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**A LONGITUDINAL ANALYSIS OF COGNITIVE DYSFUNCTION,
COPING AND DEPRESSION IN MULTIPLE SCLEROSIS**

A Thesis in

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Amanda R. Rabinowitz

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The thesis of Amanda R. Rabinowitz was reviewed and approved* by the following:

Peter A. Arnett
Associate Professor of Psychology
Thesis Adviser

Frank G. Hillary
Assistant Professor of Psychology

Kristin A. Buss
Associate Professor of Psychology

Melvin M. Mark
Interim Department Head
Professor of Psychology

*Signatures are on file in the Graduate School

Abstract

Objective: Patients with cognitive functioning deficits commonly associated with Multiple Sclerosis (MS) may be at greatest risk for depression when they also use maladaptive coping strategies. Furthermore, cognitive difficulties may directly affect an individual's ability to employ more adaptive active coping strategies, leading to depression. The current study was designed to test whether coping mediated or moderated the relationship between cognitive dysfunction and depression longitudinally in MS. **Method:** Fifty-five MS patients were assessed at two time points 3 years apart. Cognitive function was assessed at time 1, using a battery of neuropsychological tests. Coping was assessed at time one and time two using the COPE. An index of adaptive coping strategies was obtained by subtracting "Avoidant Coping" subscale scores from "Active Coping" subscale scores. Evaluative and mood symptoms of depression were assessed at time two using the Chicago Multiscale Depression Inventory. **Results:** With regard to the moderation hypothesis, after accounting for the main effects for the Cognitive Task and Coping index, the interaction term accounted for 15% of the variance in depression ($\Delta F = 10.40$; $p < .005$). With regard to the mediation hypothesis, the Sobel statistic suggested a trend towards significance ($Z = -1.78$; $p < .10$). According to the bootstrap estimates, the indirect effect of cognitive functioning on depression via coping is different from zero with 95% confidence (-2.16 ; LL 95% CI: -4.90 ; UL 95% CI: -0.12). This is consistent with the conclusion drawn from the Baron and Kenny (1986) criteria for mediation. **Conclusions:** Coping strategies, defined by the difference between active coping and avoidance coping in an individual, moderate the relationship between cognitive functioning and depression in patients with MS longitudinally. Hence, MS patients with low cognitive functioning are most at risk for experiencing depression when they use a maladaptive coping profile. Furthermore, coping partially mediates the relationship between cognitive functioning and depression longitudinally. This suggests that cognitive dysfunction influences an MS patient's ability to employ more active coping strategies, relative to avoidant strategies, which in turn may contribute to the relationship between cognitive dysfunction and depression in this sample.

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Introduction

Approximately 350,000 people in the United States suffer from Multiple Sclerosis (MS), a chronic degenerative disease of the central nervous system (CNS; Anderson et al., 1992). In patients with MS, the immune system attacks the myelin sheath encasing the axons, causing plaques and lesions throughout the CNS. Myelin is the fatty tissue surrounding nerve cells that facilitates the propagation of action potentials along the axon, and its destruction causes severe slowing of neuronal transmission. This results in impairments in CNS functioning, which can profoundly affect a variety of important functions. Some common symptoms include, but are not limited to, loss of function or feeling in limbs, loss of bowel or bladder control, sexual dysfunction, debilitating fatigue, blindness, loss of balance, pain, cognitive dysfunction, and mood changes (Goodkin, 1992; D. C. Mohr & Dick, 1998).

Depression is an extremely common symptom in MS (Anderson et al., 1992; Schapiro, 1994; A. J. Thompson, 1996). Even as far back as the days of Charcot, emotional dysfunction has been associated with this patient group (Charcot, 1877). Lifetime prevalence of major depressive disorder (MDD) following MS diagnosis is approximately 50% (Joffe, Lippert, Gray, Sawa, & Horvath, 1987). Point-prevalence rates of depression have varied more widely, and are estimated to be between 14%-57% (R. B. Schiffer, 1983; Schubert, 1993; SurrIDGE, 1969; Whitlock & Siskind, 1980); however, the best recent studies using population based samples have suggested that point prevalence rates of clinical depression are between 15-20% (Patten, Beck, Williams, Barbui, & Metz, 2003). Research suggests that emotional disorders are more common in MS patients than in chronic illness patients with comparable levels of physical disability (Schubert, 1993), including rheumatoid arthritis (Ron & Logsdail, 1989), spinal cord injury (Dalos, Rabins, Brooks, & O'Donnell, 1983), and muscular dystrophy (SurrIDGE, 1969).

Evidence suggests that both neurological and reactive mechanisms may account for the comparably high rates of depression in MS patients (Huber & Rao, 1993). It should be noted that a recent meta-analysis challenges some of this earlier work with the finding that patients with certain disorders have higher or equivalent rates of depression compared with MS patients. However, this quantitative review did confirm that depressive symptoms consistently distinguish MS patients from healthy controls, and certain other chronic illness populations (Dalton & Heinrichs, 2005).

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 have been related to difficulties in daily functioning (Higginson, Arnett, & Voss, 2000; S. M. Rao, Leo, Ellington et al., 1991). Coping style has been related to psychosocial outcomes, like depression, in MS patient populations (Aikens, Fischer, Namey, & Rudick, 1993; 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. Coping style was evaluated as both a moderator and mediator of the impact of cognitive dysfunction on depression.

Pathophysiology of MS

MS symptoms are thought to arise via an immune-mediated process occurring in individuals with genetic vulnerability for the disease. Although there is considerable clinical, prognostic, and pathophysiological heterogeneity among MS patients, the defining pathological

feature of the disease is the demyelinated plaque—a lesion characterized by the loss of myelin, the relative preservation of axons, and the presence of astrocytic scars (Noseworthy, Lucchinetti, Rodriguez, & Weinschenker, 2000). Myelin is fatty tissue comprised of oligodendrocytic glial cells. Oligodendrocytes surround the neuronal axon and facilitate the propagation of action potentials. In MS, axonal demyelination results in the slowing or blockade of neuronal transmission. Early symptoms of the disease are believed to be a result of the demyelination process. The remission of symptoms has been attributed to reduction of inflammatory edema and partial remyelination. However, as the disease progresses, irreversible axonal injury may occur. Furthermore, exhaustion of the oligodendrocyte progenitor pool can result in the inability to remyelinate. These disease processes may be responsible for the chronic and progressive decline in functioning observed in many patients (Noseworthy et al., 2000).

