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Relationship between depression, fatigue, subjective cognitive impairment, and objective neuropsychological functioning in patients with multiple sclerosis

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Abstract

Objective—This study explored the influence of depression and fatigue on subjective cognitive complaints and objective neuropsychological impairment in patients with multiple sclerosis.

Methods—Data for this study were taken from a randomized controlled trial, comparing 16 weeks of telephone-administered cognitive- behavioral therapy and telephone- administered supportive emotion focused therapy for the treatment of depression. The sample includes 127 patients with multiple sclerosis. The following self-report measures were collected pre- and post- treatment: Perceived Deficits Questionnaire, Beck Depression Inventory- II, and Modified Fatigue Impact Scale. Measures of objective cognitive functioning and the Hamilton Rating Scale for Depression were administered over the telephone.

Results—Our results showed that changes in depression and fatigue significantly predicted changes in subjective cognitive complaints from pre- to post- treatment, with patients perceiving fewer cognitive problems at post-treatment ($\beta = -.36, p < .001$ and $\beta = -.61, p < .001$ respectively). Changes in depression and fatigue were not significantly related to changes in objective neuropsychological performance. Improvements in depression and fatigue also predicted improved accuracy in perceiving cognitive abilities from pre- to post- treatment ($OR = .77, p < .001$ and $OR = .90, p < .001$ respectively).

Conclusions—The results of this study suggest that improvements in depression and fatigue through treatment do not influence objective neuropsychological performance in MS patients, but do relate to changes in subjective impairment. Furthermore, these changes improve patients' abilities to accurately perceive their cognitive functioning.

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Keywords

multiple sclerosis; cognitive function; subjective cognitive impairment; depression; fatigue

Multiple Sclerosis (MS) is a neurological disorder that often begins in young adulthood. The illness causes impairment in multiple domains of functioning and can have a profound impact on a patient's quality of life. Cognitive impairment has received increased attention over the past two decades as a common symptom of MS and is now recognized as one of the leading causes of disability among patients. Up to 65% of patients with MS experience cognitive impairment and these difficulties can occur across all stages of the illness (Amato, Zipoli, & Portaccio, 2006). The cognitive domains commonly affected in patients with MS include recent memory, working memory, processing speed, executive functioning, and visuospatial abilities (Bobholz & Rao, 2003; Rao, Leo, Bernadin, & Unverzagt, 1991a). These cognitive difficulties negatively impact employment, social relationships, and overall quality of life (Amato, Ponziani, Siracusa, & Sorbi., 2001; Rao et al., 1991b).

Despite its high prevalence, cognitive dysfunction is thought to be under-diagnosed in this population. Cognitive difficulties can occur independent of physical disability and are easily missed in a routine neurological exam (Rao, 1995). Health care providers typically depend on patient self-report to identify cognitive problems. Unfortunately, patients are generally poor reporters of their own cognitive abilities. Although some studies have found a correlation between subjective reports of cognitive impairment and objective neuropsychological performance (Marrie, Chelune, Miller, Deborah, & Cohen, 2005; Randolph, Arnett, & Higginson, 2001), most studies fail to find a substantial relationship (Christodoulou et al., 2005; Maor, Olmer, Mozes, 2001; Lovera et al., 2006; Fischer et al., 1999; Middleton, Denney, Lynch, & Parmenter, 2006). Randolph et al., (2001) found that patients were equally good reporters of their cognitive functioning when compared with spouses; however, other studies indicate that caregiver perceptions of patient cognitive abilities are more accurate than the patient's own report (Benedict et al., 2003; Benedict et al., 2004). These equivocal findings may be attributable to differing disease severity in the samples.

