognitive domains measured by the CVLT-II, SDMT, Stroop, and COWAT. The SDMT and the Stroop, like the PASAT, are measures of attention. The COWAT and CVLT-II reflect verbal fluency and verbal memory. Performance on all these tests has been found to be frequently impaired in MS (Rao 1991b), and previous research has found an association between verbal fluency scores and the MCS (Glanz 2010). The explanation may be that the PASAT and DKEFS are better at detecting those small changes in cognition which are bothersome to patients and impact daily functioning. Indeed, the PASAT is known to be particularly sensitive to detecting cognitive decline in multiple sclerosis patients over time (Rosti 2007).

The association between mental quality of life and cognitive function was confounded by physical disability, indicating that the SF-36 MCS may not be a "pure" measure of mental quality of life and that a patient's performance on the DKEFS and PASAT are affected by physical disability. Both tests do involve motor functioning: the DKEFS requires card sorting and both the DKEFS and PASAT require speech.

There was a notable difference in the effect of physical disability by gender. Physical disability was more strongly associated with mental quality of life for men than it was for women. This indicates that as men become more physically disabled, their disability may be more disruptive to their mental quality of life than it is for women. The subject pool was mostly women, as is common for MS studies. Therefore, future research with larger samples of males might explore the different experience that men have with the disease.

Quality of life as measured by the Physical Component Summary (PCS) of the SF-36 was not consistently associated with cognitive function across the data sets. This finding is inconsistent with previous studies, which have shown a significant association between the PASAT and the PCS (Glanz 2010).

Physical quality of life was also not consistently associated with the EDSS, a neurologist-rated measure of physical disability, which is somewhat counterintuitive.

The current study is inconsistent with some prior studies that found the PCS to be associated with the EDSS (Shawaryn 2002; Robinson 2009). However, the current study is consistent with a Dutch & Belgian study done by Visschedijk et al. (2004) that found no significant relationship between baseline self-rated quality of life and disability over time. In that study, the authors concluded that assessment of health-related quality of life in physical functioning reveals more practical and diverse information about a patient's limitations in daily functioning compared with scales that measure "pure" functional status, like the EDSS. They pointed out that while the EDSS is based mainly on measurement of ambulation, self-rating of health-related quality of life integrates not only the objective functional or physical aspects of the disease but also the patient's perspective on his or her health and well-being (Visschedijk 2004). This leads to a possible explanation for the current study's findings, namely that the PCS was not associated with cognitive tests because it measured physical quality of life, not mental quality of life, and was not associated with the EDSS because it measured a broader array of information regarding the patients' experience with his/her physical disability. As the findings of the current study indicate that the EDSS does not capture physical quality of life, the case can be made for incorporating specific quality of life measures into clinical care.

Cognitive Dysfunction & Depression

The findings of this study indicate, surprisingly, that the degree of cognitive impairment is not associated with depressive symptoms in multiple sclerosis. This result is qualified by the entry criteria of the M and Gs studies, which employed BDI cutoffs excluding patients with clinical depression from those data sets. Cognitive impairment might be strongly associated with clinical depression in multiple sclerosis, but this study would not have captured that association. However, since this study found no association, linear or otherwise, between depression and any cognitive test, extrapolating our findings to higher levels of depression would predict that there would also be no association between major depression and cognitive function.

The literature on depression's association with objective cognitive impairment is mixed, with some research showing that cognitive function is associated with depression

(Shawaryn 2002) and other research finding low correlations between depression and any measure of objective cognitive impairment (Maor 2001). However, as summarized by Arnett et al. in their 2008 review, studies with adequate sample sizes generally have reported a positive association between depression and cognitive dysfunction in MS of moderate to large effect size. As in the current study we employed BDI cutoffs to eliminate severely depressed patients, the data could neither confirm nor refute an association between severe, clinical depression and objective cognitive impairment.

The findings of the current study were able to show that within the range of mild to moderate depression, scores on cognitive tests were not affected by mood symptoms as measured by the BDI. This conclusion might re-affirm the logic behind eliminating depressed patients from studies of cognition in multiple sclerosis; that is, up to a certain level of depressive symptoms, cognitive function may be accurately measured without depressive symptoms exaggerating or misrepresenting the patient's true cognitive impairment.