Multiple pathogenic mechanisms have been investigated for their role in demyelination in MS. Antibodies against antigens located on the myelin sheath may infiltrate the blood-brain barrier and directly cause demyelination. Other auto-immune responses and viral infection have also been linked to demyelination in MS (Noseworthy et al., 2000). Various pathophysiological processes may be involved in disease progression. Furthermore, there is considerable variability among patients with regards to structural and immunologic disease features. These observations suggest that MS may be a series of syndromes, rather than a uniform disorder with a singular etiology and disease process (Noseworthy et al., 2000).

Proposed Etiologies of Depression in MS

It is possible that alterations in brain function caused by demyelination may be directly related to emotional disturbance in MS patients. Imaging studies have supported this possibility

by demonstrating correlations between brain injury indices and affective disturbance in MS. For example, Ron and Logsdail (1989) found significant correlations between lesions in the temporoparietal regions and flattened affect, delusions, and thought disorder. However, overall severity of psychiatric morbidity was not significantly correlated with total lesion score in their sample (Ron & Logsdail, 1989). Another imaging study compared two groups of MS patients: those with and without clinically significant affective disorders. While no between group differences were observed for total lesion volume, patients with affective disorders had significantly more temporal lobe lesions (W.G. Honer, T. Hurwitz, D.K. Li, M. Palmer, & D.W. Paty, 1987). These studies suggest that, while biological abnormalities may be related to depression in MS, total lesion volume may not be the relevant operationalization of brain abnormality for evaluating biological correlates of depression. Other more recent studies have also reported greater temporal region involvement in depressed compared with nondepressed MS patients (Berg et al., 2000; Feinstein et al., 2004; W.G. Honer et al., 1987; Pujol, Bello, Dues, Marti-Vilalta, & Capdevila, 1997; Zorzon et al., 2001).

Although some investigators have failed to find correlations between depression measures and brain pathology (Millefiorini et al., 1992; Moller, Wiedemann, Rohde, Backmund, & Sonntag, 1994; Ron & Logsdail, 1989; Sabatini et al., 1996), early negative findings have been attributed in part to methodological limitations (Feinstein, 2005). Much of the recent work in this area reports positive findings regarding lesion development and depression in MS (Bakshi, Shaikh et al., 2000; Fassbender et al., 1998; Feinstein et al., 2004; Pujol et al, 2000; Pujol et al., 1997; Zorzon et al., 2001).

Other investigators have focused on the conceptualization that depression arises due to increased demands that MS places on patients and their families. Various sequelae of MS have

been associated with psychosocial problems in MS patients. For example, physical disability has been shown to be related to poorer psychological and social outcomes (Hutchinson & Hutchinson, 1995; Vickrey, Hays, Harooni, Myers, & Ellison, 1995; Zeldow & Pavlou, 1988). Fatigue is another common symptom of MS (Krupp, Alvarez, LaRocca, & Scheinberg, 1988). MS patients are more likely than healthy controls to report that fatigue is the cause of frequent problems in everyday functioning (Krupp et al., 1988). Additionally, researchers have found that MS related fatigue was predictive of poorer physical and psychosocial functioning as measured by the Sickness Impact Profile (J.D. Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994).

Lewinsohn and colleagues have proposed a behavioral theory suggesting that disease leads to depression only if it interferes with a person's ability to function at their usual level (Lewinsohn, Hoberman, Teri, & Hautzinger, 1985). The application of Lewinsohn's model to the development of depression in MS is appropriate, as MS is a disease that can affect multiple domains of functioning (occupational, physical, social, etc.). Voss and colleagues evaluated such a model, by considering the effects of fatigue and physical disability on social role functioning in MS patients. Using structural equation modeling, they demonstrated that physical disability and fatigue were indirectly predictive of depressed mood via their effects on recreational functioning; fatigue also affected mood directly (Voss et al., 2002).

Cognitive dysfunction is another common MS symptom that may contribute to depression. Approximately 50% of MS patients display significant cognitive impairment (Brassington & Marsh, 1998; S. M. Rao, Leo, Bernardin, & Unverzagt, 1991). Like physical impairment and fatigue, cognitive dysfunction may be a source of stress that increases risk of depression in MS patients. The hypothesis that cognitive dysfunction constitutes a significant source of stress for MS patients has been supported by the finding that cognitive problems are

highly associated with deficits in everyday functioning (Higginson et al., 2000; S. M. Rao, Leo, Ellington et al., 1991). However, research findings related to the role of MS-related cognitive impairment in depression have been mixed. While some studies have found that cognitive dysfunction is related to depression (Arnett, Higginson, & Randolph, 2001; Arnett, Higginson, Voss, Bender et al., 1999; Arnett, Higginson, Voss, Wright et al., 1999; Beatty, 1998; Gilchrist & Creed, 1994), a significant relationship has not been demonstrated in all samples (Fischer et al., 1994; Good, Clark, Oger, Paty, & Klonoff, 1992; Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; R.B. Schiffer & Caine, 1991). Arnett and colleagues (2002) have suggested that this inconsistent relationship between cognitive functioning and depression may be explained by the presence of moderating variables. This claim is supported by the finding 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 (Aikens et al., 1993; Beatty et al., 1998; Jean, Beatty, Paul, & Mullins, 1997; Pakenham, 1999; Pakenham et al., 1997; Warren et al., 1991; N.M. Wineman, Durand, & Steiner, 1994).

