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A Longitudinal Analysis of Cognitive Dysfunction, Coping, and Depression in Multiple Sclerosis

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Using a longitudinal design, the authors examined coping and cognitive functioning in the development of depression in individuals with multiple sclerosis (MS). Coping style was evaluated in 2 conceptually distinct roles: as moderator and mediator of the impact of cognitive dysfunction on depression. Using indices derived from the COPE (C. S. Carver, M. F. Scheier, & J. K. Weintraub, 1989), the authors operationalized coping in 3 ways—as active, avoidant, and an index accounting for relative levels of both. Coping both moderated and partially mediated the relationship between cognitive dysfunction and depression. Moderation results suggest that the relationship between cognitive dysfunction and depression is dependent on coping style—adaptive coping protects individuals from experiencing depression related to their cognitive deficits; however, when individuals use maladaptive coping, cognitive dysfunction puts them at risk for depression. Mediational results suggest that cognitive dysfunction leads to depression partially due to cognitive dysfunction's effects on coping. That is, cognitive deficits may impair individuals' ability to use adaptive coping strategies, leaving them more likely to use maladaptive strategies. Clinical and theoretical implications of these findings are discussed.

Keywords: multiple sclerosis, cognitive functioning, depression, coping

Depression is a common symptom in multiple sclerosis (MS; Anderson et al., 1992; Schapiro, 1994; Thompson, 1996), with lifetime prevalence of major depressive disorder (MDD) after MS diagnosis at approximately 50% (Joffe, Lippert, Gray, Sawa, & Horvath, 1987), and point prevalence rates between 15% and 20% (Patten, Beck, Williams, Barbui, & Metz, 2003). Furthermore, research suggests that emotional disorders are more common in MS patients than in chronic illness patients with comparable levels of physical disability (Dalos, Rabins, Brooks, & O'Donnell, 1983; Ron & Logsdail, 1989; Schubert, 1993). The present study uses a stress and coping framework to examine the role of cognitive functioning in the development of depression in individuals with MS. Cognitive deficits are a common symptom of MS (Brassington & Marsh, 1998) and are related to difficulties in daily functioning (Higginson, Arnett, & Voss, 2000; Rao, Leo, Ellington, et al., 1991). Coping style has been related to psychosocial outcomes, such as depression, in MS patient samples (Aikens, Fischer, Namey, & Rudick, 1997; Arnett, Higginson, Voss, & Randolph, 2002; Foley, Bedell, LaRocca, Scheinberg, & Reznikoff, 1987; Jean, Paul, & Beatty, 1999; Pakenham, 1999; Pakenham, Stewart, & Rogers, 1997; Schwartz, 1999; Warren, Warren, & Cockerill, 1991). In the present study, cognitive dysfunction is conceptualized two ways—both as a source of stress and as a possible deficit in coping resources. In this framework, coping style was evaluated as both a moderator and mediator of the impact of cognitive dysfunction on depression.

Cognitive dysfunction may contribute to the development of depression in patients with MS. Approximately 50% of MS patients display significant cognitive impairment (Brassington & Marsh, 1998; Rao, Leo, Bernardin, & Unverzagt, 1991). Cognitive dysfunction may be a source of stress that increases risk of depression in MS patients. However, research findings related to the role of MS-related cognitive impairment in depression have been mixed (Arnett, Barwick, & Beeney, 2008). Arnett et al. (2002) have suggested that the inconsistent relationship between cognitive functioning and depression may be explained by the presence of moderating variables such as coping. In support of this, one cross-sectional investigation found that patients with cognitive difficulties were most likely to experience depression when they used either low levels of adaptive coping or high levels of maladaptive avoidant coping (Arnett et al., 2002). Other researchers have also evaluated coping as an intervening variable that may explain inconsistencies between MS-related disability and depression. This research suggests that emotion-focused and escape-avoidant coping are associated with negative psychosocial outcomes, whereas active problem-focused coping may be related to better

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adjustment (Aikens et al., 1997; Beatty et al., 1998; Jean, Beatty, Paul, & Mullins, 1997; Pakenham, 1999; Pakenham et al., 1997; Warren et al., 1991).

Coping is the set of cognitive processes and behaviors that people use in response to stress to reduce or manage distressing emotional states (Menninger, 1963; Valliant, 1977). Decades of coping literature suggest that coping is a major factor in the relation between stressful events and psychological and behavioral outcomes (Coyne, Aldwin, & Lazarus, 1981; Felton, Revenson, & Hinrichsen, 1984; Lazarus & Folkman, 1984). Lazarus and Folkman (1984) have proposed a stress and coping theory that identifies a two-stage process—cognitive appraisal of the stressor followed by the enactment of coping behavior—that is thought to mediate the relationship between a stressor and its immediate and long-range outcomes. The Lazarus and Folkman (1984) theory has been applied to MS and other chronic illnesses. Within this framework, adjustment to illness is thought to be determined by illness parameters (conceptualized as stressors) and mediated by the coping process (Maes, Leventhal, & De Ridder, 1996). Illness parameters typically researched in MS include illness duration, disability, and disease severity (Pakenham, 1999).