Accuracy of patient self-perceived cognitive functioning is further complicated by confounding symptoms such as depression and fatigue. Depression is highly correlated with subjective cognitive complaints (Benedict et al., 2004; Julian, Merluzzi, & Mohr, 2007; Maor et al., 2001; Middleton et al., 2006). Researchers have found that MS patients suffering from depression over-report cognitive difficulties (Benedict et al., 2004; Carone, Benedict, Munschauer, Fishman, & Weinstock-Guttman, 2005) and subjective cognitive complaints are more strongly correlated with depression than objective neuropsychological functioning (Julian et al., 2007). Research on the relationship between depression and objective neuropsychological functioning is less consistent. A review of the neuropsychology literature in MS concluded that there is no consistent relationship between depression and cognitive functioning (Brassington & Marsh, 1998). However, more recent work has suggested that there may be some subtler effects under specific circumstances. For example, Demaree, Gaudino and DeLuca (2003) have suggested that the cognitive deficits may appear only at higher levels of depression. Arnett has suggested a more complex, bidirectional relationship between depression and cognitive function in which depression may affect effortful cognition but not automatic cognition (Arnett, Barwick, & Beeney, 2008).

Fatigue is another common symptom of MS and affects up to 90% of patients with the disease (Krupp, Alvarez, LaRocca, & Scheinberg, 1988). Many patients believe that fatigue contributes to poor cognitive performance. Some studies indicate that cognitive fatigue can impair cognitive functioning in MS (Krupp & Elkins, 2000). However, most research indicates that

there is not a direct association between fatigue and actual cognitive performance (Fraser & Stark, 2003; Parmenter, Denney, & Lynch, 2003; Paul, Beatty, Schneider, Blanco, & Hames, 1998). For example, Parmenter et al. (2003) examined neuropsychological performance in patients with MS during periods of high and low fatigue. Although patients perceived that they performed more poorly during “high” fatigue periods, there were no actual differences in cognitive performance that could be attributed to fatigue.

Given the strong association between depression, fatigue, and perceived cognitive functioning, many researchers believe that perceptions of cognitive abilities are driven more by these comorbid symptoms than by actual cognitive performance. For example, Bruce and Arnett (2004) suggested that mildly depressed patients overestimate their memory impairment due to a depressive schema. Randolph, Arnett, & Freske (2004) also found that depression aggravated patients’ memory complaints due in part to depressive attitudes. Similarly, Middleton et al. (2006) concluded that patients’ perceptions of their cognitive functioning are more reflective of their emotional state and fatigue than their objective abilities. These findings are consistent with Beck’s (1967) cognitive theory of depression. This theory states that depression is associated with a negative, pessimistic view of oneself, the environment, and the future. This negative bias can lead people to misinterpret facts and exaggerate one’s problems, such as overestimating cognitive difficulties. If this negative bias led patients to overestimate their cognitive problems, then we would expect that treatment of depression would result in more accurate perceptions of one’s abilities. Unfortunately, the majority of studies examining the relationship between these constructs (depression, perceived abilities, neuropsychological performance) have been cross-sectional.

A recent study by Julian et al. (2007) examined these constructs longitudinally. The authors found an increased association between objective and subjective assessments of cognitive impairment after successful treatment of depression. These findings suggest that depression does in fact influence patients’ abilities to accurately perceive their cognitive abilities. Although important, this study was limited in that it did not include a measure of fatigue. Given the association of fatigue with depression and subjective cognitive reports, it is unclear how this variable might have influenced these results.

The purpose of the current study was to extend the findings from the Julian et al. (2007) study by examining the relationship among depression, fatigue, perceived cognitive functioning, and objective neuropsychological performance in the context of a clinical trial designed to treat depression in a sample of MS patients. The first aim of this investigation was to examine depression and fatigue as potential predictors of change in objective neuropsychological scores and subjective cognitive complaints from pre- to post-treatment. The second aim was to examine changes in depression and fatigue as predictors of patients’ accuracy in detecting cognitive impairment.

Method

These findings are based on secondary data analysis from a randomized trial comparing telephone administered cognitive-behavior therapy (T-CBT) to telephone administered supportive emotion-focused therapy (T-SEFT) to treat depression in a sample of multiple sclerosis patients. Patients’ depression symptoms significantly and substantially improved across both arms of the study; however, improvements were significantly greater for T-CBT, compared with T-SEFT on some measures of depression.¹ Additional details of this study are available in Mohr et al. (2005).

¹T-CBT compared with T-SEFT produced significantly greater reductions on the Hamilton Depression Rating Scale and evaluator-rated depressive symptoms (Mohr et al., 2005).