Coping

Coping is the set of cognitive processes and behaviors that people use in response to stress in order 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 (Andrews, Tennant, Hewson, & Vaillant, 1978; Baum, Fleming, & Singer, 1983; Billings & Moos, 1981; Collins, Baum, &

Singer, 1983; Coyne, Aldwin, & Lazarus, 1981; Felton, Revenson, & Hinrichsen, 1984; Folkman & Lazarus, 1988; Lazarus & Folkman, 1984; Menaghan, 1982; Mitchell, Cronkite, & Moos, 1983; Pearlin & Schooler, 1978; Schaefer, 1983; Shinn, Rosario, Morch, & Chestnut, 1984; Taylor, Wood, & Lichtman, 1983; Valliant, 1977). 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.

Coping may be related to outcome directly; alternatively, coping may affect outcome by buffering the impact of stress. Stress buffering models propose that coping impacts outcomes by moderating or suppressing the effects of stress (Wheaton, 1985). According to a stress-buffering model, the effects of coping should only be evident at high levels of stress (Finney, Mitchell, Cronkite, & Moos, 1984). A stress-buffering-via-suppression model posits that coping is mobilized by increased stress, and as a result dampens its causal impact. The effect of stress and coping on outcomes could also be interactive. A moderation model suggests that under certain coping conditions (i.e., when certain coping strategies are employed), stress has substantially less impact. The suppression and moderation models of stress-buffering are not mutually exclusive, and it is possible that coping is related to stress and outcome via additive and interactive mechanisms (Wheaton, 1985).

One study examining the stress-buffering effects of coping suggests that certain coping styles may have a direct effect on adjustment, while other styles (emotion and problem-focused coping, respectively, discussed subsequently) may operate by buffering the impact of stress (C. M. Aldwin & Revenson, 1987). Work in the MS literature has demonstrated that two independent coping styles (active and avoidant coping, discussed subsequently) moderated the

effect of a stressor (cognitive difficulties). In this sample, cognitive dysfunction was most likely to be associated with depression when patients used either high levels of avoidance coping or low levels of active coping (Arnett et al., 2002).

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, while 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, while problem-focused coping is associated with better adjustment and lower levels of distress (Arnett et al., 2002; Revenson & Felton, 1989; R. J. Thompson, Gil, Abrams, & Phillips, 1992). Although much of the coping research has relied on the problem-focused vs. emotion-focused distinction, this conceptualization of coping has been criticized for being too simple (Carver, Scheier, & Weintraub, 1989). Many researchers have found that responses to the Ways of Coping scale (WOC; Folkman & Lazarus, 1988), a widely used coping scale designed to assess problem- and emotion-focused coping, form several factors rather than just two (C. Aldwin, Folkman, Schaefer, Coyne, & Lazarus, 1980; C. M. Aldwin & Revenson, 1987; Coyne et al., 1981; Folkman & Lazarus, 1985; Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen, 1986; Parkes, 1984; Scheier, Weintraub, & Carver, 1986). Furthermore, some investigators have found that subtypes of emotion-focused coping are not necessarily correlated with each other or are inversely correlated, suggesting that emotion-focused coping is not a uniform construct (Carver et al., 1989).

In many theoretical contexts, it may be more useful to isolate a subset of emotion-focused coping strategies that are clearly maladaptive. Carver and colleagues (1989) have proposed a

more theoretically derived measure of coping behaviors called the COPE that incorporates 13 conceptually distinct scales. A second order factor-analysis of the COPE yields four factors, each consisting of three scales—an active coping factor (comprised of the active coping, planning, and suppression of competing activities subscales), an avoidant coping factor (comprised of the denial, mental disengagement, and behavioral disengagement subscales), a third factor comprised of seeking social support (for both emotional and instrumental reasons) and focus on emotion, and a fourth factor incorporating acceptance, restraint coping, and positive reinterpretation and growth (Carver et al., 1989). 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).

Stress and Coping in MS

Stress and coping theory, as applied to MS and other chronic illnesses, proposes that adjustment to illness is determined by illness parameters (conceptualized as stressors) and mediated by the coping process—including cognitive appraisal, coping resources, and coping strategy (Maes, Leventhal, & De Ridder, 1996). Illness parameters typically researched in MS include illness duration, disability, and disease severity (Pakenham, 1999). One study, previously discussed, examined the relationship between coping, cognitive dysfunction, and depression (Arnett et al., 2002).

The first stage of the coping process involves appraisal of the stressor. During this process, the individual evaluates whether a particular encounter with the environment is relevant to his or her well-being. For example, an encounter may be threatening (containing the

possibility for harm or loss), or challenging (holding the possibility of mastery or benefit; (Folkman et al., 1986). Although few studies have examined the relationship between appraisals and adjustment in MS, research suggests that uncertainty and threat appraisals may be related to higher levels of distress (Pakenham et al., 1997; N.M. Wineman et al., 1994), whereas challenge appraisals may be related to better adjustment (N.M. Wineman et al., 1994).

Coping resources are the personal and environmental characteristics that are available to the individual when they select and enact a coping strategy (Moos & Billings, 1982). Social support has been the most well-researched coping resource in the chronic illness literature (Pakenham, 1999). Consistent with work in other patient populations, studies on the role of social support in adjustment to MS have demonstrated that greater social support is related to better psychosocial outcomes (Long & Miller, 1991; N. M. Wineman, 1990).

Following the appraisal of the stressful situation, individuals select and enact a coping strategy, contingent on the availability of the requisite resources (Lazarus & Folkman, 1984). This stage of the coping process has received the most attention in the literature on adjustment to MS. Certain types of coping strategies have been shown to be associated with better or worse psychosocial outcomes in MS patients (Aikens et al., 1993; 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 Style and Process

In the stress and coping literature, coping has been discussed as both a process and a style (Lazarus, 1993). A style approach to coping focuses on dispositional aspects of coping, based on the assumption that individuals tend to rely on the same coping strategies in a variety of contexts over time. This conceptualization has its roots in ego-psychology's defensive styles. A

dispositional or trait approach to coping captures the idea that individual differences play a role in determining a relatively stable collection of coping behaviors. The idea that individuals display such stability in coping style is controversial. For example, Folkman and Lazarus emphasize that coping is a dynamic process that changes and develops over the course of a stressful transaction, rather than a stable style (Folkman & Lazarus, 1980, 1985; Folkman et al., 1986). Carver and colleagues (1989), however, report evidence that supports the utility of a trait approach to coping. Using a dispositional assessment of coping, Carver et al. found modest links between coping dispositions and several personality variables, and between coping dispositions and situational coping activities. These findings suggest that coping disposition represents a meaningful construct that plays a role in determining situational coping. Additionally, work done by Folkman and Lazarus demonstrates that certain coping strategies, like positive reappraisal, were relatively stable within individuals across five stressful encounters over 5 months (Folkman et al., 1986).