Traditionally, coping strategies have been conceptualized as belonging to one of two general domains: problem-focused coping and emotion-focused coping. Problem-focused coping refers to active coping behaviors aimed at altering the source of stress, whereas emotion-focused coping is intended to regulate emotional responses to a stressor (Folkman & Lazarus, 1980). Studies in the chronic illness literature have demonstrated that high levels of depression are associated with emotion-focused coping, whereas problem-focused coping is associated with better adjustment and lower levels of distress (Arnett et al., 2002; Revenson & Felton, 1989; Thompson, Gil, Abrams, & Phillips, 1992). Although much of the coping research has relied on the problem-focused versus emotion-focused distinction, this conceptualization of coping has been criticized for being too simplistic (Carver et al., 1989), and evidence suggests that these two coping subtypes may not be unitary constructs (Aldwin, Folkman, Schaefer, Coyne, & Lazarus, 1980; Aldwin & Revenson, 1987; Coyne et al., 1981; Folkman & Lazarus, 1985; Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen, 1986; Parkes, 1984; Scheier, Weintraub, & Carver, 1986). Carver and colleagues (1989) have developed a measure, the COPE, designed to assess more theoretically distinct coping strategies. Thirteen conceptually distinct scales can be derived from this measure. However, two coping factors are of particular interest: an active coping factor comprising items such as, "I concentrate my efforts to do something about my problem," and an avoidant coping factor containing items such as, "I say to myself 'this isn't real.'" Researchers have considered the active and avoidant coping factors as operationalizations of adaptive and maladaptive coping respectively (Arnett et al., 2002), and this distinction has been supported theoretically and empirically (Arnett et al., 2002; Carver et al., 1989).

Despite the fact that that cognitive dysfunction is present in about 50% of MS patients (Brassington & Marsh, 1998) and that cognitive problems have been shown to be highly associated with deficits in everyday functioning (Higginson et al., 2000; Rao, Leo, Bernardin et al., 1991), little research has been conducted examining how cognitive dysfunction may be related to coping. Cognitive dysfunction in MS can be conceptualized as a stressor, as it has been in some previous work (Arnett et al., 2002). Because coping involves cognitive processes, in addition to acting as a stressor, it may also have a direct effect on an individual's resources for enacting the cognitive and behavioral strategies that comprise coping, especially more adaptive types of coping.

Cognitive skills are invoked both during the appraisal stage and the coping stage of the Folkman and Lazarus stress and coping model (Lazarus & Folkman, 1984). This hypothesis is supported by one study that examined the relationship between executive functioning and coping behavior in patients with traumatic brain injury (Krpan, Levine, Stuss, & Dawson, 2007). The investigators found that better scores on executive functioning tasks were related to the use planful problem-solving coping, whereas worse executive performance was predictive of escape avoidant coping. Coping resources have been included in stress-buffering models of adjustment in chronic illness; however, traditionally social support has been the only coping resource examined (Pakenham, 1999).

Although previous research has begun to explore how cognitive deficits, coping, and depression in MS are related, this complex relationship remains poorly understood. The only previous study to directly address the relationship between these three variables assessed cognitive functioning, self-reported coping style, and depression symptoms cross-sectionally (Arnett et al., 2002), precluding conclusions related to temporal relationships. Bolger has criticized cross-sectional studies of coping on the grounds that the proposed outcome (in this case, depression) may be affecting coping behavior (Bolger, 1990). To address this unresolved question, a longitudinal analysis of cognitive functioning, coping style, and depression in MS patients over time must be conducted. Furthermore, previous work has failed to acknowledge the possibility that cognitive functioning may play a dual role in a stress and coping model—as both a stressor and a coping resource. If cognitive functioning is a significant coping resource, coping would be expected to partially or completely mediate the relationship between cognitive dysfunction and depression longitudinally.

Finally, coping studies have typically operationalized coping style by considering only a subset of the individual's coping behaviors. Popular coping scales consist of a series of independent subscales with a specific factor structure (Carver et al., 1989; Folkman & Lazarus, 1985). Including only one of these factors in a given analysis may not provide a complete picture of the individual's approach to coping with stress. For example, it is possible for an individual to receive high factor scores for both active and avoidant coping. It is reasonable to assume that analyses including only one of these factors would not adequately represent such an individual's coping style. For this reason, operationalizing coping style in a way that accounts for levels of both adaptive and maladaptive strategies in one index may be more meaningful in relation to psychological outcomes like depression.

The present study aims to address some of these unresolved issues by examining the relationship among cognitive functioning, coping, and depression in MS patients at two time points 3 years apart. The longitudinal nature of this design allows for the replication of previous cross-sectional work (Arnett et al., 2002), with the additional possibility of establishing temporal precedence of coping behavior relative to the outcome of interest—depression. Another strength of a longitudinal design is that it allows for evaluation of the hypothesis that coping mediates the relationship between cognitive dysfunction and depression in patients with MS.

Investigating the possibility of this relationship acknowledges the possible dual role of cognitive skills in a stress and coping model. In the present study, in addition to considering the independent effects of active and avoidant coping, a third coping variable is evaluated in a stress-buffering and mediational model that takes into account the individual's use of adaptive relative to maladaptive coping.

We hypothesize that (a) cognitive function at Time 1 will predict depression at Time 2, (b) coping at Time 1 will predict depression at Time 2, (c) coping will moderate the relationship between cognitive dysfunction and depression in a stress-buffering fashion, and (d) coping will mediate the relationship between cognitive functioning and depression. There are several plausible models that one could construct relating these three constructs. For example, it is likely that depression causes changes in cognitive dysfunction and coping. We have chosen depression as the outcome of interest in the present study to contribute to a broader theoretical model of depression in MS (Arnett et al., 2008). This model need not be incompatible with other relationships between cognitive functioning, coping, and depression.

Method

Participants and Procedure

This is a secondary analysis of a longitudinal study of cognitive and emotional functioning in MS (Arnett, Higginson, Voss, Bender, et al., 1999; Arnett et al., 2002; Randolph et al., 2000). Fifty-three participants in a longitudinal study of cognitive and emotional change in MS were examined. Participants were recruited from neurologists and a local MS society in the northwestern United States. Individuals contacting the study team were assessed for eligibility. MS diagnoses were confirmed by a board-certified neurologist who also assessed disease course on the basis of Lublin and Reingold (1996) criteria. All but 3 patients met McDonald et al. (2001) criteria for MS, with these 3 patients having possible MS. Eligibility was based on responses to a phone interview. Exclusionary criteria included (a) a history of alcohol or drug abuse, (b) a nervous system disorder other than MS, (c) severe motor or visual impairment that might interfere with cognitive testing, (d) premorbid history of a learning disability, and (e) severe physical or neurological impairment that would interfere with evaluation at the university. Motor, visual, and neurological impairment was assessed by the following questions: "Do you require adaptive equipment to aid with reading, writing, hearing, walking, or working with your hands? Are you able to read a newspaper? Are you able to move and manipulate things with your hands?" Adequate hearing and auditory processing was assessed by observation during the phone interview. Participants were assessed at two timepoints, 3 years apart. Testing sessions consisted of administration of measures assessing cognitive, physical, and emotional functioning conducted by graduate students trained by a licensed clinical psychologist and neuropsychologist. In return for participating, participants were provided with feedback on their cognitive and emotional functioning and given a written clinical report of the test results. The study was approved by the Institutional Review Board at Washington State University.

