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Negative affect predicts subsequent cognitive change in multiple sclerosis

CHRISTOPHER CHRISTODOULOU,[1] PATRICIA MELVILLE,[1] WILLIAM F. SCHERL,[1] WILLIAM S. MACALLISTER,[1,2] REBECCA L. ABENSUR,[1] REGINA M. TROXELL,[1] AND LAUREN B. KRUPP[1]

[1]Department of Neurology, State University of New York at Stony Brook, Stony Brook, New York
[2]Comprehensive Epilepsy Center, Department of Neurology, New York University, New York, New York

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Abstract

Baseline predictors of cognitive change were explored in a sample of persons with multiple sclerosis (MS). Potential predictors included demographic features, baseline clinical characteristics, and psychological state. Participants were 38 individuals diagnosed with either relapsing remitting or secondary progressive MS who did not meet criteria for a current major depressive episode. Subjects were tested at baseline and approximately 1 year in an ongoing longitudinal study of cognition in MS. Participants completed neuropsychological tests sensitive to impairment in MS. They also completed self-report measures of depression, anxiety, fatigue, apathy, and positive and negative affect. Baseline measures of negative affect (e.g., depressed mood, state anxiety, and negative affective state) consistently predicted cognitive change over the course of the study. Higher baseline levels of negative affect were associated with greater relative declines in cognitive performance. This longitudinal relation occurred in the absence of a cross-sectional relation between negative affect and overall cognition. High baseline negative affect particularly predicted a relative decline in episodic memory for newly learned verbal and visuospatial information. The negative affect measures were unique in their predictive value among all the baseline measures assessed. (*JINS*, 2009, *15*, 53–61.)

Keywords: Multiple sclerosis, Cognition, Episodic memory, Depression, Anxiety, Longitudinal study

INTRODUCTION

Cognitive impairment is among the most common and profound consequences of MS, occurring in approximately 40–65% of persons with the disorder (Peyser et al., 1980; Rao et al., 1991a). Cognitive impairment is a leading cause of disability in MS (Rao et al., 1991b). It disrupts multiple aspects of daily life, including employment and social activities (Beatty, 1993; Beatty et al., 1995; Rao et al., 1991b; Wild et al., 1991), as well as driving (Schultheis et al., 2001, 2002; Shawaryn et al., 2002). These types of effects may remain even after controlling for severity of neurological impairment, disease course, depressive symptoms, and use of medications (Rao et al., 1991b).

Cognitive impairment in MS is associated with neuroradiological findings (e.g., lesions and atrophy) (Benedict et al., 2006; Christodoulou et al., 2003). The impairment can take a variety of forms, but the most frequently affected domain involves learning and memory, especially episodic memory for newly learned verbal and visuospatial information (Beatty et al., 1996; DeLuca et al., 1998; Rao et al., 1991a; Thornton & Raz, 1997). Also quite common are deficits on tasks requiring complex attention and rapid information processing (DEsposito et al., 1996; Diamond et al., 1997; Rao et al., 1991a), executive functions (planning, problem solving, sequencing, flexible set shifting, and self-monitoring) (Arnett et al., 1997; Beatty et al., 1989a; Rao et al., 1991a), and visuoperceptual processing (Rao et al., 1991a; van den Burg et al., 1987). Language ability is relatively spared, with the exception of verbal fluency (Foong et al., 1997; Rao et al., 1991a). The degree of cognitive dysfunction in MS varies across individuals, and cognitive abilities decline at varying rates (Amato et al., 1999; Jennekens-Schinkel et al., 1990; Kujala et al., 1997).

Patients and their families face challenges in planning for the future because of difficulty predicting who will decline cognitively as their disease progresses (Beatty et al., 1989b; Bergendal et al., 2007; Kujala et al., 1997; Piras et al., 2003; Savettieri et al., 2004). Few longitudinal studies have

Correspondence and reprint requests to: Christopher Christodoulou, Department of Neurology, State University of New York at Stony Brook, HSC T12-028, Stony Brook, New York 11794-8121. E-mail: christopher.christodoulou@stonybrook.edu.

