

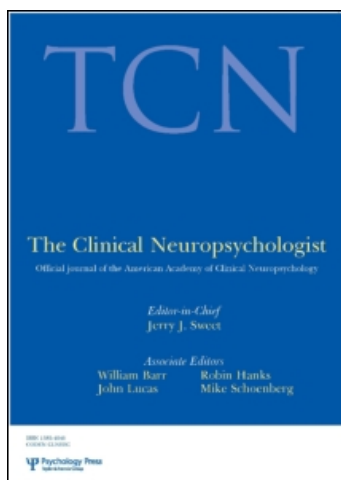
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Access details: Access Details: [subscription number 933555855]

Publisher Psychology Press

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## The Clinical Neuropsychologist

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713721659>

### Relationship Between Global Cognitive Decline and Depressive Symptoms in Multiple Sclerosis

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First published on: 17 January 2011

**To cite this Article** Barwick, Fiona H. and Arnett, Peter A.(2011) 'Relationship Between Global Cognitive Decline and Depressive Symptoms in Multiple Sclerosis', *The Clinical Neuropsychologist*, 25: 2, 193 – 209, First published on: 17 January 2011 (iFirst)

**To link to this Article:** DOI: 10.1080/13854046.2010.538435

**URL:** <http://dx.doi.org/10.1080/13854046.2010.538435>

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## Relationship Between Global Cognitive Decline and Depressive Symptoms in Multiple Sclerosis

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Cognitive impairment and depressed mood are common symptoms in multiple sclerosis (MS), which significantly impact patients' role functioning and quality of life. Cross-sectional studies indicate a modest association between cognitive impairment and depressive symptoms in MS. Longitudinal studies show inconsistent results but provide some data indicating a relationship between increasing global cognitive decline and increasing depressive symptoms over time. Establishing whether such a relationship exists represents an important first step in understanding the temporal nature of that relationship along with any treatment implications. The current study investigated this relationship by using the adjusted difference between a demographic estimate of premorbid intellectual functioning (Barona) and a performance measure of current intellectual functioning (Shipley Institute of Living) to capture long-term global cognitive decline in MS patients. Degree of global cognitive decline was then related to a self-report measure of mood, evaluative, and vegetative depression symptoms (Chicago Multiscale Depression Inventory). Global cognitive decline accounted for 5% of the variance in mood-evaluative symptoms but none of the variance in vegetative symptoms. When groups experiencing moderate, mild, and no global cognitive decline were compared on depression symptom subscales, MS patients experiencing moderate cognitive decline reported significantly higher mood and evaluative, but not vegetative, depressive symptoms than MS patients with stable cognitive functioning.

**Keywords:** Multiple sclerosis; Cognitive functioning; Cognitive decline; Mood functioning; Depression.

### INTRODUCTION

Multiple sclerosis (MS) is a chronic, degenerative, inflammatory disease of the central nervous system with an unpredictable course and a variable symptom profile. Depression and cognitive impairment are two common symptoms of the disease. Up to half or more of MS patients experience either depressive symptoms (Minden & Schiffer, 1990; Siegert & Abernathy, 2005), cognitive impairment (Amato, Zipoli, & Portaccio, 2006; Rao, Leo, Bernardin & Unverzagt, 1991), or both (Brassington & Marsh, 1998; Feinstein, 2004) at some point during the course of their illness, and these symptoms adversely affect work and social role functioning, as well as quality of life (Arnett & Smith, 2005; Benedict et al., 2005; Janardhan & Bakshi, 2002; Lobentanz et al., 2004; Rao Leo, Ellington et al., 1991). Establishing whether a relationship exists between depressive symptoms and

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Accepted for publication: October 29, 2010. First published online: January 12, 2011

long-term cognitive decline in MS represents an important first step in understanding the temporal nature of that relationship along with any treatment implications.