Measures

Depression

Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1995). The CMDI is a depression questionnaire that was specifically designed for use in patients with MS and other medical patient groups. The CMDI is a 42-item self-report measure that includes three subscales representing different types of depression symptoms: vegetative, mood, and evaluative.

Because of the potential confound involved in including vegetative symptoms of depression when evaluating depression in individuals with MS, Nyenhuis et al. (1995) have suggested that the mood subscale of the CMDI may be the most valid measure of depression in this population (Nyenhuis et al., 1998). Other studies have combined the mood and evaluative subscales to conceptualize depression (Arnett, Higginson, & Randolph, 2001; Arnett, Higginson, Voss, Bender, et al., 1999; Arnett et al., 2002; Arnett, Higginson, Voss, Wright, et al., 1999). On the basis of these precedents in the literature, a combination of the CMDI mood and evaluative subscales was used to measure depression in the present study.

Beck Depression Inventory (BDI; Beck, Ward, Mendelsohn, Mock, & Erbaugh, 1961). Although the CMDI was used as our primary measure of depression, we also included the BDI because it has been widely used in MS studies. Patients' BDI scores thus provided a reference point of comparison with previous samples published in the literature. Values reported in Table 1 for both time points are comparable with other samples reported on in the MS literature (Arnett et al., 2008).

Coping

The COPE (Carver et al., 1989). The COPE is a 52-item self-report questionnaire designed to measure a variety of coping styles used in response to stressful events. The COPE consists of 13 conceptually distinct scales made up of four-item clusters. It has traditionally been divided into two indices, each including 12 items—an active coping index made up of the Active Coping,

Table 1
Means (and Standard Deviations) for Cognitive, Coping, and Depression Variables

Variable	T1	T2
SDMT total correct in 90 s	52.8 (11.3)	49.7 (12.6)
PASAT total correct	46.6 (13.5)	49.7 (11.1)
VE time per correct switch	4.3 (1.3)	4.2 (1.4)
BDI total score	11.0 (5.6)	8.5 (8.0)
CMDI total raw score	75.2 (19.0)	76.7 (19.9)
Active coping raw score	33.8 (5.5)	33.6 (6.3)
Avoidant coping raw score	21.3 (4.9)	21.3 (4.4)
% of Sample depressed	13	19
% Receiving tx for depression between T1 & T2		30

Note. T = Time; SDMT = Symbol Digit Modalities Test (oral version); PASAT = Paced Auditory Serial Addition Task; VE = Visual Elevator subtest of the Test of Everyday Attention; BDI = Beck Depression Inventory; CMDI = Chicago Multiscale Depression Inventory; tx = treatment.

Planning, and Suppression of Competing Activities subscales; and an avoidance coping index made up of the Mental Disengagement, Behavioral Disengagement, and Denial subscales. Because each of these COPE factors is relatively independent of the other, it is possible for an individual to receive high index scores for both active and avoidant coping. To obtain a more comprehensive index of an individual's use of adaptive coping, coping was operationalized as the difference between an individual's active coping index score and their avoidant coping index score after first converting both index scores to *z* scores. This is subsequently referred to as the composite coping index.

The COPE can be used to assess situational or dispositional coping tendencies. In the present study, we hoped to elicit dispositional coping style by having participants rate what they generally do and feel in response to stress.

Cognitive Functioning

We used the cognitive functioning index (combined speeded attentional, working memory, and planning task indices) to assess a battery of neuropsychological tests shown to be most associated with depression in MS from previous work (Arnett, 2005; Arnett et al., 2001; Landro, Celius, & Sletvold, 2004; Thornton & Raz, 1997).

Reading Span Test (RST). The RST (Daneman & Carpenter, 1980) is a measure of working memory capacity (Arnett, Higginson, Voss, Wright, et al., 1999). Participants are asked to read a set of sentences while maintaining a target word in memory, with one target word after each sentence. Sets consist of three trials each, and set sizes range from two to six sentences. Scores are derived by determining the largest set in which the examinee recalled all the words for at least two of the three trials. Alternatively, scores can be calculated as the total words correctly recalled across all trials. The latter RST scoring index was included in the cognitive functioning index.

Paced Auditory Serial Addition Task (PASAT). The PASAT is a frequently used test of attention, concentration, working memory, and speed of processing. In this task, participants are to respond with the correct sum of the two most recently presented digits. We used a version of the PASAT recommended for use in MS that has 3 s between digit presentations (Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990).

Oral Symbol Digit Modalities Test (SDMT). The SDMT is a test of attention, specifically complex scanning and visual tracking (Shum, McFarland, & Bain, 1990). Like the Wechsler Digit Symbol test, this task involves substitution of numbers with novel symbols. The SDMT reverses the presentation of the Digit Symbol test so that the examinee is provided with novel symbols and instructed to answer with the corresponding number according to a key. The dependent variable was the total number of correct items completed in 90 s.