Participants

Participants were recruited through Kaiser Permanente Medical Care Group of Northern California and regional chapters of the National Multiple Sclerosis Society. Patients received a letter introducing the study and inviting them to participate. Respondents who were interested in the study received a brief telephone screen assessing depressive symptoms and several exclusion criteria. Those who met the initial screening criteria were invited to participate in a longer eligibility assessment that included assessment of all inclusion and exclusion criteria.

Inclusion criteria were (1) diagnosis of MS confirmed by the participant's neurologist², (2) functional impairment resulting in limitations in activity as measured by a score of at least 3 of a total possible score of 6 (indicating marked impact on activity) on one or more areas of functioning on Guy's Neurological Disability Scale (GNDS; Sharrack & Hughes, 1999), (3) a score of 16 or above on the Beck Depression Inventory (BDI) and 14 or above on the Hamilton Rating Scale of Depression, (4) ability to speak and read English, (5) at least 18 years of age.

Exclusion criteria were (1) severe cognitive impairment meeting criteria for dementia (i.e., patients who scored below the fifth percentile on 2 of 4 neuropsychological tests were determined to have dementia sufficient to be excluded), (2) current participation in psychotherapy, (3) severe psychopathology, including psychosis, current substance abuse, or plan and intent to commit suicide; (4) current MS exacerbation, defined as a sudden increase in symptoms within 24 hrs that had not yet remitted, (5) physical deficits that prevented participation in treatment or assessment, including inability to speak or read and write, (6) medication use other than antidepressants that affect mood (e.g., steroidal anti-inflammatories).

Of the 748 patients who completed the initial telephone screening, 223 met the preliminary criteria for a full eligibility assessment. Of those patients, 150 were found eligible for randomization. Of these 150 patients, 23 (15.3%) refused randomization. The remaining 127 patients were randomized to one of two 16-week psychotherapy treatments, telephone-administered cognitive-behavioral therapy (T-CBT; n=62) and telephone-administered supportive emotion-focused therapy (T-SEFT; n=65). The current analyses includes participants from both treatment conditions (n=127).

Measures

Self-report materials were mailed to participants with stamped addressed return envelopes. Interview assessments were conducted over the telephone. Participants were asked to complete self-report measures on the same day as the telephone assessment. All assessments were administered at baseline (prior to randomization to treatment) and at post-treatment (week 16).

Neuropsychological Functioning—Objective cognitive functioning was assessed using telephone-administered neuropsychological tests. A composite neuropsychological index was created using measures of three cognitive domains commonly observed to be impaired among patients with MS (Bobholz & Rao, 2003; Brassington & Marsh, 1998): (1) verbal fluency was assessed using the Controlled Oral Word Association Test (Lezak, 1995) (2) attention and concentration was assessed using Digit Span and Letter-Number Sequencing (Wechsler, 1991) (3) verbal memory was assessed using the delayed free recall score of the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 2000). Alternate forms of the CVLT, digit span, and COWAT were used for follow-up assessments. Telephone administration of these tests, or their equivalents, has been shown to be valid, reliable, and

²Patients' MS diagnoses were confirmed by their neurologist either within the managed care organization or in the community. We are not aware of the type of diagnostic procedures used by each neurologist. While it would have been desirable to have systematic diagnostic procedures for the sample, it was not possible for this study.

highly correlated with face-to-face administrations (Debanne et al., 1997; Unverzagt et al., 2007; Welsh, Breitner, & Magruder-Habib, 1993) and has been used in previous telephone administered studies with MS patients (Mohr et al., 1999; Mohr et al., 2000). Previous research (Mohr et al., 2000) has led to the development of a set of instructions that requests that the patient be alone in a room with no distractions and not near a computer and that the patient have no writing implements within reach.