Cross-sectional studies have demonstrated a modest association between degree of cognitive impairment and level of depressive symptoms in individuals with MS (Arnett, Barwick, & Beeney, 2008; Arnett, Higginson, & Randolph, 2001; Demaree, Gaudino, & DeLuca, 2003; Gilchrist & Creed, 1994; Thornton & Raz, 1997), especially those studies that included more severely depressed patients and which employed depression measures that controlled for potential overlap between vegetative depressive symptoms and MS disease symptoms (Feinstein, 2006). Longitudinal studies have yielded more inconsistent results. Most studies used small or high-attrition samples, shorter time periods ( $\leq 2$  years), or depression measures that failed to examine mood symptoms separately from vegetative symptoms. Typically, they assessed depressive symptoms only incidentally, did not report changes in depression severity over time, and did not examine the correlation between changes in depression severity and changes in cognitive impairment (Camp et al., 2005; Ivnik, 1978; Jonsson et al., 2006; Kujala, Portin, & Ruutiainen, 1997; Mariani et al., 1991; Schiffer & Caine, 1991; Sperling et al., 2001; Zivadinov et al., 2001). Perhaps as a result, these studies found no significant relationship between increasing levels of cognitive impairment and increasing depressive symptoms in MS patients over time.

A few longitudinal studies have reported results suggesting a relationship between changes in depressive symptoms and changes in cognitive dysfunction in MS over time. Camp and associates (2005) found a significant increase in depression scores among 99 patients with primary progressive (PP) MS at 1-year follow-up, along with a significant correlation between depression scores and neuropsychological performance at the same time point. Feinstein, Kartsounis, Miller, Youl, and Ron (1992) used a measure of depression that minimized overlap between depression and disease symptoms to evaluate a sample of 48 patients with clinically isolated lesions (CIL). They found significantly increased depression scores and cognitive dysfunction after 5 years among patients who developed PP MS compared to patients who developed relapsing remitting (RR) MS or to patients who retained their initial CIL status. In a 3-year longitudinal study of cognitive functioning in 24 patients with PP MS, Denney, Lynch, and Parmenter (2008) found that patients who were cognitively impaired at baseline had higher depression scores at follow-up than those who were cognitively unimpaired at baseline, although the difference was not significant. Piras and colleagues (2003), despite the exclusion of severely depressed individuals from a sample of 12 RR MS patients who were followed over a period of almost 9 years, found a small but significant increase in global cognitive deterioration along with a small but non-significant increase in the number of patients with minor depression at follow-up.

The study that found the clearest evidence of a decline in cognitive functioning accompanied by an increase in depressive symptoms over time was conducted over the longest time period, recruited one of the largest patient samples, had one of the lowest attrition rates, and employed a depression measure that minimized overlap with disease symptoms. Amato and colleagues (Amato et al., 1995; Amato, Ponziani, Siracuse, & Sorbi, 2001) examined comparative levels of cognitive functioning and depressive symptoms over a period of 10 years among 50 RR or PP

MS patients and 70 healthy control (HC) participants matched on age, sex, and education. After the fourth year they found that MS patients performed significantly worse on neuropsychological tests and scored significantly higher on a depression measure than HC participants. These differences remained significant after 10 years: MS patients' cognitive performance worsened by one-half to one standard deviation from baseline and the number of MS patients classified as depressed ( $>13$  on the Hamilton Rating Scale for Depression) increased from 15 at baseline to 22 in the tenth year.

To date, the only longitudinal study to explicitly examine the relationship between degree of cognitive impairment and level of depressive symptoms in MS patients found that negative affect—including depressed mood—was a significant predictor of cognitive change after one year in 38 individuals with RR or secondary progressive MS (Christodoulou et al., 2009). The researchers used a depression measure that controlled for potential confounds between depression and disease symptoms along with a measure of global cognitive performance that combined different functional domains. Although there was no significant change over time in global cognitive performance or depressive symptoms for the MS sample as a whole, higher levels of negative affect at baseline were associated with greater declines in cognitive performance over a period of 1 year.

Establishing a clear association between increasing depression symptoms and long-term cognitive decline in MS is a crucial first step in elucidating the temporal nature of that relationship if one exists. However, several clinical and methodological issues make it difficult to capture any such association. First, longitudinal studies run the risk of patient attrition, which can bias statistical results. In studies with larger samples, attrition rates ranged from a low of 10% (Amato et al., 2001) to a high of 30–35% (Camp et al., 2005; Piras et al., 2003; Sperling et al., 2001). Patients who discontinued the study often were significantly older and had significantly lower baseline scores on cognitive tests than patients who completed the study (Camp et al., 2005; Denney et al., 2007).