Visual Elevator subtest from the Test of Everyday Attention (TEA). The Visual Elevator (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994) is a timed test of attentional switching or cognitive flexibility. Examinees are instructed to determine the floor on which a visually presented elevator is located. The elevator starts on the first floor and moves one floor each presentation, with arrows indicating changes in direction. All floors and arrows are presented on a single page for each of 10 trials. Two scores may be derived for performance on this subtest: a raw total accuracy score and a timing score. The dependent variable in our study was average time per switch for correct items. The Visual Elevator test has been shown to be highly correlated with performance on the Wisconsin Card Sorting Test (Robertson et al., 1994).

Tower of London (TOL). The TOL task (Davis, Bajszar, & Squire, 1994) was included to measure planning ability. The TOL requires participants to plan ahead to determine the order of moves necessary to rearrange five colored beads from an initial position to a goal position. In our study, the task was presented on a computer monitor. Participants used a mouse to move the beads in a window on the left of the screen (working area) until they achieved the arrangement on the right of the screen (goal position). Each of six task trials begins with a different goal position. There is no time limit for the task, but examinees are encouraged to achieve a solution as quickly as possible. The number of moves per trial and the total time per trial were used as dependent variables.

Disability

Expanded Disability Status Scale (EDSS; Kurtzke, 1983). The EDSS is the most widely used rating scale for assessing MS-related disability. Possible scores range from 0 to 10, with higher ratings indicating more severe impairment. The scale predominately relies on ambulation as an indication of physical disability.

Results

Fifty-three MS patients were included in the study (31 relapsing–remitting, 15 secondary progressive, 6 primary progressive, and 1 progressive relapsing). Thirty-nine of the participants were female. At Time 1, the mean (plus or minus the standard deviation) for participant age was 46.6 $\pm$ 7.6 years, with 14.9 $\pm$ 2.3 years of education and an EDSS score of 4.5 $\pm$ 9.4. Symptom duration at Time 1 was 14.0 $\pm$ 9.4 years, and diagnosis duration was 7.6 $\pm$ 5.9 years. At Time 2, participant age was 49.4 $\pm$ 7.7 years, with 15.4 $\pm$ 2.5 years of education and an EDSS score of 4.7 $\pm$ 1.6. Symptom duration at Time 2 was 16.9 $\pm$ 9.2 years, and diagnosis duration was 10.4 $\pm$ 6.0 years. Means and standard deviations for depression, coping, and cognitive functioning scores can be found in Table 1. The COPE and its indices in our sample were demonstrated to be reliable (the Cronbach's alpha for the COPE total score and for the active and avoidant indices were 0.88, 0.79, and 0.75, respectively).

Relationships among demographic (age and gender) and disease-related (course, duration, symptom duration, and EDSS score) variables and depression were assessed, and no variables were significantly correlated with CMDI mood and evaluative depression scores. Hence, no demographic and disease-related variables were included as covariates in subsequent analyses. For all cognitive tasks, *z* scores were calculated. An index of cognitive functioning was created by taking the mean of these *z* scores. All zero-order correlations between the variables constituting the cognitive index were significant at an α of 0.05 or lower and ranged in magnitude from 0.34 to 0.69. A reliability analysis of the cognitive index was conducted, and the Cronbach's alpha for this index is 0.82, suggesting adequate reliability. The *z* scores were also calculated for the avoidant and active coping scales; an adaptive coping index that takes both of the latter indices into account was calculated by subtracting the avoidant scale *z* score value from the value for the active coping scale (this will be

subsequently referred to as the composite coping index). We calculated all z scores using the MS sample as the reference group. The MS sample was chosen as a reference group so that the z scores for each component of the cognitive index, as well as the coping indices, would reference the same sample. This facilitates the interpretation of these index scores and the relationships between them. Such an approach is also appealing because it provides a reference point based on participants tested in the context of the present study rather than a mix of different samples tested under different circumstances. Correlations among the coping and cognitive indices, as well as CMDI mood and evaluative depression scores at both time points, are reported in Table 2. Thirty percent of the sample (16 participants) sought treatment for depression between evaluation time points (see Table 2). Of these 16 patients, all 16 of them began an antidepressant medication (these included tricyclic antidepressants and selective serotonin reuptake inhibitors), and 7 of them participated in psychotherapy.

Hypothesis 1: Cognitive Function at Time 1 Will Predict Depression at Time 2

This hypothesis was tested by regressing the CMDI mood and evaluative score at Time 2 on the cognitive index at Time 1. The effect of the cognitive index on depression was significant ($R^2 = .16$, $p < .005$).

Hypothesis 2: Coping at Time 1 Will Predict Depression at Time 2

This hypothesis was tested by regressing the CMDI mood and evaluative score at Time 2 on the coping indices (all at Time 1) in three separate regression models—one model for each coping variable of interest. Regression analyses revealed that neither the active nor avoidant coping indices at Time 1 significantly predicted depression at Time 2 (for the active coping index: $R^2 = .03$, $p < .50$; for the avoidant coping index: $R^2 = .07$, $p < .10$). However, the composite coping index at Time 1 significantly predicted CMDI mood and evaluative score at Time 2 ($R^2 = .08$, $p < .05$).

Hypothesis 3: Coping Will Moderate the Relationship Between Cognitive Dysfunction and Depression in a Stress-Buffering Fashion

This hypothesis was tested using interaction variables created by multiplying the cognitive index score (from Time 1) with each of the coping variables of interest (also at Time 1; active coping, avoidant coping, and the composite coping index). Using multiple hierarchical regression to predict CMDI combined mood and evaluative score at Time 2, the cognitive index was entered in the first step, the coping variable was entered in the second step, and the interaction term was entered in the third step. Regression analyses revealed support for all three moderation predictions. As Table 3 illustrates, for the active coping analyses, the interaction term entered into the regression model after the main effects for the cognitive task and active coping indices still accounted for 14% of the variance in depression at Time 2, $\Delta F = 9.90$, $p < .005$. For the avoidant coping analyses, the interaction term entered into the model after the main effects for the cognitive task and avoidant coping indices still accounted for 7% of the variance in depression, $\Delta F = 4.60$, $p < .05$. Finally, for the domposite coping analysis, after accounting for the main effects for the cognitive task and composite coping index, the interaction term accounted for 15% of the variance in depression, $\Delta F = 10.40$, $p < .005$.