From a process perspective, coping changes over time in response to the dynamic situational context in which it occurs (Lazarus, 1993). The process perspective emphasizes state aspects of coping, with attention to the influence of context on an individual's choice of coping strategy. Work in this area has found that people employ several coping strategies in every stressful situation (Folkman & Lazarus, 1980), that some coping strategies are more stable over time than others (Folkman et al., 1986), and that coping changes from one time to another during the course of a stressful encounter (Folkman & Lazarus, 1985). These findings on process aspects of coping offer an important contribution to the understanding of emotional and cognitive responses to stress. However, as Lazarus acknowledges, the major limitation of an extreme contextualization of coping is that it fails to capture a functional portrait of the whole

person (Lazarus, 1993). Ideally, the decision to assess coping from a state or trait perspective should be determined by the outcome of interest. In the present study, coping is conceptualized from a style perspective, based on the assumption that dispositional coping should be more relevant to chronic psychological outcomes like depression.

Cognitive Dysfunction and Coping

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; S. M. 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 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.

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 higher scores on executive functioning tasks were related to the use of planful problem solving coping, whereas poorer 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 prior research has begun to explore how cognitive deficits, coping, and depression in MS are related, this complex relationship remains poorly understood. The only prior 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). In order 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 function plays 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 may be more meaningful in relation to psychological outcomes like depression.

Present Study

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 prior 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 or partially 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 proposed project, 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.

Hypotheses

Hypothesis 1: An inverse relationship between cognitive functioning and depression will be demonstrated by a regression model using cognitive function at time 1 to predict depression at time 2.

Hypothesis 2: An inverse relationship between coping (defined as the use of adaptive relative to maladaptive coping strategies) and depression will be demonstrated by a regression model using coping at time 1 to predict depression at time 2.

Hypothesis 3: Coping at time 1 will moderate the effect of cognitive functioning at time 1 on depression at time 2, in a stress-buffering fashion (see figure 1).

Hypothesis 4: Coping at time 2 will mediate the relationship between cognitive functioning at time 1 and depression at time 2 (see figure 2).

Figure 1. Conceptual model of Coping as a Moderator of the relationship between Cognitive Dysfunction and Depression (Hypothesis 3).

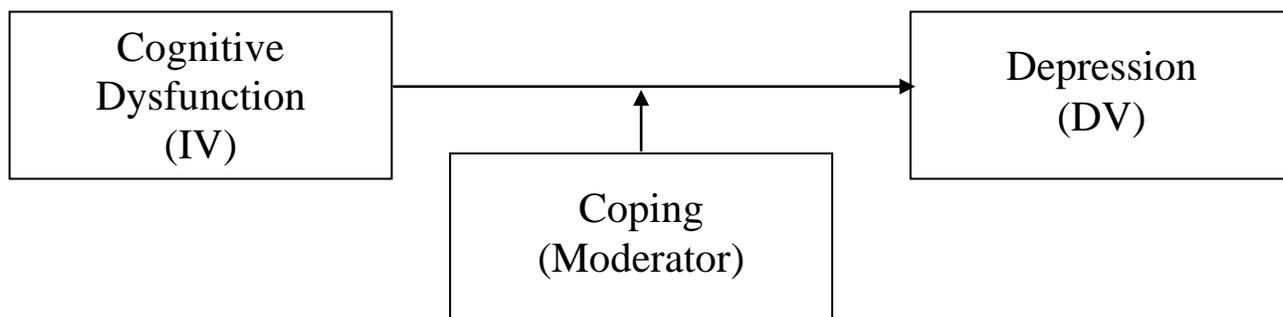
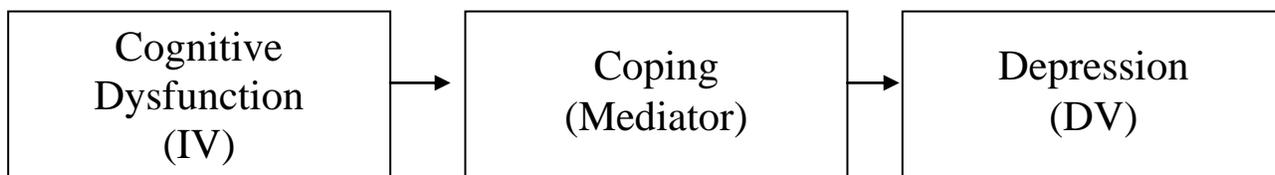
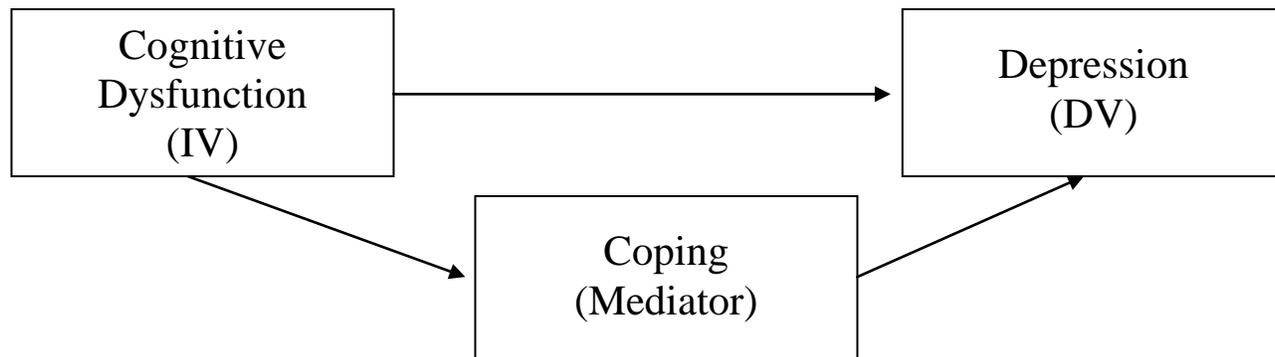


Figure 2. Conceptual models of Coping as a Mediator and Partial Mediator of the relationship between Cognitive Dysfunction and Depression (Hypothesis 4).