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examined cognitive decline in MS (Bergendal et al., 2007; Kujala et al., 1997; Sperling et al., 2001). Little is known about possible predictors of cognitive change (Wallin et al., 2006), though there is some indication that clinical variables such as Expanded Disability Status Scale (EDSS) (Amato et al., 2001) and secondary progressive (SP) disease course (Amato et al., 2006; Bergendal et al., 2007; Feinstein et al., 1992) may be risk factors, especially over a long period of time such as 10 years (Amato et al., 2001, 2006). Among demographic variables, age has been shown to predict cognitive decline in MS over the long term (Amato et al., 2001, 2006). In addition, education has been posited to play a protective role in disorders such as Alzheimer's disease (by contributing to "cognitive reserve"), but any effects in MS are unknown (Stern, 2006). The impact of psychological factors on future decline in MS is unknown, though stress has been found to precede the appearance of new brain lesions (Mohr et al., 2000), with possible implications for cognitive decline. In addition, cross-sectional studies have found that depressive symptoms such as depressed mood and depressive evaluations correlate with cognitive dysfunction in MS (Arnett, 2005; Arnett et al., 1999a, 1999b).

The current exploratory study examined a variety of potential baseline predictors of later cognitive change in an available sample of MS subjects who were participating in an ongoing longitudinal study of cognition. Predictors included demographic features (e.g., education, age, gender), baseline clinical characteristics (e.g., MS type, EDSS), and psychological profile (e.g., anxiety, depression, mood, apathy, fatigue).

METHOD

Participants

Participants were recruited from Long Island, New York, as part of an ongoing longitudinal study of cognition in MS. The study was approved by an institutional review board, and all subjects provided written informed consent. Inclusion required MS diagnosis (McDonald et al., 2001), EDSS $\leq$7.0 (Kurtzke, 1983), and education $\geq$10 years. MS disease–modifying medications (e.g., interferon beta, glatiramer acetate) were allowed. Participants had to be neurologically stable for at least 30 days prior to study entry and annual assessment. They also had to be willing to maintain their current medication use (or nonuse) during the study period to the extent possible. The focus of the overall longitudinal study was to identify the characteristics of subjects that decline cognitively over the course of the study. Because depression might lower initial cognitive performance and mask cognitive decline over time, persons meeting Diagnostic and Statistical Manual, 4th edition (DSM-IV) criteria for a current major depressive episode were excluded at screening, using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1997), administered by an individual trained and experienced in its use (over 100 prior SCID administrations; the SCID was not administered at follow-up). Concurrent antidepressants and antispasticity agents were permitted. Exclusion criteria included current use of benzodiazepines, due to their potential adverse effect on cognition, current alcohol or substance abuse, history of head injury, or other medical conditions known to affect cognition (e.g., various forms of non–MS-related dementia, history of learning disability).

Procedures

Subjects were tested at baseline and at approximately 1 year. Participants completed a set of neuropsychological tests from standard MS cognitive batteries comprising tests known to be commonly impaired in persons with MS: the Brief Repeatable Battery (BRB) (Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990) and the Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2002). Tests taken from the BRB included two measures of episodic learning and recall, the Selective Reminding Test (SRT) six-trial version (Buschke & Fuld, 1974; Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990; Scherl et al., 2004), which measures verbal memory, and the 10/36 Spatial Recall Test (10/36) (Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990), which measures visuospatial memory. Tests taken from the MACFIMS were the Judgment of Line Orientation (JOLO) (Benton et al., 1975), a test of basic visual perceptual skills, and Delis–Kaplan Executive Function System (D-KEFS) Card Sorting Test (Benedict et al., 2002; Delis et al., 2001), which measures reasoning and problem-solving skills. The remaining tasks are common to both the BRB and MACFIMS; they included a version of the Symbol Digit Modalities Test (SDMT) of sustained concentration, and speeded visual information processing modified to require a verbal response (Benedict et al., 2002; Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990; Smith, 1973); the Paced Auditory Serial Addition Test (PASAT) (Benedict et al., 2002; Gronwall, 1977; Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990), a task assessing working memory, sustained concentration, and information processing speed; and Controlled Oral Word Association (COWA) (Benton & Hamsher, 1989; Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990; Spreen & Strauss, 1998), which measures speeded verbal output to a target letter. Most tasks (SRT, 10/36, SDMT, PASAT, and COWA) were also administered prior to baseline in a prebaseline session designed to control for practice effects. The exceptions were the D-KEFS Card Sorting Test and the JOLO, both of which have only two versions.