The nature of these interactions is illustrated in Figure 1. Separate regression lines were calculated for first and third quartile scores on the cognitive task index for each of the coping regression models. Multicollinearity statistics were examined for all above models, and these suggested that multicollinearity was not problematic.[1]

Table 2
Correlations Between Time 1 and Time 2 Cognitive, Coping, and Depression Indices

	Depression		Coping		Cognitive functioning	
Variable	T1	T2	T1	T2	T1	T2
Depression T1	—	.59**	−.54**	−.36*	−.49**	−.41**
Depression T2	.59**	—	−.28*	−.45**	−.40**	−.25
Coping T1	−.54**	−.28*	—	.57**	.33*	.38**
Coping T2	−.36*	−.45**	.57**	—	.34**	.32*
Cognitive functioning T1	−.49**	−.40**	.33*	.38**	—	.88**
Cognitive functioning T2	−.41**	−.25	.38**	.32*	.88**	—
EDSS T1	.06	.00	−.06	−.05	−.33*	−.33*
ICC	.58		.57		.87	

Note. Correlations are Pearson's, unless otherwise specified. T = Time; Coping = active coping z score minus avoidant coping z score derived from the COPE measure; Depression = Chicago Multiscale Depression Inventory mood and evaluative subscales; Cognitive functioning = mean z score from the Symbol Digit Modalities Test (oral version), Paced Auditory Serial Addition Task, Visual Elevator subtest of the Test of Everyday Attention, Tower of London, and Reading Span Test; EDSS = Expanded Disability Status Scale; ICC = intraclass correlation coefficient.

[1] Maruyama (1997) suggested a number of indications of multicollinearity. These indications reviewed by Maruyama are derived from a variety of sources. We outline some of these now and note how our data came out in relation to them: (a) when simple correlations between predictor variables are greater than .80 or .90 (The absolute [i.e., independent of sign] zero-order correlations between our predictors ranged from .33 to .57, with a mean correlation of .42.); (b) when a factor analysis of the predictor variables yields a very large condition number (Values greater than 100 are considered indicative of multicollinearity. The condition numbers in our analysis ranged from 1.0 to 1.8.); (c) when the variance inflation factors (VIFs) get high (None should be greater than 6 or 7. The VIFs for our predictor variables ranged from 1.0 to 1.2.); (d) when regression weights change radically due to the inclusion of single variables (Changes in regression weights from between steps in our analysis ranged from to 1.5 to −0.5.); and (e) when signs on beta weights are inappropriate. In our analysis, the signs for the zero-order correlations between the predictor variables and the dependent variable were the same as the signs of the regression weights for all variables. Another measure of multicollinearity commonly used is tolerance. A low tolerance value (i.e., near 0) indicates extreme collinearity, and a high value (near 1) indicates that the variable is relatively independent of other variables. In our data, tolerance values ranged from .78 to .97. Taken together, these data suggest that, although our predictor variables were not completely independent, the six indicators of mulicollinearity we examined were all negative, suggesting that multicollinearity was not a major problem in these data.

Table 3
Moderation Tests: Hierarchical Regression Analyses for Cognitive Task and Coping Indices Predicting Depression

Variable	*B*	*SEB*	β	R^2	ΔR^2	ΔF	*p*
Cognitive task index and active coping index predict depression							
Step 1: Cognitive task index	−6.27	1.84	−0.42	0.16	0.16	9.64	<.005
Step 2: Active coping index	−2.99	1.48	−0.26	0.18	0.01	0.78	*ns*
Step 3: Interaction term	8.37	2.66	0.41	0.32	0.14	9.90	<.005
Cognitive task index and avoidant coping index predict depression							
Step 1: Cognitive task index	−3.87	2.14	−0.26	0.16	0.16	9.64	<.005
Step 2: Avoidant coping index	0.96	1.61	0.08	0.18	0.02	0.91	*ns*
Step 3: Interaction term	−4.40	2.05	−0.30	0.25	0.07	4.58	<.05
Cognitive task index and composite coping index predict depression							
Step 1: Cognitive task index	−3.89	1.94	−0.26	0.16	0.16	9.64	<.005
Step 2: Composite coping index	−1.26	0.94	−0.17	0.19	0.02	1.46	*ns*
Step 3: Interaction term	4.44	1.38	0.39	0.33	0.15	10.42	<.005

Hypothesis 4. Coping Will Mediate the Relationship Between Cognitive Functioning and Depression

In the tests of mediation, the cognitive index from Time 1 is the independent variable, coping at Time 2 is the mediator, and CMDI combined mood and evaluative score at Time 2 is the dependent variable.

Baron and Kenny (1986) recommended using the Sobel test to evaluate the significance of the indirect effect of the independent variable on the dependent variable through the mediator (Sobel, 1982). However, the Sobel test assumes that the indirect effect is normally distributed, and this assumption may not always hold, particularly when sample size is small (Bollen & Stine, 1990; Preacher & Hayes, 2004). A bootstrapping approach may be more appropriate for estimating the size and the significance of mediation effects (Bollen & Stine, 1990; Preacher & Hayes, 2004). The SPSS macro published by Preacher and Hayes (2004) was thus used to calculate the Sobel's *Z* and to generate estimates and confidence intervals for the indirect effects using a bootstrapping method with 5,000 resamplings from the data set (sample size = 50).