A composite neuropsychological index score was created from the 4 individual scores. Most of the individual measures were significantly correlated with one another (r s ranged from .24–.68) at post-treatment; however, the COWAT was not significantly related to digit span or letter-number sequencing. A composite measure of neuropsychological functioning was used in this study because our objective was to compare a global measure of subjective impairment with global levels of objective cognitive functioning. Therefore, a composite measure of neuropsychological functioning was more appropriate for this study than analyses of specific domains. Previous studies examining correlates of cognitive functioning have used similar composite indices (Arnett, Higginson, Voss, Randolph, & Grandey, 2002; Julian et al., 2007). All variables were normed using published norms from non-MS patient samples and transformed into t-scores³. T-scores for the 4 measures were aggregated to create a single pre- and post- treatment composite Neuropsychological Performance (NP) scores.

Perceived Cognitive Functioning—Subjective cognitive complaints were measured using the Perceived Deficits Questionnaire (PDQ; Sullivan, Edgley, & Dehoux, 1990). The PDQ is a part of the MS Quality of Life Inventory (MSQLI), an MS-specific health-related QOL instrument. The MSQLI has been shown to have internal reliability and construct validity in a large sample of North American subjects (Fischer et al., 1999). 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 scale ranging from 0 (never) to 4 (almost always). Total scores range from 0 to 80, with higher scores representing greater perceived cognitive impairment.

For all analyses involving our accuracy score (i.e., second aim of the study), this variable was reverse scored and normed using T-scores created by using non-MS patient norms reported in Sullivan et al. (1990).

Depression—Depression was assessed using a telephone-administered version of the Hamilton Rating Scale for Depression (HDRS; Hamilton, 1960), a semistructured interview. The telephone version of the HDRS was developed and validated for use with the Medical Outcomes Study version of the HDRS (Potts, Daniels, Burnam, & Wells, 1990). Raters received training involving listening to and rating previous tapes and engaging in mock interviews. Inter-rater reliability from monthly reliability checks, using interclass correlations, averaged 0.89 (range, 0.75–0.97).

The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) was also administered as a measure of self-reported depression severity in this study. We selected the HDRS as the primary measure of depression for this study because it is objective, and because using two self-report measures can create spuriously large associations due to similar assessment methods. The BDI-II was highly correlated with the HDRS ($r = .71$, $p < .001$ at post-treatment; post-treatment values were used since pre-treatment associations have a restricted range due to depression inclusion criteria). All analyses using the HDRS were also performed using the

³Age-based norms were used for WAIS subtests (Wechsler, 1991), age and education-based norms were used for COWAT (Heaton et al., 2004), and age and gender-based norms were used for CVLT (Delis et al., 2000).

BDI-II. The results duplicated those reported for the HDRS. Accordingly, we will footnote the findings for the BDI-II analyses, but not present them in tables.

Fatigue—Fatigue impact was measured using the Modified Fatigue Impact Scale Total score (MFIS; Ritvo et al., 1997). The MFIS is a widely used fatigue measure in MS research. The measure contains 21-items (e.g., “Because of my fatigue in the last 4 weeks, I have limited my activities”). The internal reliability for administration in this study was $\alpha = .92$.

Functional Impairment—Multiple sclerosis related functional impairment was assessed using the Guy’s Neurological Disability Scale (GNDS), a standardized structured interview. This is a structured interview that assesses 11 basic areas of function (e.g., limb function and vision) and produces a single score that is highly related ($r = 0.81$) to objective measures of functional impairment based on neurological examination (Sharrack & Hughes, 1999). We dropped the item assessing mood because it is confounded with our primary study variables. Each item rates a basic area of functioning from 1 (no symptoms) to 5 (a specific criterion reflecting extremely severe impairment). A 3 on any item reflects the point at which the functional impairment interferes with normal daily functioning.

Treatments

Participants were randomized to one of two 16-week telephone-administered psychotherapies, T-CBT or T-SEFT. All treatments were administered by doctoral-level psychologists with 1 to 5 years of postdoctoral clinical experience. T-CBT is a structured cognitive-behavioral therapy based on standard CBT for depression (Beck, 1995; Beck, Rush, Shaw, & Emery, 1979). T-SEFT is an adaptation of the manual developed by Greenberg, Rice, and Elliott (1993) for process-experiential psychotherapy. T-SEFT has been shown to produce equivalent reductions in depression among medically healthy depressed patients (Watson, Gordon, Stermac, Kalogerakos, & Steckley, 2003). Perceptions of cognitive functioning were not specifically targeted in either treatment protocol. Additional details of the treatments and therapists are provided in Mohr et al. (2005).