Caregiver Report of Patient Cognitive Impairment

Caregivers' perceptions of patients' cognitive deficits, as measured by both the MSNQ-I and the MNPI, were associated with objective cognitive function. The two cognitive tests associated with the MSNQ-I were the PASAT, a measure of auditory information processing speed, flexibility, and calculation ability, and the CVLT-II, a measure of verbal association fluency. The two cognitive tests have working memory and verbal response in common. In the PASAT numerical information is kept in working memory long enough to perform a calculation; in the CVLT-II verbal information must be rehearsed and encoded into long-term memory for later recall. The cognitive domains measured by the PASAT and CVLT-II are also important in conversational skills, as the PASAT measures auditory processing and the CVLT-II measures verbal fluency. The current study is consistent with previous findings that caregivers are accurate reporters of patient cognitive function (Smith 2010) and more specifically that the MSNQ-I is strongly negatively correlated with both the CVLT-II and the PASAT (Benedict 2003).

Physical disability as measured by the EDSS was found to be a confounder in the relationship between the MSNQ-I and the PASAT. This indicates that physical

disability, as measured by the EDSS, may strongly influence caretakers' perceptions of the patients' cognitive disability. The EDSS also correlated with patients' performance on the PASAT, which measures working memory, divided attention, and information processing speed. The PASAT is commonly used in the MS population because rate of information processing is dependent on subcortical brain systems and white matter tracks, areas that are preferentially affected in this demylinating disease (Fisk 2001). The PASAT is strongly correlated to frontal, parietal, and total lesion burden (Sperling 2001). The PASAT's correlation with the EDSS in this study may indicate that the PASAT is a sensitive reflection of overall disability in multiple sclerosis. Thus, patients with lowered scores on the PASAT are likely to have other impairments that impact their EDSS score.

In the current study, patients whose caretakers perceived them to have a higher level of cognitive deficits had lower performance on the PASAT than patients whose caretakers perceived fewer cognitive deficits. This points to the conclusion that the PASAT reflects those cognitive deficits which impact daily life, the kinds of activities a caretaker would be observing. Indeed, the PASAT has been found to reflect functional status in everyday activities (Kalmar 2008).

In sum, the data from this study supports the idea that caregivers – although influenced by physical disability – are generally accurate reporters of patients' cognitive disability.

Patient Self-Report of Cognitive Impairment

In the current study we found that patients' perception of their cognitive functioning, as measured by the Perceived Deficits Questionnaire (PDQ), was not associated with objective cognitive impairment with the exception of the PASAT, and the PDQ's association with the PASAT was weak. The PDQ was, however, highly correlated with depression, even though the subjects were selected to be non-depressed. In other words, patients do not have an accurate sense of their own deficits and their self-report of cognitive impairment may be more indicative of mood symptoms than objective cognitive impairment.

There was an interesting gender difference on the relationship between perceived deficits and cognitive function as measured by the California Verbal Learning Test II

(CVLT-II). For men, performance on the CVLT-II was associated with the PDQ, but this association was not found for women. That is, males with higher cognitive function as measured by the CVLT-II perceived themselves as having fewer deficits than men with lower cognitive function. This may indicate that men's perception of their own deficits is more influenced by verbal ability than it is for women. Impaired verbal ability may be more intrusive on daily activities for men. However, the majority of the subjects in this study were women, and therefore the conclusions that can be drawn regarding gender differences are limited and should be explored further in data sets with a larger proportion of men.

The EDSS score, a measure of physical disability, was notably not correlated with self-perceived cognitive disability. This indicates that a patient's perception of his or her own cognitive difficulties is not related to his or her physical functioning. On the other hand, the EDSS score was highly correlated with the MSNQ-I, a measure of caregivers' perception of patients' cognitive difficulties, indicating that while a patient can separate the physical from the cognitive, the caregiver's perception of cognitive disability is influenced by the patient's physical disability.

The current study's finding that self-reported cognitive disability in multiple sclerosis is better explained by depression than by actual cognitive decline is consistent with other studies in the MS literature. Maor et al. (2001) found a substantial discrepancy between perceived and objective cognitive functioning, with the MS patients consistently overestimating their cognitive problems. Gold et al. (2003) found no association between subjective and objective measures of cognitive impairment, and observed this discrepancy even in patients with very low depression scores, with both under- and overestimation of cognitive function occurring.

A large study by Middleton et al. (2006) concluded that patient perceptions of global cognitive functioning are not associated with objective cognitive performance. However, that study found patients were able to accurately assess their function on specific cognitive tasks. A study by Christodoulou et al. (2005) looked at perceived cognitive dysfunction and neuropsychological performance in MS patients over time. At baseline, and also at the end time point, self-reported deficits were not related to neuropsychological measures. However, change in overall neuropsychological

performance over time was correlated with change in the PDQ.