Full Mediation



Partial Mediation



Methods

Participants and Procedures

A secondary analysis was conducted using data from 55 participants in a longitudinal study of cognitive and emotional change in MS. Participants were recruited from neurologists and a local MS society in the northwestern United States. Individuals contacting the study team were assessed for eligibility. All participants in the study had definite or probable MS, diagnosed by board-certified neurologists according to Poser et al.'s criteria (Poser et al., 1983). 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 may interfere w/ cognitive testing, (d) premorbid history of a learning disability, and (e) severe physical or neurological impairment that would interfere with evaluation at the university. Testing was conducted at Washington State University. Participants were assessed at two time points, 3 years apart. Informed consent was obtained at the initial testing session. Testing sessions consisted of administration of measures assessing cognitive, physical, and emotional functioning, delivered 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.

Measures

Depression

Chicago Multiscale Depression Inventory (CMDI; David L. Nyenhuis et al., 1995)—The CMDI is a self-report 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, which includes

three subscales representing different types of depression symptoms: vegetative, mood, and evaluative.

The CMDI scale development process involved more than 1000 participants. Item analyses at various stages of development included both correlational and principal component analyses. A confirmatory factor analysis (CFA) using data from an age-, gender-, and race-stratified standardization sample ($n = 420$) demonstrated an acceptable fit of a hypothesized five-factor solution, which separated the vegetative depression scale into three separate factors—Fatigue, Sleep Disturbance, and Cognitive Inefficiency (D. L. Nyenhuis et al., 1998).

The appropriateness of the CMDI as a measure of depression in individuals with MS was demonstrated in a study by Nyenhuis et al (1995). Results showed that the percentage of participants in the clinical range of depression, as measured by the CMDI mood scale, was significantly lower than when it was as measured by the Beck Depression Inventory (BDI; (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) or by the combination of the mood, evaluative, and vegetative CMDI scales (17.7% with CMDI mood scale; 30.5% with BDI; 26.6% with CMDI total). Importantly, MS patients in this sample did not differ significantly from matched normal controls in the extent of their mood symptoms, while they were significantly higher on both evaluative and vegetative symptoms (D. L. Nyenhuis et al., 1995).

Due to the potential confound involved in including vegetative symptoms of depression when evaluating depression in individuals with MS, Nyenhuis and colleagues (1995) have suggested that the mood subscale of the CMDI may be the most valid measure of depression in this population (D.L. Nyenhuis et al., 1998). Other studies have combined the mood and evaluative subscales to conceptualize depression (Arnett et al., 2001; Arnett, Higginson, Voss, Bender et al., 1999; Arnett et al., 2002; Arnett, Higginson, Voss, Wright et al., 1999). Due to the

current precedent in the literature, a combination of the CMDI mood and evaluative subscales has been chosen as the operationalization of depression in the present study.

Coping

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 4-item clusters. The COPE has traditionally been divided into two indices—an Active Coping index made up of the Active Coping, 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. In order to obtain a more comprehensive index of an individual's use of adaptive coping, coping will be 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.

The COPE can be used to assess situational or dispositional coping tendencies. Lazarus (1993) posits that some coping strategies are consistently applied over a variety of stressful situations, and therefore are likely to reflect dispositional coping style. Other coping styles are employed less consistently and appear to be more situation-specific. 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

Cognitive Functioning Index (Combined Speeded Attentional, Working Memory, and Planning Task Indices)—Cognitive functioning was assessed using a battery of neuropsychological tests shown to be most associated with depression in MS from prior work (Arnett, 2005; Arnett et al., 2001; Landro, Celius, & Sletvold, 2004; Thornton & Raz, 1997).

The Reading Span Test (RST)

The RST (M. Daneman & P. A. 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 following 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. Both methods produce scores that have been demonstrated as good predictors of reading comprehension and verbal reasoning (M. Daneman & P. A. Carpenter, 1980; Daneman & Merikle, 1996; Just & Carpenter, 1992).

The RST correlates in the .5 to .7 range with other measures of verbal ability in samples of college students (M. Daneman & P.A. Carpenter, 1980; Turner & Engle, 1989) and in an aphasic sample (Caspari, Parkinson, LaPointe, & Katz, 1998). Findings regarding the reliability of the RST have been mixed, with one study reporting a low reliability estimate (test-retest reliability of .41; Waters & Caplan, 1996), and other studies finding high reliability in the .75 to .85 range (Salthouse & Meinz, 1995; Shah & Miyake, 1996). Total number of words correctly recalled will be the RS scoring index used in the proposed project.