Data Analysis Plan

The first aim of the study was to examine depression and fatigue as potential predictors of change in objective neuropsychological scores and subjective cognitive complaints from pre- to post- treatment. This was evaluated using hierarchical multiple regression, with post-treatment neuropsychological functioning and subjective cognitive complaints as the outcome variables. HDRS and FIS were examined separately as predictors. We began each analysis by entering potentially confounding clinical and demographic variables (age, education, years since diagnosis). We also entered pre-treatment levels of our outcome variable in this block. Next, we entered pre-treatment levels of the FIS or HDRS. Post-treatment FIS or HDRS scores were entered into the final block.

The second aim was to examine changes in depression and fatigue as predictors of patients’ accuracy in detecting cognitive impairment. To examine this aim, we created a dichotomous accuracy variable. The first step in creating this accuracy variable was to calculate discrepancy scores to determine the degree to which patients’ subjective cognitive complaints matched their actual cognitive performance as measured by the composite NP score. Discrepancy scores were created by subtracting the mean subjective cognitive functioning T scores from the mean NP T scores. This variable was computed for pre and post-treatment scores. Because we are using normed data, a zero score is defined as reflecting accurate perceptions, while reliable deviations from zero reflect over- and under-estimation of cognitive abilities. We considered a reliable deviation from zero to be one standard deviation. Participants were categorized into three groups (underestimators, accurate, or overestimators) based on the direction and degree of

discrepancy between their subjective complaints and objective scores. Patients with positive discrepancy scores reported worse subjective cognitive functioning than was detected on their objective NP scores. These patients were categorized as “underestimators” of their cognitive abilities if their discrepancy scores were greater than one standard deviation above zero. Patients with negative discrepancy scores reported better subjective cognitive functioning than was detected on their objective NP scores. These patients were categorized as “overestimators” of their cognitive abilities if their discrepancy scores were less than one standard deviation below zero. All other patients were classified as “accurate” estimators. Table 4 includes the number of patients categorized into each group at baseline and post-treatment. Given the very low number of overestimators, this group of patients was classified in the same category with “accurate” patients. This resulted in a dichotomous accuracy classification at baseline and 16 weeks (accurate = 0, underestimators = 1).

Given our interest in assessing change in accuracy as a function of treatment, we used the accuracy classification to create a “change in accuracy” score. This change in accuracy score was computed by subtracting the classification score at post-treatment from the classification score at pretreatment. This resulted in a change in accuracy score with 3 categories: patients who became more accurate ($n = 22$), patients whose accuracy did not change ($n = 84$), and patients who became less accurate ($n = 9$). We were interested in predictors of improvement in accuracy; therefore, we excluded the latter group from all analyses involving this variable.⁴ This resulted in a dichotomous accuracy variable (1= improved accuracy; 0= no change in accuracy).

Binary logistic regression was used to examine HDRS and FIS scores as predictors of post-treatment accuracy. The HDRS and FIS were examined separately as predictors. In each set of analyses, independent variables were entered hierarchically, with post-treatment accuracy as the outcome variable. We began each analysis by entering potentially confounding clinical and demographic variables (age, education, years since diagnosis). Next, we entered pre-treatment levels of FIS or HDRS scores. Finally, we entered post-treatment FIS or HDRS scores.

Results

Descriptive Statistics

Participants ($n = 127$) averaged 47.96 ($SD = 9.85$) years in age. A total of 98 (77.2%) were female. One hundred-fourteen (89.8%) were Caucasian, six (4.7%) were African-American, two (1.6%) were Hispanic, two (1.6%) were Native American, one (.8%) was Asian/Pacific Islander, and two (1.6%) were “other”. Level of education ranged from 12 to 22 years, with an average of 15.36 ($SD = 2.56$) years. Participants had been diagnosed for an average of 11.24 years, with a range of <1 year to 57.79 years. One hundred-thirteen (88.9%) had a relapsing form of MS (relapsing-remitting, secondary progressive or progressive relapsing), thirteen (10.2%) had primary progressive MS and one patient’s disease course was unknown. Functional impairment assessed with the GNDS total score averaged 23.37 ($SD = 6.28$) at baseline.