Neuropsychological performance in the MS sample was compared to that of healthy persons. A group of 38 healthy controls completed the same tasks at prebaseline and baseline. A *Z* score was calculated for each test score based on the performance of the controls at baseline

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[i.e., for each test score, mean healthy performance = 0, standard deviation (*SD*) = 1]. Seven *Z* scores (one from each cognitive task) were combined into a mean to measure overall cognitive performance. The seven scores contributing to the cognitive *Z* score mean were as follows: SRT total recall, 10/36 total recall, SDMT total correct, PASAT 2- and 3-s trials combined total, COWA total words, JOLO total correct, and D-KEFS confirmed correct sorts. The primary outcome of the present study was change in cognitive *Z* score mean, calculated by taking the follow-up testing *Z* score mean and subtracting the baseline *Z* score mean.

Participants also completed a series of well-validated psychological questionnaires at baseline and approximately 1 year assessing depressive symptoms, anxiety, positive and negative affect, fatigue, and apathy. The Center for Epidemiological Studies Depression Scale (CESD) (Radloff, 1977) was one of two questionnaires assessing depressive symptoms. The other depression measure was the Chicago Multiscale Depression Inventory (CMDI) (Nyenhuis et al., 1998), a questionnaire designed specifically for use in MS and other medical patient groups. It has vegetative, mood, and evaluative scales consisting of 14 items each. The CMDI makes it possible to separate out neurovegetative symptoms of depression which are a potential confound in medical populations such as MS (Nyenhuis et al., 1995). Additional measures included the state version of the State Trait Anxiety Inventory (STAI) (Spielberger, 1983), the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988), a well-validated measure of state-related positive and negative affect, and the Apathy Evaluation Scale (AES) (Marin et al., 1991), a measure of apathy, defined as a lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress. The Fatigue Severity Scale (FSS) (Krupp et al., 1989), a common MS measure, was used to assess fatigue. As with the neuropsychological tests, *Z* scores for MS subjects on the psychological questionnaires were normed on the responses of healthy controls tested in our laboratory.

Statistical Analyses

In this exploratory study, we chose to examine baseline variables measured within four general classes (demographic variables, clinical aspects of MS, affect-related self-report measures, and non–affect-related self-report measures) to determine whether the class as a whole helped predict cognitive change. Each class was initially examined with a multiple regression analysis using simultaneous entry of predictors. If (and only if) the overall multiple regression effect was significant, a more detailed exploration of the component variables was undertaken, primarily using Pearson correlations. An alpha less than .01 was used for all analyses to reduce the likelihood of chance results. Analyses were performed using SPSS 15.0 unless stated otherwise.

RESULTS

Sample Characteristics

The 38 persons in the MS sample were predominantly female (58%) and Caucasian (97%), with a mean age of 45.5 years (*SD* = 8.4) and a mean of 14.9 years of education (*SD* = 2.2). The 38 persons in the healthy control group used in the calculation of *Z* scores did not differ from the MS group in terms of gender (71% female), race (92% Caucasian), age (*M* = 44.9, *SD* = 9.7), or education (*M* = 15.3, *SD* = 2.0). The MS sample was diagnosed with either relapsing remitting (*n* = 28) or SP (*n* = 10) MS (McDonald et al., 2001) with a median EDSS (Kurtzke, 1983) score of 3.5 (range 1.0–6.5). Most were receiving MS disease–modifying therapies (interferon beta = 20, glatiramer acetate = 10, none = 8). Mean time between their prebaseline and baseline testing was approximately 1.5 months (*M* = 44.97 days, *SD* = 37.578) and between baseline and follow-up testing was approximately 13.5 months (*M* = 407.63 days, *SD* = 72.83).

Baseline Cognitive and Affective Features

The sample showed mild difficulties on the neuropsychological test battery. Compared to a local sample of 38 healthy persons of similar demographic background, the MS persons averaged approximately 1.5 *SD* below the mean of the healthy sample (Table 1), performing most poorly on the SDMT (*Z* score mean = −1.14) and best on the JOLO (*Z* score mean = 0.12). For the sample as a whole, there was no significant cognitive change over the study period, though there was a good deal of inter-subject variability. The primary outcome measure, change in cognitive *Z* score mean, appeared to be normally distributed.