Second, cognitive dysfunction in MS appears to be characterized by gradual and global decline over the long term along with considerable individual variability, which can make it difficult to identify mood factors associated with cognitive dysfunction using highly specific cognitive tests (Amato et al., 2001; Camp et al., 2005; Feinstein et al., 1992; Kujala et al., 1997). Examining global decline rather than specific deficits may allow any association between cognitive dysfunction and depression symptoms to emerge more clearly. It may also have greater clinical relevance, as general intellectual decline has been associated with deterioration in daily adaptive functioning in other neurological conditions (Hart, Wade, Bean, & Gibson, 2010; Holtzer et al., 2003; Njegovan, Hing, Mitchell, & Molnar, 2001; Vidoni, Honea, & Burns, 2010).

Third, the overlap between vegetative symptoms of depression and MS disease symptoms may obscure an existing relationship between cognitive dysfunction and depression. Studies using a depression measure that controls for this potential confound have found an association between cognitive functioning and mood and evaluative, but not vegetative, symptoms of depression (Arnett, Higginson, Voss, Bender et al., 1999; Arnett, Higginson, Voss, Wright et al., 1999;). Finally, some studies have suggested that greater cognitive impairment occurs in MS patients

showing moderate to severe depression (Arnett et al., 2001; Demaree et al., 2003) and that higher levels of depressive symptoms occur in MS patients showing greater cognitive decline (Amato et al., 2001). These results raise the possibility that the longitudinal relationship between depressive symptoms and cognitive dysfunction might be nonlinear (Siegert & Abernethy, 2005).

We attempted to address the above concerns in the current study. Instead of using a longitudinal design to characterize long-term global cognitive decline in our sample, we used the difference between a demographic measure of premorbid intellectual functioning, the revised Barona-Chastain regression formula (Barona & Chastain, 1986), and a performance measure of current intellectual functioning, the Shipley Institute of Living Scale (Zachary, 1996). We chose the Barona-Chastain regression formula as a measure of premorbid functioning because it is resistant to the unpredictable neurological insults characteristic of MS, thus reducing individual cognitive variability. Although estimates derived from the Barona-Chastain regression formula can be affected by the curtailment in education and occupation that sometimes occurs with MS, other methods for estimating premorbid intellectual functioning, including oral reading test and intelligence subtest performance measures, are subject to similar limitations, making the Barona a reasonable choice for measuring premorbid intellectual functioning. Similarly, we chose the Shipley as a measure of current functioning because we wanted to focus on the assessment of global intellectual decline and thus reduce individual cognitive variability. Also, the Shipley provides a good estimate of overall intellectual functioning that is highly correlated with Wechsler Full Scale IQ (Hays, Emmons, Wagner, & Stallings, 1997; Weiss & Schell, 1991). Because individuals with MS who participate in research studies have usually been diagnosed for several years, this approach provided an attrition-free and economical alternative to conducting a 10–15-year prospective study.

We used a depression measure that allows mood and negative evaluative symptoms to be examined separately from vegetative symptoms in order to avoid overlap with MS disease symptoms. We examined correlations between global cognitive decline and depressive symptoms, but we also compared MS patients showing moderate global cognitive decline to those showing no decline to address the possibility of a non-linear relationship between these constructs. We predicted that MS patients in the group showing global cognitive decline would report higher levels of mood and evaluative, but not vegetative, symptoms than MS patients showing no decline.

## METHOD

### Participants

Participants were 180 individuals with MS from the northeastern and northwestern United States recruited through local neurologists, MS support groups, and MS newsletters. Participants were excluded if the initial screening interview indicated the presence of neurological conditions other than MS, motor or visual impairment that might interfere with cognitive testing, significant prior head trauma, a diagnosis of learning disability or previous educational difficulties, or a

history of alcohol or drug abuse. Data from 6 MS participants were excluded from analyses because it was discovered after testing that the MS diagnosis was unclear (1 participant); there had been a prior history of stroke (1), loss of consciousness (1), or treatment with electroconvulsive therapy (1); or the participant was unable to complete a major portion of the assessment battery (2). The final sample thus consisted of 174 MS participants.

### Procedures

All participants gave informed consent according to institutional guidelines and were treated in accordance with the ethical standards of the American Psychological Association (APA). A board-certified neurologist evaluated all participants for MS or possible MS and assessed illness duration and disease course (Lublin & Reingold, 1996). All participants received a diagnosis of definite MS according to revised McDonald criteria (Polman et al., 2005), except for eight individuals who were diagnosed with possible MS. As employed by Arnett and colleagues (2001), a self-report version of Kurtzke's Expanded Disability Status Scale (EDSS; Kurtzke, 1983) was used to determine degree of neurological disability. In this version the EDSS was converted to questionnaire form in consultation with a board-certified neurologist, patients rated themselves on this questionnaire within 1 week prior to testing, and the EDSS rating was then made by an experienced neuropsychologist with expertise in MS (P.A.). Self-report EDSS measures have shown good intraclass correlation with conventional EDSS measures ( $ICC = .84$ ; Solari et al., 1993). No participants were experiencing a clinical exacerbation at the time of, or 1 month prior to, evaluation. Participants completed all measures described below in addition to a larger battery of neuropsychological tests on a single day of testing. In return for their participation, all individuals were paid and received a written report and verbal feedback on the results of the evaluation.