The Paced Auditory Serial Addition Task (PASAT)

The PASAT (D. M. A. Gronwall & Sampson, 1974) is a frequently used test of attention, concentration, working memory, and speed of processing. In the standard version of the test, four series of numbers are presented to the participant at increasing speed (2.4, 2.0, 1.6, and 1.2 seconds per digit). In the proposed study, a version of the PASAT recommended for use in MS that has 3 seconds between digit presentations is used (S. M. Rao, and the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990). Participants are to respond with the correct sum of the two most recently presented digits. For example, if the digits ‘8’, ‘2’ and ‘3’ were presented, the participant should respond with the correct sums—10 and then 5. Extensive research demonstrates that the PASAT is sensitive to neurological impairment associated with traumatic brain injury (TBI) and MS (Bleiberg, Garmoe, Halpern, Reeves, & Nadler, 1997; Crossen & Wiens, 1988; DeLuca, Johnson, & Natelson, 1993; Diamond, DeLuca, Kim, & Kelley, 1997; J. D. Fisk & Archibald, 2001; D. Gronwall & Wrightson, 1974; D. M. A. Gronwall & Sampson, 1974; Macciocchi, Barth, Alves, Rimel, & Jane, 1996; Ponsford & Kinsella, 1992; Stuss, Stethem, & Hugenholtz, 1989). In fact, it has been chosen for use as the only cognitive measure in the recently developed Multiple Sclerosis Functional Composite because of its sensitivity to cognitive dysfunction in MS (Fischer, Rudick, Cutter, & Reingold, 1999).

Researchers have found positive correlations between PASAT scores and scores on other tests thought to measure attention. Moderate to high correlations have been reported for Trails B, and the following Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III) Working Memory and Processing Speed subtests—Digit Span Backward and Total, Digit Symbol, and Arithmetic (Baird, 2004; Crawford, 1998; DeLuca et al., 1993; Dyche & Johnson, 1991a, 1991b; J. D. Fisk & Archibald, 2001; D. Gronwall & Wrightson, 1974; Johnson, Roethig-Johnston, &

Middleton, 1988; Madigan, DeLuca, Diamond, Tramontano, & Averill, 2000; McCaffrey & Westervelt, 1995; O'Donnell, Macgregor, Dabrowski, Oestreicher, & Romero, 1994; Radanov, Hirlinger, Di Stefano, & Valach, 1992; Sherman, Strauss, & Spellacy, 1997; Shucard et al., 2004; Tombaugh, 2002). Factor analytic studies have found that the PASAT and WAIS subtests form a typical three factor solution—Verbal, Performance, and an attention factor called Freedom from Distractibility—with the PASAT loading most heavily on the attention factor (Deary, Langan, Hepburn, & Frier, 1991; Sherman, Strauss, Spellacy, & Hunter, 1995).

Several studies have reported high reliability statistics for the PASAT. Correlations between scores on individual trials range from .76 to .95 (MacLeod & Prior, 1996; Ponsford & Kinsella, 1992; Sherman et al., 1997). A Cronbach's alpha of .90 was obtained from scores on the four standard PASAT trials (Crawford, 1998). Split-half correlations of between .92 and .96 have been reported (Egan, 1988; Johnson et al., 1988). Test-retest coefficients for both short and long test-retest intervals have been reported to be in the .90 to .97 range (Dyche & Johnson, 1991a; McCaffrey, Westervelt, & Haase, 2001; Sjogren, Olsen, Thomsen, & Dalberg, 2000; Stuss et al., 1989). In the proposed study, the dependent variable for the PASAT will be total correct out of 60 possible additions.

The 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. Digit Symbol instructs examinees to write symbols below the digits 1 through 9 according to a key, as quickly as possible for 90 seconds. The score is the number of symbols correctly matched in 90 seconds. SDMT reverses the presentation of the Digit Symbol test such that the examinee is provided with novel symbols and instructed to

answer with the corresponding digit according to a key. The other distinguishing characteristic of the SDMT is that it allows for assessment via two different response modalities—written and oral. In the proposed project the oral form of the SDMT will be used in order to provide an assessment of attention less influenced by motor impairment common to the MS patient population. The SDMT has 110 items, and the total score is the number of correct items completed in 90 seconds.

Researchers have found the SDMT is sensitive to ‘organic’ cerebral dysfunction, dementia, and depression (Pfeffer et al., 1981; Smith, 1982). In a sample of patients with MS, SDMT scores were found to be positively correlated with the Environmental Status Scale (ESS)—a broad measure of functional disability (including domains like employment, transportation, economic status, and social activity) based on patient interview (Higginson et al., 2000). Correlations between the SDMT and the Wechsler Digit Symbol test have been found to be as high as test-retest reliability coefficients for the SDMT (Bowler, Sudia, Mergler, Harrison, & Cone, 1992). However, SDMT raw scores run consistently lower than scores on Digit Symbol (Lezak, Howieson, & Loring, 2005).

Improvement in scores due to practice effects has been found for both the written and oral versions of the SDMT for a one-month retest interval, with correlation coefficients of .80 and .76 respectively (Smith, 1982). With a year-long interval, test-retest reliability is .78 (Snow, Tierney, Zorzitto, Fisher, & Reid, 1988).

Visual Elevator subtest from the Test of Everyday Attention (TEA)

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 timing score will be used in the proposed project, and is calculated as average time per switch for correct items. The timing score has been shown to be correlated with a measure of functional disability (ESS score) in a sample of patients with MS (Higginson et al., 2000). It has also been shown to be highly correlated with performance on the Wisconsin Card Sorting Test, a classic measure of executive function in the neuropsychological literature (Robertson et al., 1994).

Tower of London (TOL)

The TOL task (Davis, Bajszar, & Squire, 1994) is included as a test of 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 the proposed 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 TOL has been shown to be sensitive to frontal lobe damage in a TBI patient population (Levin, Goldstein, Williams, & Eisenberg, 1991). Scoring indices selected for the proposed project are the number of moves per trial and the total time per trial.

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

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. 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 is referred to as the Composite Coping Index subsequently). All z-scores were calculated using the MS sample as the reference group.

Hypothesis 1. Cognitive function at time 1 will predict depression at time 2. This hypothesis was tested by regressing the Cognitive Index at time 1 on CMDI mood and evaluative score at time 2. The effect of the Cognitive Index on depression was significant ($R^2 = .16$, $p < .005$). For regression coefficients and test statistics see Table 1.

Hypothesis 2. Coping at time 1 will predict depression at time 2. This hypothesis was tested by regressing the coping indices (all at time 1) on CMDI mood and evaluative score at time 2 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 ($R^2 = .08$, $p < .05$). Parameter estimates and tests statistics for all three models are summarized in Table 1.