While participants were not clinically depressed at baseline as defined by DSM-IV criteria, they displayed some mild elevation on self-report measures of psychological state as compared to the local sample of healthy persons, though there was a good deal of variability between subjects (Table 2). The highest elevations were on measures of vegetative symptoms of depression (*Z* score mean = 1.94) and fatigue (*Z* score mean = 1.88). There was no significant change on any of the psychological self-report measures, with the exception of a decrease in the CMDI vegetative subscale at follow-up.

Predicting Changes in Cognitive Function

The prediction of cognitive change was examined with four multiple regression analyses, each assessing a different class of baseline predictors. The analysis examining demographic variables (age, education, and gender) was found to be nonsignificant ($R = .207$, $p = .681$), as was the analysis of MS-related clinical variables (MS type, EDSS, use of disease-modifying therapy) ($R = .152$, $p = .865$). An analysis of non–affect-related self-report measures (AES and FSS) was also not significant ($R = .216$, $p = .435$). The analysis of affect-related self-report measures (CESD, CMDI subscales combined, PANAS Negative,

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Table 1. Mean (*SD*) performance on neuropsychological tests at baseline and follow-up

	Baseline		Follow-up	
	Raw score	*Z* score	Raw score	*Z* score
SRT Total	49.92 (9.51)	−0.80 (1.01)	50.71 (9.09)	−0.72 (0.97)
SRT CLTR	30.76 (15.03)	−0.75 (0.86)	31.21 (14.71)	−0.72 (0.84)
SRT Delay	7.21 (3.12)	−0.71 (1.09)	7.53 (2.70)	−0.60 (0.94)
10/36 Total	19.84 (5.08)	−0.88 (1.06)	20.05 (6.25)	−0.84 (1.31)
10/36 Delay	7.18 (1.92)	−0.42 (0.86)	7.00 (2.61)	−0.51 (1.17)
SDMT	49.39 (12.63)	−1.14 (1.11)	51.55 (13.53)	−0.95 (1.19)
PASAT	78.37 (26.60)	−0.52 (1.30)	77.24 (23.89)	−0.58 (1.17)
COWA	28.03 (9.51)	−0.82 (0.95)	26.24 (8.79)	−1.00 (0.88)
D-KEFS Card Sort	8.92 (2.53)	−0.41 (1.07)	9.66 (2.39)	−0.10 (1.01)
JOLO	24.45 (4.22)	0.12 (0.85)	24.42 (4.38)	0.12 (0.89)
Cognitive *Z* score mean		−0.64 (0.80)		−0.58 (0.80)

Note. SRT Total = Selective Reminding Test total words recalled over six trials; SRT CLTR = Selective Reminding Test consistent long-term retrieval; SRT Delay = Selective Reminding Test delayed recall; 10/36 Total = 10/36 spatial recall total recall over three trials; 10/36 Delay = 10/36 spatial recall delayed recall; SDMT = Symbol Digit Modalities Test total score; PASAT = Paced Auditory Serial Addition Test total for 2- and 3-s trials; COWA = Controlled Oral Word Association total score for three letters; D-KEFS Card Sort = Delis–Kaplan Executive Function System Card Sorting Test confirmed correct sorts; JOLO = Judgment of Line Orientation total correct; Cognitive *Z* score mean = *Z* score mean for SRT Total, 10/36 Total, SDMT, PASAT, COWA, Card Sorting, and JOLO.

PANAS Positive, and STAI) was statistically significant ($R = .677$, $R^2 = .458$, $p = .001$) (Table 3). To estimate cross-validation shrinkage for the significant affect result, an adjusted R^2 was calculated using the Stein formula, finding that the affect measures predicted approximately 25% of the variability in cognitive change (adjusted $R^2 = .254$, adjusted $R = .504$) (Stevens, 2002).

Exploring Specifics of the Relation Between Baseline Affect and Cognitive Change

As evident in correlations presented in Table 4, the strongest relations between baseline affect measures with overall cognitive performance were found for three measures of negative affect (CMDI Mood subscale, STAI State, and PANAS Negative), which we combined to create a negative affect *Z* score mean (Table 4).

The effect of baseline negative affect on cognitive change occurred in the absence of a cross-sectional relation between Negative Affect *Z* score and Cognitive *Z* score at either baseline ($r = .064$, $p = .702$) or follow-up ($r = -.065$, $p = .716$). Nor was the relationship between negative affect and cognition reciprocal, since baseline Cognitive *Z* score did not predict change in Negative Affect *Z* score ($r = .096$, $p = .589$). In addition, controlling for baseline Cognitive *Z* score did not alter the relation between baseline negative affect and change on the cognitive *Z* score ($pr = -.630$, $p < .001$). Baseline measures of negative affect tended to most strongly predict changes in cognitive measures of verbal (SRT) and visuospatial (10/36) episodic memory (Table 4).