The findings in the current study are inconsistent with other research that has found some association between patient self-report and objective cognitive function (Kinsinger 2010; Randolph 2001). A study by Carone et al. (2005) found that self-report of cognitive performance was significantly associated with one cognitive test – the CVLT – out of a battery of four cognitive tests. Those patients who overestimated their cognitive ability when compared to informant ratings tended to be less depressed, less conscientious, and more cognitively impaired with greater behavioral disinhibition and unemployment as compared to patients who underestimated their cognitive ability. Patients overestimating their cognitive ability were also characterized by greater degrees of cognitive impairment, euphoria, and caregiver distress (Carone 2005).

Hoogervorst et al. (2001) found an association between subjective and objective cognitive function, but the association was non-linear; that is, patients who were the most cognitively impaired did not self-report the most impairment. Rather, the investigators found that mildly disabled patients with (close to) normal PASAT scores had subjective complaints regarding their cognition, while severely disabled patients with very poor PASAT scores did not.

Marrie et al. (2005) conducted a cross-sectional study remarkably similar to the current study in design and scope, using the PDQ to measure subjective complaints of cognitive deficits and the BDI for depressive symptoms, but using a different neuropsychological test battery: the Wechsler intelligence & memory scales. Unlike in the current study, Marrie et al. found subjective complaints of cognitive deficits were associated with objective findings of neuropsychological impairment. Immediate memory and processing speed from the Wechsler were associated with being subjectively impaired independent of emotional status, physical disability, physical fatigue, and age. A decrease in immediate memory was associated with an increased risk of subjective complaints that was most pronounced in young individuals. Consistent with the findings by Hoogervorst et al. (2001), marked declines in processing speed were associated with a reduced risk of subjective impairment; in other words, individuals with subtle changes in cognition perceived themselves as impaired, while those with more dramatic changes in cognition did not perceive themselves as impaired (Marrie 2005).

In contrast to Marrie et al., Hoogervorst et al., and Carone et al., the current study found no association between perceived deficits and objectively measured cognitive function. As the current study, with the M and Gk data sets combined, had twice the sample size of the Marrie et al. study, it is unlikely that a real association between the PDQ and objective cognitive tests was missed due to lack of power. The differences in results between the Marrie et al. study and the current study might be explained by the difference in the cognitive battery employed; the Wechsler battery may be better at picking up those impairments in processing speed and memory which patients use to evaluate their own subjective cognitive function. The differences in results between the current study and the Marrie et al. study could be due to differing patient populations and composition of study participants, although Marrie's sample was also largely white and half of the subjects complained of cognitive impairment. The differences in results may also be explained by differing statistical methods. While Marrie et al. used a PDQ cutoff with a bivariate outcome to examine the presence or absence of subjective cognitive deficits, the current study used the PDQ as a continuous variable.

The literature is mixed regarding the accuracy of multiple sclerosis patient's subjective cognitive dysfunction, but the current study supports the conclusion that perceived cognitive deficits do not correlate with actual performance on cognitive tests. The current study also adds support to the finding that self-report of cognitive dysfunction by multiple sclerosis patients is more indicative of depression than actual cognitive decline. Future directions in research should include examining changes in self-perception of deficits and cognitive function over time and using more specific self-report measures.

Caregiver vs. Patient Report of Cognitive Deficits

This study's results indicate that patients and caregivers generally agreed on the level of patient deficits. That is, patient perceived deficits as measured by the PDQ correlated with caregivers' perception of deficits as measured by the MSNQ. However, the results conflicted. It appeared that caregivers' assessments accurately reflected patient cognition on some tests (the CVLT-II and the PASAT), while patients' assessments were not an accurate reflection of any objectively measured cognitive

function. It is counterintuitive that patients and caregivers would agree on the level of deficits, if patients were inaccurate reporters while caregivers were accurate reporters. Further complicating matters, it appeared that patients were strongly influenced by depressive symptoms in their self-perception of cognitive deficits, while caregivers' assessments were not associated with patient depressive symptoms. This created a muddled picture.

The picture is clarified by Table 14, which shows that within each data set the results were consistent, and the results for the combined data set were being pulled to significance by the Gk data. Within the M data set, patients and caregivers did not agree in their assessment of patient cognitive function. Patients were influenced by depressive symptoms in their self-perception of deficits but caregivers were not significantly influenced by patients' mood. Additionally, in the M data set the MSNQ-I was associated with the EDSS, indicating that caregivers' assessment of patient cognitive function was influenced not only by cognition as measured by the PASAT, but also by patients' level of physical disability.