### Measures

**Barona and Chastain demographic formula.** This formula (Barona & Chastain, 1986) uses demographic variables including age, sex, race, education, occupation, geographic region, and urban-rural residence to estimate WAIS-R FSIQ as a measure of premorbid intellectual functioning. Correlations between the Barona demographic formula and the WAIS-R FSIQ range from  $r = .65$  to  $r = .76$  (Axelrod, Vanderploeg, & Schinka, 1999; Barona & Chastain, 1986; Griffin, Mindt, Rankin, Ritchie, & Scott, 2002).

**Chicago Multiscale Depression Inventory.** The Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1995) is a 42-item, self-report questionnaire specifically designed for use with medical patient populations. It has three subscales each consisting of 14 words or phrases that measure mood, evaluative, and vegetative depression symptoms. Examinees are asked to rate the extent to which each word describes them during the past week on a scale of 1 to 5.

**Shipley Institute of Living Scale.** This scale (Zachary, 1996) is a self-administered instrument comprised of a 40-item Vocabulary subtest and a 20-item Abstraction subtest that each take 10 minutes or less to complete. Together, the subtests yield an estimate of WAIS-R FSIQ. When used with psychiatric or neurologic populations, correlations between the Shipley Total Score and the WAIS-R FSIQ range between  $r = .74$  and  $r = .85$  (Frisch & Jessop, 1989; Hays et al., 1997; Wiess & Schell, 1991; Zachary, 1996).

### Global cognitive decline

Regression-based formulas for estimating premorbid IQ are reliable, easy to compute, and, where neither educational nor occupational attainment has been affected, unconfounded by illness or injury factors. They have been shown to provide reasonably accurate approximations of premorbid functioning, especially for individuals in the average range (Axelrod et al., 1999; Ball, Hart, Stutts, Turf, & Barth, 2007; Tracy, McGrory, Josiassen, & Monaco, 1996). However, several authors (Basso, Bornstein, Roper, & McCoy, 2000; Griffin et al., 2002; Veiel & Koopman, 2001) have pointed out that regression formulas tend to restrict the range of predicted variables to the middle of the spectrum by underestimating premorbid IQ for individuals at the upper end (i.e.,  $IQ > 120$ ) and overestimating premorbid IQ for individuals at the lower end (i.e.,  $IQ < 80$ ). Hence, the Barona and similar formulas provide a biased estimate of change from premorbid to postmorbid IQ, underestimating decline for individuals whose premorbid IQ is above the mean and overestimating decline for individuals whose premorbid IQ is below the mean. These biases limit the accuracy of regression-based formulas when used to estimate change from premorbid to postmorbid IQ in individual cases.

Veiel and Koopman (2001) offer a solution to the problem. They provide a correction formula for “debiasing” the difference between estimated premorbid IQ and measured current IQ, which results in an adjusted estimate of the true decline between premorbid and current IQ for each individual. The formula is

$$D_{\text{adjusted}} = (IQ_{\text{estimate}} - 100) * r_{tt'} / R^2 - (IQ_{\text{measured}} - 100) \quad (1)$$

where  $D_{\text{adjusted}}$  denotes the adjusted or unbiased estimate of true decline from premorbid to postmorbid IQ,  $IQ_{\text{estimate}}$  is the regression estimate of premorbid IQ,  $IQ_{\text{measured}}$  is the performance measure of current IQ,  $r_{tt'}$  is the reliability of the test used to measure current IQ, and  $R$  is the correlation between the regression estimate of premorbid IQ and the measure of current IQ. We employed this correction formula in our study, using the Barona demographic estimate for  $IQ_{\text{estimate}}$ , the Shipley Total Score for  $IQ_{\text{measured}}$ ,  $r_{tt'} = .80$  for the reliability of the Shipley, and  $R = .65$  for the correlation between the Barona and the Shipley. Using this formula, a positive value of  $D_{\text{adjusted}}$  indicates a decrease from premorbid to postmorbid IQ whereas a negative value indicates an increase from premorbid to postmorbid IQ.