Table 2. Mean (*SD*) scores on psychological questionnaires at baseline and follow-up

	Baseline		Follow-up	
	Raw score	*Z* score	Raw score	*Z* score
CMDI Mood Subscale Total	13.74 (4.80)	0.47 (1.35)	12.81 (4.38)	0.21 (1.23)
CMDI Evaluative Subscale Total	6.92 (1.67)	0.59 (1.94)	6.86 (1.73)	0.52 (2.01)
CMDI Vegetative Subscale Total[a]	23.87 (7.33)	1.94 (1.76)	21.22 (7.18)	1.30 (1.72)
CESD total score	11.89 (8.50)	0.92 (1.39)	10.70 (7.67)	0.72 (1.26)
STAI State total score	27.79 (15.16)	0.48 (1.26)	24.47 (12.26)	0.21 (1.02)
PANAS Positive	31.26 (7.59)	−0.65 (0.95)	30.49 (8.76)	−0.75 (1.10)
PANAS Negative	12.16 (5.38)	0.33 (1.70)	11.78 (3.68)	0.21 (1.16)
AES total	28.61 (7.19)	0.68 (1.30)	28.08 (7.67)	0.58 (1.38)
FSS mean	4.59 (1.54)	1.88 (1.37)	4.42 (1.45)	1.73 (1.29)
Negative Affect *Z* score mean		0.43 (1.07)		0.23 (.92)

Note. CMDI = Chicago Multiscale Depression Inventory; CESD = Center for Epidemiological Studies Depression Scale; STAI = State Trait Anxiety Inventory; PANAS = Positive and Negative Affect Scale; AES = Apathy Evaluation Scale; FSS = Fatigue Severity Scale; Negative Affect Z-Score Mean = Z-Score Mean for CMDI Mood, STAI State, PANAS Negative.
[a]Change from baseline to follow-up, $p < .05$.

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Table 3. Summary of simultaneous multiple regression analysis for affect variables predicting change in cognitive function (R^2 = .458)

	B	*SE B*	Beta	Tolerance
CESD Total	0.016	0.010	0.375	0.291
CMDI Combined	−0.112	0.058	−0.406	0.383
PANAS Negative	−0.019	0.010	−0.271	0.861
PANAS Positive	−0.008	0.008	−0.161	0.638
STAI State	−0.014	0.005	−0.569**	0.429

Note. CMDI Combined = Chicago Multiscale Depression Inventory *Z* score mean combination of subscales; CESD = Center for Epidemiological Studies Depression Scale; STAI = State Trait Anxiety Inventory; PANAS = Positive and Negative Affect Scale.
**$p \leq .01$ (two-tailed).

DISCUSSION

Baseline measures of negative affect (e.g., depressed mood, state anxiety, and momentary negative affect) consistently predicted cognitive change over approximately 1 year in persons with MS. The finding is striking because persons meeting criteria for major depression were excluded from the study. It raises the possibility that even among persons without clinical depression, negative affect symptoms in MS may have adverse consequences, though this cannot be firmly established from the present exploratory correlational investigation. The longitudinal relation occurred in the absence of a cross-sectional relation between negative affect and overall cognition. High baseline negative affect particularly predicted a relative decline in episodic memory for newly learned verbal and visuospatial information. The negative affect measures were unique in their predictive value among the baseline measures assessed, a group that included demographic, clinical, cognitive, and psychological variables.

Affective disturbance is clearly an important issue in MS regardless of its relation to cognition. The prevalence of affective disturbance in MS is among the highest of any medical disorder (Joffe et al., 1987; Minden et al., 1987; Minden & Schiffer, 1990; Patten et al., 2000; Sadovnick et al., 1996), higher than in otherwise healthy persons (Patten et al., 2003), higher than in those with other chronic medical illnesses (Patten et al., 2003), and even higher than in other neurological disorders, including temporal lobe epilepsy and amyotrophic lateral sclerosis (Schiffer & Babigian, 1984). Major depression has received the most research attention among affective disorders in MS. Lifetime prevalence of major depression in MS has been estimated at 25–50% (Chwastiak et al., 2002; Joffe et al., 1987; Minden et al., 1987; Patten et al., 2000; Sadovnick et al., 1996; Siegert & Abernethy, 2005). Anxiety disorders in MS have received less research attention, but they are often comorbid with depression, and have an estimated prevalence of 36% in MS (Korostil & Feinstein, 2007).