Preliminary analyses

Simple Associations—The bivariate correlations among the main study variables are provided in Table 1 and Table 2. A bonferroni adjustment was applied to these analyses to control for alpha slippage. This set the significance level at $p < .004$ for the 12 tests. Subjective

⁴All subsequent analyses were also conducted with this group included (patients who became less accurate) along with those whose accuracy scores did not change. Findings were very similar to the results reported in this paper.

cognitive impairment was significantly, negatively associated with the composite NP score at time 1 and time 2. A stronger association occurred at post-treatment compared to pre-treatment; however, a statistical test of the difference between the two correlations indicates that they are not significantly different ($p > .02$). Subjective cognitive impairment was also significantly associated with the HDRS and FIS at both time points. Objective neuropsychological functioning was not significantly associated with the FIS or HDRS. HDRS and FIS were significantly correlated at both time points.

Change from time 1 to time 2—Paired t-tests were conducted to determine significant changes in study variables from time 1 to time 2. Results are presented in Table 3. There was significant change in 2 of the 4 individual neuropsychological measures (memory, $p < .001$; fluency, $p < .05$) as well as the composite NP score ($p < .001$), such that participants demonstrated significant improvement on these measures from pre to post-treatment. Neuropsychological measures of attention (digit span and letter-number sequencing) did not change from pre- to post-treatment. There was a significant change in subjective cognitive complaints, with patients perceiving fewer cognitive difficulties at post-treatment. As expected, HDRS and FIS scores improved over the course of treatment ($p < .001$; $p < .001$).

Depression and fatigue predicting changes in objective and subjective cognitive functioning

Our first set of analyses examined changes in FIS and HDRS scores as predictors of changes in subjective cognitive complaints and objective neuropsychological functioning. First, we examined neuropsychological functioning as an outcome. All neuropsychological scores that demonstrated significant change from pre- to post-treatment were examined as outcome variables (memory, fluency, and the composite NP score). Each predictor variable (HDRS and FIS) was examined separately. Change in HDRS and FIS scores did not significantly relate to changes in any of the neuropsychological scores (all $ps > .24$).

Next, we examined subjective cognitive complaints as the outcome. Again, each predictor variable (HDRS and FIS) was examined separately. Residualized HDRS, $\beta = -.36$, $p < .001$,⁵ and FIS, $\beta = -.61$, $p < .001$, scores both significantly predicted change in subjective cognitive abilities. These findings indicate that improvements in depression and fatigue through treatment are associated with fewer perceived cognitive problems at post-treatment.

Depression and fatigue predicting accuracy⁶

Results indicate that post-treatment HDRS (controlling for baseline HDRS) was associated with increased frequency of patients improving their accuracy from pre- to post-treatment ($OR = .77$, $p < .001$). Post-treatment FIS scores (controlling for baseline FIS) also significantly predicted post-treatment accuracy ($OR = .90$, $p < .001$).

Next we conducted a logistic regression analysis in which both predictors (HDRS and FIS) were entered simultaneously. This was done to establish the extent to which these constructs made distinct contributions. The results of this analysis are shown in Table 5. Change in HDRS and FIS scores both made unique contributions to accuracy in this model ($OR = .84$, $OR = .90$, respectively, $ps < .05$).⁷ These findings indicate that as depression and fatigue decrease, the probability of patients becoming more accurate at perceiving their cognitive abilities increases.

⁵Results for BDI-II were similar, $\beta = -.40$, $p < .001$.

⁶We also examined treatment condition as a predictor of accuracy and it was not significant ($p = .28$), indicating that there were no differences in this variable for the two treatment conditions.

⁷Findings were similar when BDI-II was entered alone as a predictor, $OR = .85$, $p < .001$, as well as when it was entered simultaneously with fatigue, $OR = .89$, $p < .05$.