### Data analytic strategy

All statistical analyses were conducted using SPSS 17.0. The sample size assured sufficient power to detect small to moderate effects at the .05 significance

level (Cohen, Cohen, West, & Aiken, 2003). Data were examined to ensure that assumptions of normality, linearity, homogeneity, and homoscedasticity were met. Pearson's  $r$  correlations were calculated to determine whether decline from premorbid (Barona) to current (Shipley) global cognitive functioning, as determined using the correction formula, was significantly related to mood, evaluative, and vegetative depressive symptoms as measured by the CMDI. Regression analyses were conducted to determine the amount of variance in depressive symptoms that was explained by global IQ decline. Any clinical or demographic variables that were significantly correlated with the CMDI subscales were forced into the first block of the regression analysis. Finally, three groups of MS patients were formed according to degree of global cognitive decline: (a) a declined group ( $n=48$ ) in which current cognitive functioning had declined by 15 IQ points or more from premorbid levels; (b) an improved group ( $n=40$ ) which showed improvement compared to premorbid levels; and (c) a no decline group ( $n=86$ ) which showed declines of greater than 0 but less than 15 IQ points from premorbid levels.

Groups were compared on demographic and clinical variables using chi-square or one-way analysis of variance (ANOVA), with any variables that significantly differed between groups included as covariates in subsequent analyses. The influence of medication on cognitive functioning was evaluated in three ways. Groups were compared on the proportion of patients in each group taking medications that might influence cognitive functioning, the total number of medications being taken that might influence cognitive performance or mood, and participants' reported ratings on the degree to which medications influenced their cognitive functioning on the day of testing. For the CMDI depression subscales, groups were compared using ANOVA or ANCOVA, with significant effects followed up using Tukey's (equal variances) or Dunnett's T3 (unequal variances) pairwise comparisons. Measures of effect size (Cohen's  $d$ ) were calculated as the difference between group means divided by the pooled SD in order to demonstrate the magnitude of the difference between the two groups.

## RESULTS

For the overall groups, average age in years was 47.0 ( $SD=8.6$ ), years of education was 14.5 ( $SD=2.2$ ), premorbid IQ was 107.5 ( $SD=5.4$ ), and measured IQ was 104.0 ( $SD=8.6$ ). Median level of physical disability was 4.5 ( $SD=1.5$ ), as measured by EDSS, and diagnosis duration in years was 11.5 ( $SD=8.5$ ). All participants were Caucasian (100%) and mostly (81%) female. Approximately three quarters (71%) had a relapsing-remitting diagnosis, less than one quarter (20%) had a secondary progressive diagnosis, and the remaining 8% had a primary progressive course.

Global cognitive decline was significantly correlated with mood ( $r=.20, p < .01$ ) and evaluative ( $r=.23, p < .01$ ) but not vegetative ( $r=.03, p > .10$ ) depressive symptoms. As the mood and evaluative depression symptom subscales were significantly and highly correlated with each other ( $r=.84$ ), they were combined in all subsequent analyses. EDSS was significantly correlated with the vegetative ( $r=.31, p < .001$ ) and mood-evaluative ( $r=.15, p < .05$ ) symptom subscales and so was included in regression analyses.