Table 4. Correlation of baseline negative affect and change in cognitive function during the study

Cognitive change	Baseline affect							
Follow-up to baseline	Negative Affect *Z* score	CMDI Mood	CMDI Evaluative	CMDI Vegetative	CESD Total	STAI State	PANAS Negative	PANAS Positive
Cognitive *Z* score	−.626**	−.457**	−.241	−.342*	−.313	−.523**	−.434**	.068
SRT Total	−.221	−.217	−.298	−.111	−.025	−.164	−.125	−.040
SRT CLTR	−.423**	−.409*	−.318	−.282	−.244	−.358*	−.211	.051
SRT Delay	−.319	−.335*	−.341*	−.332*	−.233	−.277	−.133	.115
10/36 Total	−.567**	−.343*	−.083	−.211	−.270	−.474**	−.449**	.259
10/36 Delay	−.346*	−.188	.075	−.142	−.327*	−.358*	−.241	.145
SDMT	−.327*	−.208	−.196	−.341*	−.229	−.201	−.305	−.181
PASAT	−.191	−.014	.021	.126	.057	−.219	−.187	−.114
COWA	−.219	−.282	−.207	−.296	−.222	−.230	−.021	.106
D-KEFS Card Sort	−.357*	−.272	.177	−.191	−.262	−.280	−.251	.053
JOLO	−.039	−.091	−.320	−.121	−.025	−.040	.028	.007

Note. CMDI = Chicago Multiscale Depression Inventory; STAI = State Trait Anxiety Inventory; PANAS = Positive and Negative Affect Scale; CESD = Center for Epidemiological Studies Depression Scale; Negative Affect *Z* score = mean of CMDI Mood, STAI State, PANAS Negative Affect; SRT Total = Selective Reminding Test total words recalled over six trials; SRT CLTR = Selective Reminding Test consistent long-term retrieval; SRT Delay = Selective Reminding Test delayed recall; 10/36 Total = 10/36 spatial recall total recall over three trials; 10/36 Delay = 10/36 spatial recall delayed recall; SDMT = Symbol Digit Modalities Test total score; PASAT = Paced Auditory Serial Addition Test total for 2- and 3-s trials; COWA = Controlled Oral Word Association total score for three letters; D-KEFS Card Sort = Delis–Kaplan Executive Function System Card Sorting Test confirmed correct sorts; JOLO = Judgment of Line Orientation total correct; Cognitive *Z* score = *Z* score mean for SRT Word Total, SRT CLTR, SDMT, PASAT, COWA, Card Sorting, and JOLO.
**$p \leq .01$ (two-tailed).
*$p \leq .05$ (two-tailed).

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We know of no other studies that have assessed the influence of baseline negative affect on cognitive change in MS, though there are cross-sectional studies that have examined the relation between these two general domains. The relation of anxiety to cognition in MS has not been extensively studied. One cross-sectional study found a relation between anxiety scores and performance on the Trail Making Test (Stenager et al., 1994). Another MS investigation did not find a relation between the presence of an anxiety disorder and the presence of cognitive impairment, though a trend was reported (Korostil & Feinstein, 2007). In the general population, anxiety has been linked to altered and slowed information processing (Andrews & Anderson, 1998) and to selective processing of threatening and negative information (Beck & Clark, 1997).

Initial cross-sectional studies of depressive symptoms in MS reported no relation with cognition (Clark et al., 1992; Millefiorini et al., 1992; Rao et al., 1991a), though Rao et al. (1991a) noted a trend. More recent investigations have uncovered a relation between depression and cognition by employing more sophisticated and appropriate measures of depression that separate out vegetative symptoms and focus on the core attributes of negative mood (e.g., sadness) and negative evaluations (e.g., ruminative thoughts of self-criticism) (Arnett, 2005; Arnett et al., 1999a, 1999b). Persons with high levels of negative mood and/or negative evaluations have been found to have specific difficulty on tests with high working memory demands and involving complex speeded attention and executive functions (Arnett, 2005; Arnett et al., 1999a, 1999b, 2001; Thornton & Raz, 1997).