For the composite coping analysis, the Sobel statistic suggested a trend toward significance ($Z = -1.78$, $p < .10$). According to the bootstrap estimates, the indirect effect of cognitive functioning on depression through coping is different from zero with 95% confidence (−2.16; lower level 95% confidence interval [CI]: −4.90; upper level 95% CI: −0.12). Hence, the bootstrap estimates suggest that the mediation effect for composite coping is significant at $\alpha = 0.05$. Figure 2 illustrates the nature of the mediation relationship. The active and avoidant coping variables were examined separately. Neither the Sobel statistics nor the estimates based on the bootstrapping method supported the hypotheses that these coping indices mediated the relationship between cognitive functioning and depression.

The Composite Coping Index

The rationale behind using the composite coping index follows from the idea that individuals would arrive at similar composite coping scores in different ways—that is, with meaningfully different combinations of avoidant and active coping index scores. Similarly, individuals reporting the same levels of active coping may be using very different levels of avoidant coping, and vice versa. The composite coping index was hypothesized to be superior to the active and avoidant indices used separately on the basis of the assumption that relative levels of active and avoidant coping should be more related to depression than either factor in isolation. Table 4 illustrates a selection of individual cases that demonstrate that participants did exhibit meaningfully different coping profiles and that these differences were related to their depression scores.

Discussion

In the present study, we used a longitudinal design to address some unresolved issues regarding the relationship among cognitive functioning, coping, and depression in MS patients. Coping was evaluated in two conceptually distinct roles: as a moderator of the relationship between cognitive dysfunction and depression and as a mediator of the relationship between cognitive dysfunction and depression. The moderator and mediator roles are not mutually exclusive, and a priori hypotheses speculated that analyses would reveal support for coping in both moderation and mediation roles.

Coping as a moderator suggests that the relationship between cognitive dysfunction and depression may be different under different coping conditions (e.g., when active coping is high, vs. when active coping is low). We hypothesized that when an individual uses high levels of adaptive coping, or low levels of maladaptive coping, cognitive dysfunction will have little effect on depression: An adaptive coping profile will protect individuals from experiencing depression that is due to their cognitive deficits. However, when individuals use low levels of adaptive coping, or high levels of maladaptive coping, cognitive dysfunction will put them at risk for depression. Coping as a mediator suggests that cognitive dysfunction may affect depression indirectly through its effect on coping. That is, it is cognitive functioning's effect on coping style that is responsible for increased likelihood of depression. In other words, cognitive functioning is a coping resource. Furthermore, it may be that cognitive deficits impair individuals' ability to use adaptive coping strategies and leave them more likely to use maladaptive coping strategies. Such a suggestion is consistent with Tennen et al.'s (2000) report that emotion-focused strategies (e.g.,

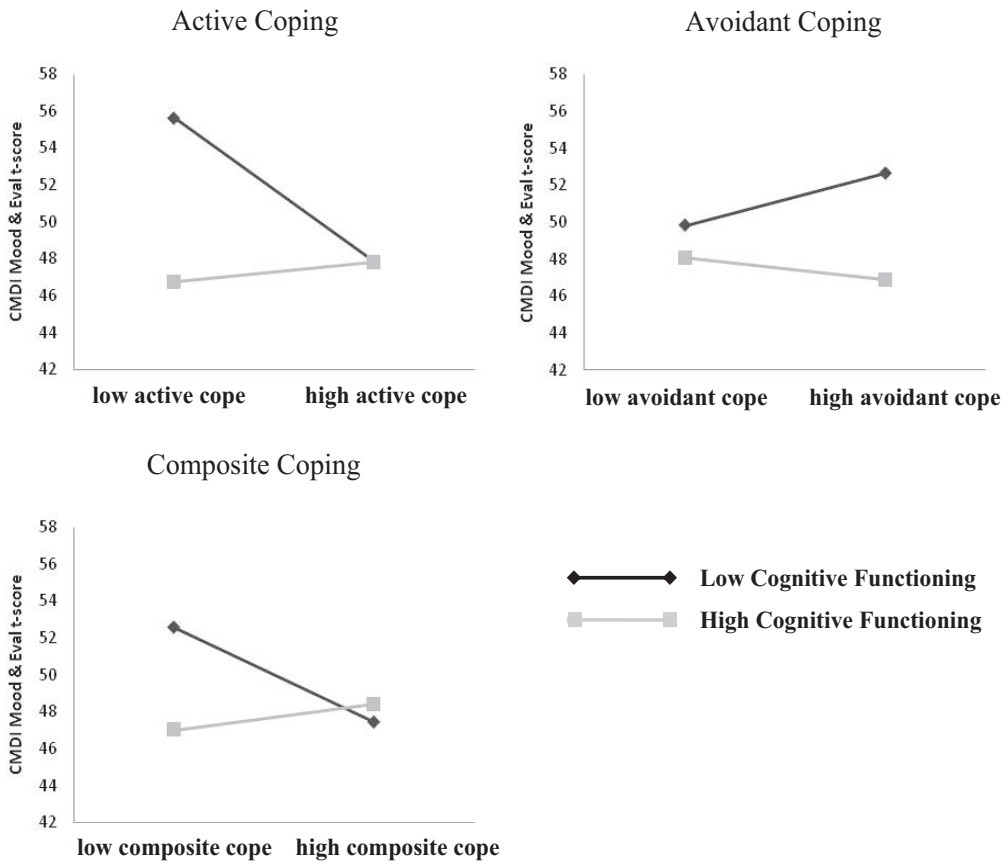

Figure 1. Active coping moderation model: simple slopes for low and high cognitive functioning. For the active, avoidant, and composite coping models, respectively, the unstandardized simple slopes for participants scoring high on the cognitive index are 0.78, −1.02, and 0.73; the unstandardized simple slopes for participants scoring low on the cognitive index are −5.67, 2.37, and −2.68.

avoidant coping) tend to be relied upon more once problem-focused strategies (e.g., active coping) have been tried and failed.

To operationalize coping, we used three different indices of coping behavior derived from the COPE (Carver et al., 1989): the Active Coping subscale, the Avoidant Coping subscale, and an index of adaptive coping obtained by taking the difference of the two subscales. The results of the study support that coping is a significant moderator and mediator of the relationship between cognitive dysfunction and depression.