Discussion

Given the dearth of longitudinal research examining the relationship between depression, subjective cognitive complaints, and objective neuropsychological performance, this study focused on how the relationship between these constructs might change in the context of a clinical trial for depression. These findings suggest that treatment of depression and fatigue symptoms can influence patients' abilities to accurately perceive their cognitive performance.

Past research has found that subjective cognitive complaints are influenced more by depression and fatigue than actual cognitive abilities (Benedict et al., 2004; Maor et al., 2001; Middleton et al., 2006). This study supports those findings by showing that subjective cognitive complaints are correlated with depression and fatigue at pre- and post- treatment. However, depression and fatigue were not significantly related to performance on objective neuropsychological assessment.

This study also identified significant improvements in objective neuropsychological performance from pre- to post-treatment on two of the four individual measures (memory and fluency) and the composite NP score. However, these changes were not predicted by improvements in depression or fatigue. These changes are likely due to practice effects which are often seen with repeated administrations of neuropsychological assessments (e.g., Fischer et al., 2000). Research examining the association between depression and objective cognitive functioning has been equivocal (Arnett et al., 2008). Although some studies have found an association between depression and objective measures, many of these studies were limited by cross-sectional or correlational designs and involved small samples (Arnett, 2005; Arnett, Higginson, & Randolph, 2001; Demaree et al., 2003; Gilchrist & Creed, 1994). Despite these limitations, some researchers have speculated that depression might cause cognitive difficulties and that the amelioration of depression may lead to improved cognitive functioning (e.g., Demaree et al., 2003; Arnett et al., 2001). The current study does not support the hypothesis that depression contributes to neuropsychological impairment in MS. A strength of the current study in comparison to previous research is the study design. In contrast to longitudinal studies in which unmeasured variables have the potential to cause spurious associations, this study manipulated depression and fatigue through behavioral treatment in the context of a clinical trial.

Although improvements in depression and fatigue did not influence objective cognitive functioning, these changes did influence subjective cognitive complaints. Changes in depression and fatigue from pre- to post-treatment were associated with significantly lower levels of perceived cognitive problems. These findings replicate previous evidence that depression influences subjective reports of cognitive impairment (Julian et al., 2007). Furthermore, these findings extend the literature by demonstrating that fatigue is an important predictor of subjective cognitive complaints.

We also examined changes in participants' accuracy at detecting their cognitive abilities. We found that changes in depression and fatigue significantly predicted whether or not patients were classified as improving their accuracy at detecting their cognitive abilities. These findings suggest that depression and fatigue can decrease accuracy of patient reported cognitive impairment and that accuracy can be improved with successful treatment of these symptoms.

Although this research contributes important findings, its limitations should be noted. First, this study excluded patients with the most severe levels of cognitive impairment. Previous research suggests that the relationship between objective abilities and subjective cognitive impairment differs for patients with severe versus moderate impairment (Carone et al., 2005). Therefore, we are unable to generalize of our findings to the most impaired patients. Second, the objective assessments were performed over the telephone. While telephone administration

has been validated in other samples (Debanne et al., 1997; Unverzagt et al., 2007; Welsh et al., 1993), these findings do not necessarily generalize to our sample and our specific set of measures. Further research is needed to validate the telephone-administered neuropsychological battery used in the current study. Third, although we did not find a significant association between depression and objective cognitive functioning, it is possible that a third variable not examined in this study could influence this relationship. For example, research by Rabinowitz and Arnett (2009) suggests that the relationship between objective cognitive functioning and depression varies according to the patient's coping style. Complex analyses examining moderators and mediators were beyond the scope of this paper, but future work would benefit from examining these relationships, especially in an experimental design.

A final limitation of the current study is that the evaluation included only a limited number of neuropsychological measures. It is possible that depression might cause impairment in other neuropsychological domains that were not included in this investigation. For example, some researchers suggest that specific aspects of executive functioning (i.e., planning) and speeded information processing are related to depressive symptoms in MS (Arnett et al., 2001; Denney, Lynch, Parmenter, & Horne, 2004) and we did not include measures of these specific domains. Further research involving longitudinal designs and more comprehensive neuropsychological batteries are needed to better understand these distinctions.