**Table 1.** Demographic variables, illness variables, and depressive symptoms for three "cognitive decline" MS groups

	Declined (>15 IQ points)	No decline (<15, >0 IQ points)	Improved (<0 IQ points)
<i>Demographic variables</i>		<i>Mean (SD)</i>	
<i>N</i>	48	86	40
Age (yrs)	47.2 (7.7)	46.7 (9.1)	47.5 (8.7)
Education (yrs)	15.7 <sub>a</sub> (2.6)	14.5 <sub>b</sub> (1.8)	13.1 <sub>c</sub> (1.3)
Barona premorbid IQ	111.9 <sub>a</sub> (5.2)	107.3 <sub>b</sub> (4.2)	102.7 <sub>c</sub> (3.3)
Shipley current IQ	96.9 <sub>a</sub> (9.7)	105.0 <sub>b</sub> (6.4)	110.3 <sub>c</sub> (5.1)
	<i>Total (%)</i>		
Sex (male)*	17 (35%)	14 (16%)	2 (5%)
<i>Illness variables</i>		<i>Total (%)</i>	
EDSS (median)	5.0 (1.6)	4.0 (1.5)	4.5 (1.6)
Diagnosis duration (yrs)	10.7 (7.7)	11.7 (8.5)	12.1 (9.5)
<i>Clinical course</i>			
Relapsing-remitting	28 (58%)	66 (77%)	30 (75%)
Secondary progressive	12 (25%)	16 (18%)	7 (18%)
Primary progressive	5 (11%)	4 (5%)	3 (7%)
Progressive relapsing	3 (6%)	0 (0%)	0 (0%)
<i>Depressive symptoms</i>		<i>Mean (SD)</i>	
CMDI Mood	24.6 (10.4)	21.6 (8.0)	20.9 (6.9)
CMDI Evaluative	22.1 <sub>a</sub> (10.0)	18.5 <sub>b</sub> (6.3)	18.3 <sub>b</sub> (6.3)
CMDI Vegetative	36.1 (10.6)	35.3 (9.9)	35.2 (8.3)

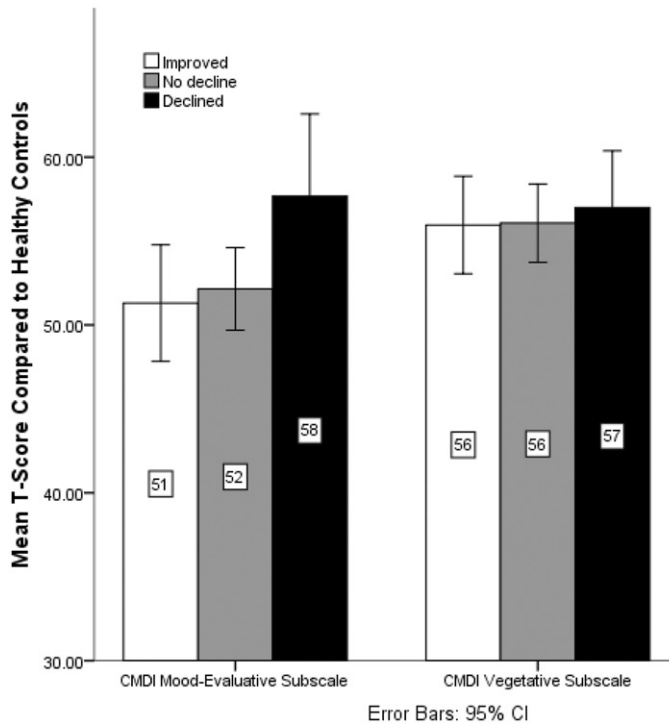
EDSS = Kurtzke's Expanded Disability Status Scale (Kurtzke, 1983). Means in the same row that do not share the same subscript differ at  $p < .01$  in Tukey's post hoc test.

\* $\chi^2$  significant at  $p < .05$ .

After controlling for EDSS, global cognitive decline accounted for 5% of the variance in mood-evaluative depression symptoms,  $F\Delta(2, 171) = 7.8$ ,  $R^2 \Delta = .05$ ,  $p < .01$ , and none of the variance in vegetative depression symptoms,  $F\Delta(2, 171) < 1.0$ ,  $R^2 \Delta = .00$ ,  $p > .10$ .

The three MS groups with declined, no decline, or improved global cognitive functioning showed no significant differences in age, disability level, duration of illness, or medication usage. However, the declined group had a significantly higher education level than the no decline group, and the no decline group, in turn, had a significantly higher education level than the improved group. Barona premorbid IQ also differed significantly between MS groups, with the declined group showing the highest estimate and the improved group the lowest estimate. As would be expected, Shipley estimated current IQ significantly differed between all three groups, with the declined group having the lowest score and the improved group the highest (see Table 1).

Chi-square analysis showed that a significantly greater proportion of the declined MS group was male,  $\chi^2(2) = 13.9$ ,  $p < .001$ , with a trend toward a greater proportion having secondary progressive course type,  $\chi^2(6) = 11.8$ ,  $p < .07$ .



**Figure 1** Mean level of mood-evaluative and vegetative depressive symptoms in MS groups based on degree of long-term, global cognitive decline.

Course type was the only variable that was significantly correlated with the CMDI (vegetative subscale) and so was included as a covariate in the relevant analysis.