The findings for this study from the Gk data set conflicted with those from the M data set. In the Gk data set the PDQ and MSNQ-I were highly correlated, indicating that patients and caregivers were in strong agreement (see Table 14). In the Gk data set both caregivers and patients were strongly influenced by depressive symptoms, as both the PDQ and the MSNQ-I were strongly correlated with the BDI. Thus the Gk data yields a picture that is entirely different from the M data: patients and caregivers agreed in their assessments and were both strongly influenced by patient mood symptoms.

The M and Gk data sets were consistent regarding the importance of the PASAT in assessing MS cognitive dysfunction. In the M data set, caregivers' assessments were strongly associated with patient performance on the PASAT. In the Gk data, patient's self-perception was significantly associated with the PASAT. It appears, therefore, that both patients' and caregivers' impressions of patient cognitive dysfunction are related to those cognitive domains measured by the PASAT. The importance of the PASAT makes some sense as MS patients have been shown to be consistently impaired on the PASAT, which is an especially sensitive test to differentiate multiple sclerosis patients from controls (Fisk 2001). The PASAT is a difficult task which measures working memory

but also places demands on information processing speed, or efficiency of information processing and motor response production (Fisk 2001). In everyday conversations patients would use the skills measured on the PASAT – listening, working memory, information processing speed, and motor response production in the form of speech. Deficits noted in conversation would reasonably be reflected by caregivers in their assessment of patients.

In sum, the current study found inconsistent results across the data sets used, and cannot conclude whether patients and caregivers were in agreement regarding patient cognitive functioning.

Limitations

The study was limited by its cross-sectional design. While associations between objective cognition, self-perception, caregiver perception, and depression are interesting and informative at one time point, changes over time are more relevant to clinical practice.

Another limitation of the study was the use of three data sets which, while very similar, did not overlap on all measures used, may have had a few of the same patients participating in more than one study, and did not use identical recruitment: M and Gk required cognitive dysfunction as an entry criterion while Gs did not, and Gs required fatigue while M and Gk did not. The data from all three data sets was de-identified and cross-checking of patients from one data set to another to ensure that no patients were double-counted was not possible, although the study coordinator estimated no more than 10 patients may have overlapped. Only the main data set, the M set, contained all the measures of interest with the full cognitive battery, therefore confirmations or rejections of findings from the M data set based on other data sets were limited. For example, as can be seen in Table 10, the EDSS was found to be a confounder in the relationship between with the MSNQ-I and the PASAT in multiple regression, but this finding could not be replicated in the Gk data as its strict de-identification disassociated demographic variables such as the EDSS from cognitive and other measures.

There was a potential selection bias as patients were recruited from the clinic and community and had to be willing to take a drug or supplement for a period of time to

participate. Therefore it is likely that none of the three data sets captured a representational cross-section of the MS population, instead preferentially capturing those with the time and willingness to participate.

The impact of depression was unable to be fully explored in this study as the subjects were selected to be non-depressed, with BDI cutoffs that varied by study. Therefore the potential impact of mood was likely reduced. In this data set of non-depressed patients, depressive symptoms were found to be associated with perception of deficits but not with actual cognitive performance. There is evidence that objective neuropsychological functioning in MS is not significantly associated with depression (Kinsinger 2010) and it would have been interesting to examine this question using a population that included depressed patients. Given previous findings that depression is associated with the MCS and fatigue is associated with the PCS (Newland 2009), including subjects with a full range of BDI scores would also have been more informative in addressing quality of life.

Implications

The current study was able to add to current understanding of cognitive dysfunction in multiple sclerosis. Specifically, the current study provided evidence that cognitive dysfunction is associated with mental quality of life, is not associated with mild to moderate depression, and is accurately reported by caregivers.

The current study found interesting gender differences that have not, to our knowledge, been reported in previous studies. We found that physical disability was more strongly associated with mental quality of life for men than it was for women. We also found that for men, but not women, verbal function was associated with perception of cognitive deficits. These gender differences in the disease experience should be explored in future research with larger samples of men.

The results regarding the discrepancy between patient and caregiver reports have important implications. A patient's complaints of cognitive difficulty are often the basis for a referral for neuropsychological assessment. Thus, a patient's or caregiver's accuracy in reporting cognitive difficulties matters to clinical practice. The present data suggest that patients are not accurate reporters of their own cognition and global

cognitive complaints are likely to be associated with depressive symptoms. However, the present data also suggest that caregivers' reports of patient cognitive impairment reflect only a small subset of cognitive difficulties and are influenced by both patient physical disability and depressive symptoms. Therefore, use of brief objective screening for cognitive impairment at regular intervals may be the best way to ensure that MS patients are appropriately evaluated and treated for neurocognitive impairment.

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