Despite these limitations, our findings have important clinical implications. Accurate detection of cognitive dysfunction in MS is essential for guiding appropriate treatments. Our findings suggest that patient reports of their cognitive abilities are not always accurate, particularly if the patient is experiencing depression or fatigue. Unfortunately, healthcare providers typically rely on patient reports to detect cognitive difficulties. A large literature has shown that both depression and fatigue can be treated with behavioral and/or pharmacological interventions (Mathiowetz, Finlayson, Matuska, Chen, & Luo, 2005; Mohr, et al., 2005; Mohr, et al., 2000; Stankoff, et al., 2005). These findings suggest that an added advantage of intervention for depression and fatigue is that it may reduce complaints about cognitive impairment and improve patients' abilities to accurately perceive cognitive functioning. Not only would this improvement aid health providers in making treatment decisions, but it would potentially improve patients' quality of life.

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Table 1Intercorrelations of Primary Study Variables at Time 1 ($n = 127$)

Variable	1	2	3	4
1. Perceived Deficits Scale	...			
2. Composite NP Score	-.23**	...		
3. HDRS	.37***	-.02	...	
4. FIS	.67***	-.22	.27**	...

Note. HDRS = Hamilton Rating Scale for Depression; FIS = Fatigue Impact Scale;

**
p < .01;

p < .001

Table 2Intercorrelations of Primary Study Variables at Time 2 ($n = 122$)

Variable	1	2	3	4
1. Perceived Deficits Scale	...			
2. Composite NP Score	-.37***	...		
3. HDRS	.45***	-.16	...	
4. FIS	.68***	-.23	.58***	...

Note. HDRS = Hamilton Rating Scale for Depression; FIS = Fatigue Impact Scale;

**
p < .01;

p < .001

Table 3

Pre- and post-treatment outcomes for primary variables of interest

	Pre-treatment mean (SD)	Post-treatment mean (SD)	<i>t</i>	<i>P</i> -value
HDRS	21.51 (3.71)	13.42 (6.42)	13.62	<.001
FIS	61.43 (11.70)	48.59 (13.78)	11.71	<.001
PDQ	43.15 (14.29)	35.05 (14.56)	-7.65	<.001
NP score	46.11 (6.56)	49.32 (6.76)	-7.08	<.001
Attention				
L-N Seq.	9.50 (2.48)	9.59 (2.53)	-.57	.057
Digit Span	17.45 (3.99)	17.55 (4.01)	-.59	.056
Fluency	35.98 (10.51)	37.85 (10.28)	-2.52	<.013
Memory	39.40 (12.90)	50.55 (12.23)	-10.07	<.001

Note. HDRS = Hamilton Rating Scale for Depression; FIS = Fatigue Impact Scale; PDQ = Perceived Deficits Scale; NP score = Composite Neuropsychological Performance score; L-N Seq. = Letter-Number Sequencing. PDQ scores are normed t-scores.

Table 4

Discrepancy score categories at baseline and post-treatment

	Baseline	Post-treatment
Underestimators	81	64
Accurate	41	50
Overestimators	2	3

Table 5
Logistic Regression Analysis of Depression and Fatigue predicting changes in Accuracy

Predictor	β	SE β	Wald's χ^2	df	p	e^{β} (odds ratio)
Step 1						
Years	.046	.031	2.202	1	.138	1.047
Age	.002	.038	.002	1	.962	1.002
Education	-.232	.138	2.850	1	.091	.793
Step 2						
Baseline HDRS	.190	.095	4.002	1	.045	1.209
Baseline FIS	.051	.032	2.440	1	.118	1.052
Step 3						
Post-treatment HDRS	-.178	.077	5.303	1	.021	.837
Post-treatment FIS	-.102	.039	6.797	1	.009	.903

Note. HDRS = Hamilton Rating Scale for Depression; FIS = Fatigue Impact Scale; Cox and Snell R² = .288, Nagelkerke R² = .452, Hosmer and Lemeshow Goodness-of-fit test = 4.774 (df = 8; p = .781).
Years = # years diagnoses with MS.