Table 1. Main effects of Cognitive Functioning and Coping Indices at time 1 on depression at time 2.

	B	SEB	β	R ²	Adj R ²	ΔF	p-level
Hypothesis 1. Cognitive function at time 1 will predict depression at time 2.							
	-6.05	1.94	-0.40	0.16	0.14	9.78	<.005
Hypothesis 2. Coping at time 1 will predict depression at time 2.							
Active Coping Index							
	-2.04	1.59	-0.18	0.03	0.01	1.64	<i>ns</i>
Avoidant Coping Index							
	3.05	1.62	0.26	0.07	0.05	3.55	<i>ns</i>
Composite Coping Index							
	-0.209	1.02	-0.28	0.08	0.06	4.22	<.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 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. Separate regression models were evaluated for the three coping variables of interest.

Regression analyses revealed support for all three moderation predictions. Parameter estimates and test statistics for the moderation analyses are summarized in Table 2. As Table 2 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 Composite 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 ($\Delta F = 10.40$; $p < .005$).

Table 2. Moderation tests: Hierarchical regression analyses for Cognitive Task and Coping Indices predicting depression.

Variable	B	SEB	β	R^2	Adj R^2	ΔR^2	ΔF	p-level
Cognitive Task Index and Active Coping Index Predict Depression								
Step 1								
Cognitive Task Index	-6.27	1.84	-0.42	0.16	0.15	0.16	9.64	<.005
Step 2								
Active Coping Index	-2.99	1.48	-0.26	0.18	0.14	0.01	0.78	ns
Setp 3								
Interaction Term	8.37	2.66	0.41	0.32	0.27	0.14	0.14	<.005
Cognitive Task Index and Avoidant Coping Index Predict Depression								
Step 1								
Cognitive Task Index	-3.87	2.14	-0.26	0.16	0.15	0.16	9.64	<.005
Step 2								
Avoidant Coping Index	0.96	1.61	0.08	0.18	0.14	0.02	0.91	ns
Setp 3								
Interaction Term	-4.4	2.05	-0.3	0.25	0.2	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	0.15	0.16	9.64	<.005
Step 2								
Composite Coping Index	-1.26	0.94	-0.17	0.19	0.15	0.02	1.46	ns
Setp 3								
Interaction Term	4.44	1.38	0.39	0.33	0.29	0.15	10.4	<.005

The nature of these interactions is illustrated in Figures 3 – 5. Separate regression lines were calculated for the maximum and minimum scores on the Cognitive Task Index for each of the coping regression models. For the Active, Avoidant, and Composite Coping models respectively the unstandardized simple slopes for participants scoring high on the Cognitive Index are 6.30, -3.92, and 3.66; the unstandardized simple slopes for participants scoring low on the Cognitive Index are -25.58, -12.83, and -13.24.

Figure 3. Active Coping moderation model: simple slopes for Low and High Cognitive Functioning.

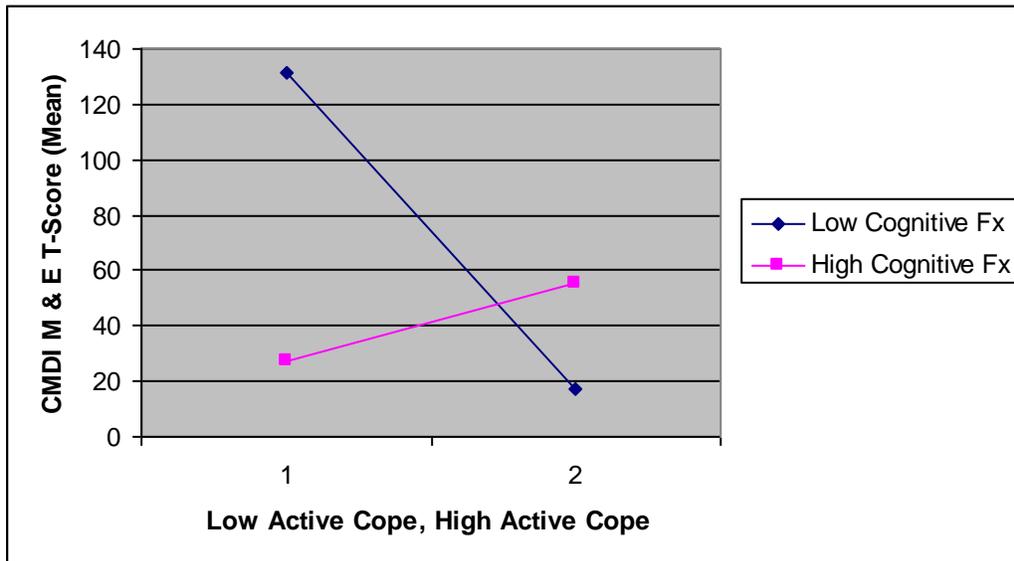


Figure 4. Avoidant Coping moderation model: simple slopes for Low and High Cognitive Functioning.