The results for depression in cross-sectional studies of the general population are generally similar to those in the MS literature (Thornton & Raz, 1997). One difference is that depression's impact on episodic learning and memory has been more clearly demonstrated in the otherwise healthy population (Thornton & Raz, 1997; Zakzanis et al., 1998), though recent MS research using more sophisticated measures of depression has reported some relations to episodic memory (Arnett, 2005). No such relation was found in the current study, possibly because of a restriction of range on depressive symptomology brought on by the exclusion of persons experiencing a current major depressive episode. As in MS, cross-sectional studies in Alzheimer's disease have also had more difficulty identifying a relation between depression and episodic memory abilities (Backman et al., 1996; Fahlander et al., 1999). It has been hypothesized that the neurodegenerative effects of Alzheimer's disease on memory overshadow the effects of depression on memory in cross-sectional Alzheimer's patient comparisons (Fahlander et al., 1999). Likewise in MS, it is possible that the high prevalence of episodic memory disturbance (Rao et al., 1991a) introduces enough variability between subjects to make it difficult to uncover a cross-sectional relation.

In any case, the longitudinal impact of depression on episodic memory appears more pronounced in neurological as well as otherwise healthy persons, and our initial results are consistent with this pattern, even with the limited range of depressive symptoms in the current sample. For example, otherwise healthy depressed elderly persons have an increased risk of cognitive decline (Paterniti et al., 2002). Furthermore, depressed persons are more likely to develop Alzheimer's disease (diagnosis of which requires memory impairment) and a recent National Institutes of Health consensus report strongly recommends further research to examine the link between depression and Alzheimer's disease (Geerlings et al., 2000; Green et al., 2003; Kessing & Andersen, 2004; Modrego & Ferrandez, 2004; Speck et al., 1995). Detrimental longitudinal effects of depression have been noted for a variety of other neurological disorders (epilepsy, stroke, Parkinson's disease, and Alzheimer's disease), and some have hypothesized that depression-induced hippocampal atrophy is a key mechanism (Kanner, 2005). From this perspective, stress and depression damage the hippocampus by causing hippocampal atrophy (Campbell et al., 2004; Videbech & Ravnkilde, 2004), reducing hippocampal neurogenesis (Campbell & Macqueen, 2004; Warner-Schmidt & Duman, 2006), and presumably impairing cognitive functions reliant on the hippocampus (Cabeza & Nyberg, 2000; Squire et al., 2004; Squire & Zola-Morgan, 1991).

Stress also may have a negative impact on the MS disease process. A meta-analytic review in 2004 (Mohr et al., 2004) determined that there is a consistent association between stressful life events and subsequent exacerbation in MS, though some have questioned this relation (Galea et al., 2004; Hintzen et al., 2004). In a prospective study, negative everyday stress not specifically related to MS (e.g., a disruption of routine or a conflict at work or with family) was found to predict gadolinium-enhanced lesions 8 weeks later (Mohr et al., 2000). Interestingly, stress is also known to play an important role in causing or precipitating depressive episodes (Duman & Kehne, 2007). The size of the effect of stress on MS exacerbation is modest, but it is clinically meaningful, equaling the strength of MS disease–modifying medications in reducing exacerbations (Filippini et al., 2003). While the studies reviewed have not focused on cognition, the implication is that cognitive decline would occur over time as a consequence of inflammation and disease exacerbation.

While the current results dovetail with prior findings, it must be noted that this study was exploratory in nature and had a number of limitations. It was based on a relatively small sample and excluded persons with a current major depressive episode, so its generalizability to such persons is unclear. Also, no history of depression measure was administered, so it is possible that prior episodes of depression might have influenced baseline negative affect or rate of cognitive decline in some way. In addition, the current sample limited some predictors such as education ($\geq$10 years) and EDSS ($\leq$7.0), which may have reduced the likelihood they would influence cognition.

The current results clearly need replication in a prospective longitudinal study with a broader sample that includes persons with major depression. It will also be important to clarify the nature of any replicable effects of negative affect

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on cognitive decline in MS. For example, are any such effects specific to episodic memory or are they more general? Are they generated by damage to the hippocampus or by a more general effect on the MS disease process? Efforts to treat cognitive and affective disturbances in MS will likely benefit from a better understanding of the nature of their relation.

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