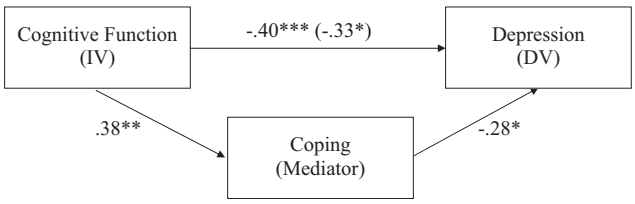

Figure 2. Standardized regression coefficients for the relationship between cognitive dysfunction and depression mediated by composite coping. The coefficient in parenthesis is the effect of cognitive task index on depression controlling for the composite coping index. * $p < .05$. ** $p < .01$. *** $p < .005$.

These findings help to clarify the relationship among cognitive dysfunction, coping, and depression in MS patients. First, these results are consistent with previous work demonstrating that coping moderates the relationship between cognitive dysfunction and depression cross-sectionally (Arnett et al., 2002). Additionally, the present study extends these findings in several important ways. The longitudinal nature of the study design has allowed for establishing temporal precedence of coping relative to the outcome of interest—depression. Furthermore, the longitudinal design enables the rigorous evaluation of the hypothesis that coping mediates the relationship between cognitive dysfunction and depression in MS. Considering coping as a mediator, for the first time, acknowledges the possible dual role of cognitive capacity in a stress and coping model—as both a possible stress-causing symptom of the illness and a coping resource. Highlighting that cognitive deficits may deplete coping resources has important implications for how coping should be understood and addressed in MS patients who may have significant cognitive impairment.

The Composite Coping Index

Another contribution of the present study is the unique way in which coping style was operationalized. In addition to examining

Table 4
Coping and Depression Scores for a Selection of Six Individual Cases

Case	Active *z* score	Avoidant *z* score	Composite coping	Depression *t*
Cases 1 & 2 matched on active coping				
1	1.6	0.5	1.1	61.1
2	1.6	−0.3	1.9	50.6
Cases 3 & 4 matched on avoidant coping				
3	−1.5	0.9	−2.4	63.7
4	0.6	0.9	−0.3	41.8
Cases 5 & 6 matched on composite coping				
5	0.6	3.8	3.2	62.1
6	−2.5	0.7	3.2	64.4

Note. Pairs of cases matched on one of the three coping variables: active coping *z* score and avoidant coping *z* score (both derived from the COPE) and composite coping (active coping *z* score minus avoidant coping *z* score); Depression = Chicago Multiscale Depression Inventory mood and evaluative scales.

active coping as an index of adaptive coping strategies and avoidant coping as an index of maladaptive coping strategies, we included a composite index that took into account the relative contributions of both active and avoidant coping. Many previous studies that have examined the impact of coping style on psychosocial outcomes have operationalized coping by using only one of the independent coping subscales or higher order factors from either the Ways of Coping Scale (Folkman & Lazarus, 1988) or the COPE (Carver et al., 1989). There are obvious strengths of this approach. Carver and colleagues provided both theoretical and empirical support that the COPE's four higher order coping factors are conceptually distinct (Carver et al., 1989). It follows that these independent factors should be evaluated separately to ascertain the impact of each coping style on an outcome of interest.

There are also limitations to Carver et al.'s (1989) approach. Specifically, it fails to provide a complete functional portrait of the individual's coping style. There is a precedent in the literature of using the COPE's active coping factor as an index of adaptive coping strategies and using the avoidant coping factor as an index of maladaptive coping (Arnett et al., 2002; Carver et al., 1989). This previous work has broadened our understanding of what these coping factors measure and how they are related to important psychosocial outcomes. A logical next step is to begin to consider how these subtypes of coping behavior co-occur in an individual—both within and across stressful situations—and how these distinct styles interact to influence outcomes. The present study begins to address this issue by combining the active and avoidant factor scores to obtain an index of adaptive relative to maladaptive coping. The utility of this approach is supported by the finding that this composite index was a better predictor of depression than either of the independent factor scores. Additionally, of the three coping variables examined, only the composite coping variable was a significant mediator of the relationship between cognitive dysfunction and depression.

Further support for utility of the composite coping index comes from the examination of individual cases (see Table 4). As Table 4 illustrates, individuals matched on the active or avoidant coping index did have very different scores for the remaining coping index (Cases 1 through 4), and these differences may be related to differences in reported depression. Furthermore, Cases 5 and 6 achieved the same composite coping score in very different ways (i.e., with different combinations of active and avoidant coping). Despite their dissimilar coping profiles, these two individuals reported similar levels of depression.

Clinical Implications

There are distinct clinical implications of the demonstrated importance of coping in both its moderator and its mediator roles. The finding that coping is a significant moderator of the relationship between cognitive dysfunction and depression suggests that interventions targeting coping behaviors may be successful in preventing or alleviating depression in MS patients. Although several research studies have examined the role of coping in adjustment to chronic illness (Aikens et al., 1997; Arnett et al., 2002; Foley et al., 1987; Jean et al., 1999; Pakenham, 1999; Pakenham et al., 1997; Schwartz, 1999; Warren et al., 1991), coping scales are seldom used clinically. The COPE is easily and quickly administered and scored. The present findings offer guidelines for interpreting self-reported coping in a clinically relevant way in MS patients. This work, along with other research (Aikens et al., 1997; Arnett et al., 2002; Foley et al., 1987; Jean et al., 1999; Pakenham, 1999; Pakenham et al., 1997; Schwartz, 1999; Warren et al., 1991), suggests that when chronic illness patients use high levels of avoidant coping, or low levels of active coping, they are at high risk for developing depression, particularly under conditions of disease-related stress. The results of the present study support that this relationship holds longitudinally—that is, maladaptive coping style precedes depression. It is possible that administering the COPE in clinical settings could help identify individuals who are at risk for developing depression and that talk therapy interventions designed to teach more adaptive coping strategies may be an effective preventative treatment for these individuals. Research has supported the efficacy of cognitive–behavioral therapy (CBT) for depression in depressed MS patients (Mohr, 1999; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001; Mohr, Hart, & Goldberg, 2003; Mohr et al., 2000). Given that CBT focuses on adaptive coping and skill building, CBT's efficacy for treating depression in MS may be due to direct effects on coping behaviors. It should be noted that 7 of the MS patients in this sample participated in psychotherapy for depression between time points, which may have, in part, contributed to the

results reported. However, this subgroup is too small for any rigorous examination of a relationship between depression treatment and coping or depression.