To evaluate the hypothesis that MS patients experiencing greater global cognitive decline would report higher levels of mood-evaluative, but not vegetative, depressive symptoms than MS patients experiencing no such decline, the three MS groups were compared on CMDI subscales (means and standard deviations for all CMDI subscales are reported in Table 1). The ANCOVA showed no significant difference between groups on the vegetative subscale,  $F(3, 170) < 1.0, p > .10$ . On the combined mood-evaluative index, ANOVA revealed a significant group effect,  $F(2, 171) = 3.5, p < .05$ , with post hoc comparisons indicating significantly higher mood-evaluative symptoms in the declined compared to the improved group and a trend toward significantly higher symptoms in the declined compared to the no decline group. Cohen's  $d$  indicated a small to medium effect size of .46 (see Figure 1).

## DISCUSSION

The results of the study confirmed our prediction. MS patients whose global cognitive functioning declines by one standard deviation or more from premorbid

levels report significantly higher combined mood-evaluative, but not vegetative, depressive symptoms than MS patients whose global cognitive functioning remains at or above premorbid levels. The relationship between mood-evaluative depressive symptoms and long-term global cognitive decline shows a small to moderate effect size.

Our results are consistent with those longitudinal studies indicating a relationship between cognitive functioning and depressive symptoms over time (Amato et al., 2001; Arnett, 2005; Camp et al., 2005; Christodoulou et al., 2009; Feinstein et al., 1992). Although depressive symptoms can occur in the absence of cognitive decline and vice versa, it appears that MS patients experiencing greater global cognitive decline are likelier to report more mood-evaluative depressive symptoms. Because community-dwelling individuals with MS, as in our sample, are less likely to be experiencing cognitive dysfunction, the relationship between cognitive decline and depressive symptoms might emerge even more clearly in a clinic sample.

Establishing a clear association between increasing depression symptoms and long-term cognitive decline in MS is a crucial first step in elucidating the temporal nature of that relationship. Understanding the causal direction of that relationship would be a logical next step, as it would help to guide treatment intervention more effectively. For example, if depression leads to cognitive decline, then treating the depression should improve cognitive functioning. If cognitive decline leads to depression, then therapies that enhance cognitive functioning should improve mood. Alternatively, if cognitive dysfunction is resistant to intervention, therapies for depression can be modified to allow for cognitive impairment. Finally, if MS pathophysiology underlies both depressive symptoms and cognitive decline, interventions that slow disease process should be the focus of treatment.

Several factors might account for the association between increasing global cognitive decline and concomitant depressive symptoms in MS patients. Evidence points to the shared pathophysiology underlying both disease and depression processes in MS (Pucak, Carroll, Kerr, & Kaplin, 2007), and some of these same neural pathways appear to be involved in cognitive dysfunction. In MS, atrophy and lesion burden in frontal cortices have been implicated in both depression (Bakshi et al., 2000; Benesova, Niedermayerova, Mechl, & Havlikova, 2003; Feinstein et al., 2004; Zorzon et al., 2001) and cognitive impairment (Arnett et al., 1994; Benedict et al., 2002; Pujol et al., 2001; Rovaris et al., 1998; Swirsky-Sacchetti et al., 1992). In addition to frontal areas, thalamic areas also show a high proportion of lesion burden and atrophy in MS patients (Benedict, Weinstock-Guttman et al., 2004; Bermal et al., 2005; Cifelli et al., 2002), and recent studies have demonstrated that thalamic atrophy is associated with cognitive impairment (Houtchens et al., 2007) and perhaps mood disturbance (Berg et al., 2000; Sabatini et al., 1996). Thus, the relationship between cognitive impairment and increasing depressive symptoms in MS might reflect underlying lesion burden and regional atrophy in thalamic nuclei as well as frontal cortices.

Inflammation and changes in hypothalamic-pituitary-adrenal axis (HPA) functioning offer another possibility to account for the association between cognitive decline and depressive symptoms in MS. Dysregulation of HPA axis functioning occurs in MS (Huitinga, Erkut, van Beurden, & Swaab, 2003;

Michelson et al., 1994) and in depression (Glaser & Kiecolt-Glaser, 2005; Swaab, Bao, & Lucassen, 2005), with increased activation of the HPA axis associated with an inflammatory response. Studies have linked HPA axis dysregulation and inflammation to depressive symptoms and cognitive impairment in MS patients (Fassbender et al., 1998; Heesen, Gold, Raji, Wiedemann, & Schulz, 2002; Pucak et al., 2007). However, HPA axis dysregulation is also common in non-depressed MS patients and thus cannot be the sole factor accounting for the relationship between depressive symptoms and long term global cognitive decline in MS.

Finally, evidence indicates that co-occurring depressive symptoms and cognitive impairment are associated with poor adherence to disease modifying therapies (Costello, Kennedy, & Scanzillo, 2008; Klauer & Zettl, 2008). In turn, individuals who fail to adhere to effective treatment regimens are more likely to experience an increase in disease-related sequelae, including emotional and cognitive difficulties. Interventions to improve treatment adherence problems caused by depression and cognitive dysfunction might best disrupt this vicious cycle, in which emotional and cognitive difficulties and poor treatment compliance are mutually reinforcing.

Our results are consistent with studies suggesting that male sex (Beatty & Aupperle, 2002; Savettieri et al., 2004) and secondary progressive course type (Filippi et al., 1994; Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Huijbregts, Kalkers, de Sonneville, de Groot, & Polman, 2006) are possible risk factors for cognitive decline in MS patients. Intriguingly in our study, the declined MS group also had the highest estimated premorbid IQ. Although some MS studies have reported similar findings (Schwid, Goodman, Weinstein, McDermott, & Johnson, 2007), others have found greater long-term deterioration among MS patients who are more cognitively impaired at baseline (Camp et al., 2005; Kujala et al., 1997). Such contradictory results cannot be interpreted clearly, but findings similar to those in our study have emerged in elderly populations where education, as a proxy for cognitive reserve, postpones the clinical onset of dementia but also accelerates cognitive decline after onset (Andel, Vigen, Mack, Clark, & Gatz, 2006; Geerlings et al., 2000).

The current study was limited because it was not an actual longitudinal study and thus did not track cognitive and mood changes over time in our MS sample. Rather it used the adjusted difference between estimates of premorbid and current IQ as a rough but efficient proxy for cognitive changes in MS patients over time. It also used measures of premorbid and current IQ that have some psychometric limitations in estimating overall intellectual functioning. However, the data were sufficiently strong to support an association between long-term global cognitive decline and increasing depressive symptoms, albeit an association with only a modest effect size.

The greater cognitive decline seen in the declined group as compared to the no decline and improved groups might represent a statistical artifact, as the declined group had the highest estimated premorbid IQ but also the greatest proportion of men, who are ascribed higher IQ estimates using the Barona and Chastain (1986) regression formula. However, this explanation does not account for the significantly higher education level or the significantly lower current IQ score seen in the declined

group as compared to the other two groups. As neither reported education nor Shipley estimated current IQ directly incorporate gender differences, the larger discrepancy between premorbid and current IQ estimates in the declined group as compared to the no decline and improved groups can be partially but not wholly accounted for by gender bias in the Barona and Chastain demographic formula for estimating premorbid IQ.

The average level of mood-evaluative depressive symptoms reported by MS patient groups in this study was not in the clinical range ( $t$ -scores  $< 60$  for all three groups as seen in Figure 1), nor was it significantly higher than the level reported for healthy controls in other studies (Nyenhuis et al., 1995). Thus, the results of the current study—namely, the modest relationship between increasing mood-evaluative depressive symptoms and increasing long-term global cognitive decline—might not generalize to a clinically depressed MS population. In the current study, however, the group whose global cognitive functioning had declined showed significantly higher levels of mood-evaluative depression symptoms than those groups whose functioning had maintained or improved. These findings raise the possibility that the relationship between global cognitive decline and increasing depressive symptoms might emerge even more clearly in a sample of depressed MS patients. Further studies comparing degree of cognitive decline and level of reported depression symptoms in community versus clinic samples might help to clarify which hypothesis is more accurate.

Our study relied on patient reports of depressive symptoms rather than clinician rated measures of major depressive disorder. However, dimensional symptom assessment—specifically the parsing of mood, evaluative, and vegetative depressive symptoms as was done in this study—can detect effects that are not always revealed by categorical assessment. Because MS patients experiencing greater global cognitive decline also appear to be at greater risk for depression and are thus more vulnerable to subsequent losses in work and social role functioning as well as in quality of life, both sequelae need to be studied together over time in the hope that a better understanding of the causal relationship between them will lead to more successful treatments and outcomes.

## ACKNOWLEDGMENTS

This paper was based on a master's thesis by the first author from the Pennsylvania State University. We wish to give special thanks to neurologists in the Pennsylvania and Washington regions who contributed their time to this project by verifying diagnoses and course ratings for MS participants.

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