The finding that coping was a significant mediator of the relationship between cognitive dysfunction and depression suggests that individuals with high levels of cognitive dysfunction may have difficulty using active coping strategies as a result of their disability. There are important clinical implications of this finding. As a result of cognitive dysfunction, depressed patients with neuropsychological deficits may be different from depressed patients without neuropsychological dysfunction in their ability to integrate and apply skills learned in therapy. Clinicians who serve these clients must be aware that cognitive limitations may interfere with therapeutic change in this way. To increase treatment efficacy, therapists may need to augment traditional CBT interventions for depression to make them more accessible to cognitively compromised clients.

Limitations

There are limitations of the present study that should be highlighted. The sample size is relatively small, with 53 participants. Hence, the study may have been underpowered to identify small-to-moderate effects. This may explain why the active and avoidant coping indices were not statistically significant mediators of the relationship between cognitive dysfunction and depression. However, the fact that significant moderation and mediation effects were demonstrated for the composite coping index, and that significant moderation effects were demonstrated for all three coping indices (composite, active, and avoidant), suggests that these effects are robust.

Another possible limitation of the present study is that depression was operationalized on a continuous scale using the CMDI, as opposed to using a diagnostic interview to distinguish between subthreshold depression symptoms and MDD diagnosis. Because depression was not diagnosed, conclusions based on these results should be extended to individuals with a diagnosis of MDD with great caution. One advantage, however, to having operationalized depression continuously is that it has allowed for the examination of clinically relevant depression symptoms in individuals who may be subthreshold for an MDD diagnosis. Because these symptoms have a significant impact on quality of life, understanding the possible causal and preventative correlates of sub-MDD depressive symptoms may have significant implications for improving patients' welfare.

The cognitive index used to operationalize cognitive functioning includes measures of speeded attention, working memory, and planning. These domains of cognitive functioning were selected for the present study based on previous work demonstrating that these cognitive functions are most associated with depression in MS patients (Arnett, 2005; Arnett et al., 2001; Landro et al., 2004; Thornton & Raz, 1997). Additionally, this collection of cognitive skills is consistent with conceptualizations of executive functioning (Baddeley, Sala, Robbins, & Baddeley, 1996; Miyake & Shah, 1999), and previous work supports the role of executive functioning in adaptive coping (Krpan et al., 2007). However, certain cognitive domains were not included in the operationalization of cognitive functioning. Notably, no measure of long-term memory was included in the cognitive index. Future work on the relationship between cognitive dysfunction and coping should evaluate which cognitive domains are most relevant to coping and depression in MS patients.

In the present study, coping was operationalized from a dispositional perspective. Coping has also been conceptualized from a process perspective, which highlights that coping changes over time in response to the dynamic situational context in which it occurs (Lazarus, 1993). This perspective acknowledges the important influence of context on an individual's choice of coping strategy. Research on coping as a process has offered an important contribution to the understanding of emotional and cognitive responses to stress, and application of this perspective is yet to be applied to an understanding of cognitive dysfunction and depression in MS patients.

The most significant limitation of the present study is its correlational design, which precludes causal statements regarding the roles of cognitive dysfunction and coping in depression. In this sample, both coping style and depression were relatively stable (see Table 2). A maladaptive coping style may lead to depression in individuals with MS; however, on the basis of these data, one could just as easily infer that depression is driving coping style. Future work should aim to extend these findings by examining the efficacy of coping-based interventions for the treatment of depression in MS. Although there are studies that have evaluated CBT therapy in depressed individuals with MS (Mohr, 1999; Mohr et al., 2001, 2003; Mohr et al., 2000), this work has not explicitly measured or evaluated coping as a mediator or moderator of therapeutic change. Furthermore, coping style may influence an individual's approach to the testing situation. Therefore, it is quite plausible that coping is causally related to performance on cognitive tests. Very little in the current literature has addressed the relationship between cognitive functioning and coping. The present findings suggest that this relationship may be clinically meaningful in neurological populations. Much could be done in future work to illuminate the nature of this relationship.

It is important to note that the best fitting moderation model accounted for 33% of the variance in predicting depression in this population. Depression in MS is complex and influenced by multiple factors at the neurobiological, psychological, behavioral, and environmental levels. Furthermore, the extent to which these factors lead to depression may be idiosyncratic across individuals. Our group's recent model of depression in MS highlights this complexity (Arnett et al., 2008). The models presented here suggest that interactive and mediational relationships between cognitive functioning and coping explain a significant, perhaps clinically relevant, proportion of the variance in depression. It is likely that other factors (brain pathology, fatigue, social support, etc.) also play an important role in depression risk for MS patients.

Summary and Conclusions

The results of the present study support that coping is both a moderator and partial mediator of the relationship between cognitive dysfunction and depression in MS patients. These findings have important clinical implications that should be evaluated in future research. This work, along with other research that has contributed to a model of depression in MS (Arnett et al., 2008), has led to an improved understanding of the factors that affect quality of life for MS patients. This understanding comes with the

promise that clinicians can effectively intervene to improve quality of life for this patient group. The extent to which the present findings may extend to other populations is an empirical question that could be addressed by future research.

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