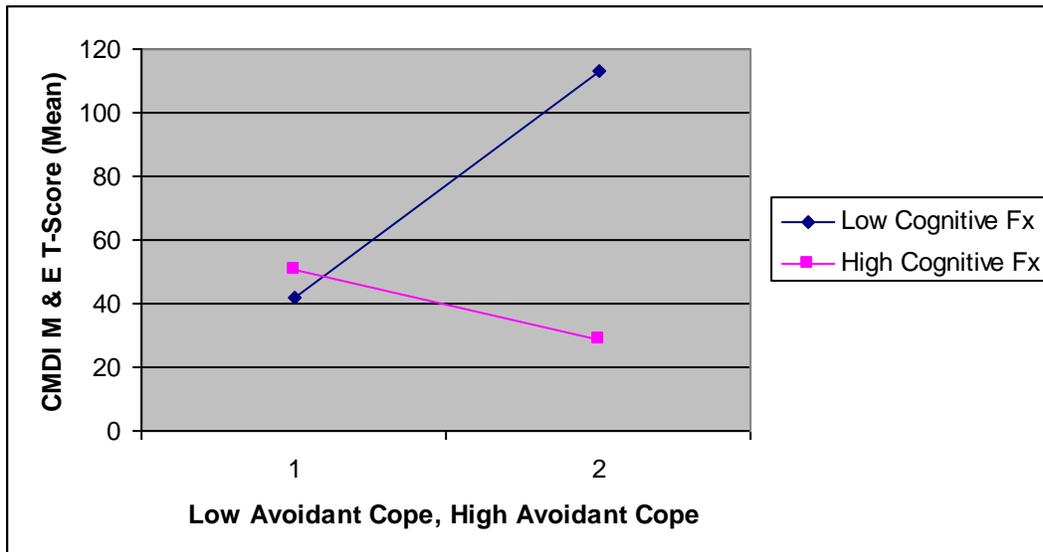
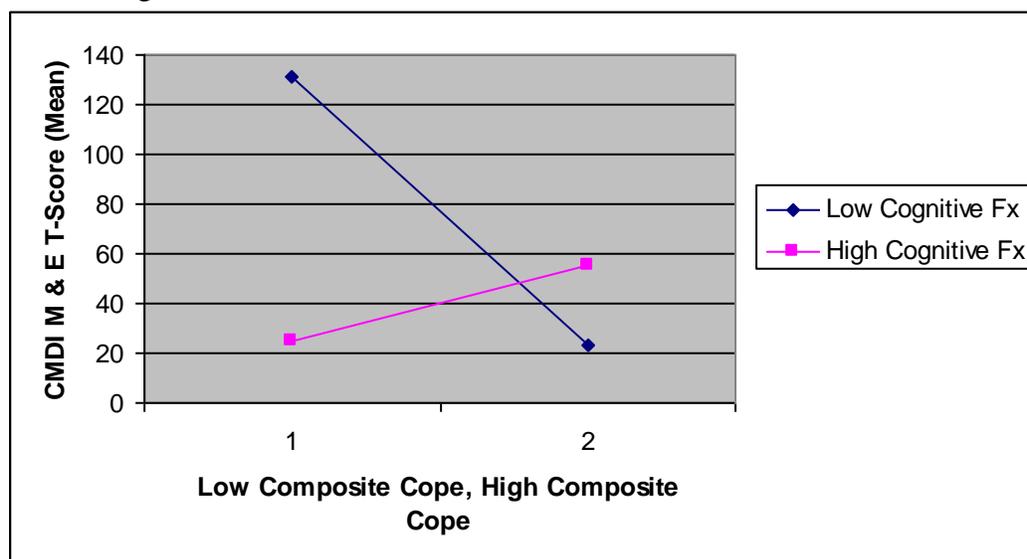


Figure 5. Composite Coping moderation model: simple slopes for Low and High Cognitive Functioning.



Hypothesis 4. Coping will mediate the relationship between cognitive functioning and depression. Three analytic strategies were employed to test this hypothesis. 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. Separate analyses were conducted for each of the coping variables of interest.

Regression analyses were conducted to test Baron and Kenny's criteria for assessing mediation for each of the three coping variables of interest (Baron & Kenny, 1986). Results of the Composite Coping analyses support the hypothesis that the coping partially mediates the relationship between cognitive functioning and depression (see Table 3). Applying Baron and Kenny's criteria to the Active and Avoidant Coping analyses separately did not support the hypothesis that coping mediates or partially mediates the relationship between cognitive functioning and depression.

Table 3. Mediation Tests: Baron and Kenny's (1986) criteria applied to the Composite Coping Index as a mediator of the relationship between the Cognitive Task Index and CMDI combined mood and evaluative depression scores.

Regression Model	B	SEB	t	p-value
b(YX)	-8.06	2.31	-3.49	0.001
b(MX)	1.06	0.37	2.88	0.006
b(YM.X)	-2.08	0.86	-2.4	0.02
b(YX.M)	-5.87	2.39	-2.46	0.018

In the models above, Y is CMDI mood and evaluative depression scores (time 2), X is Cognitive Task Index (time 1), and M is Composite Coping Index (time 2).

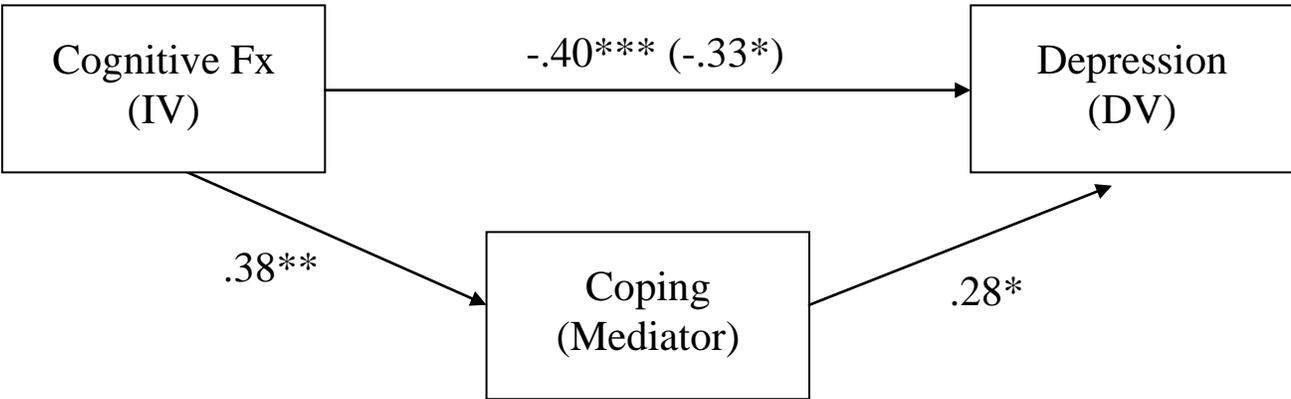
Baron and Kenny (1986) recommend using the Sobel test to evaluate the significance of the indirect effect of the independent variable on the dependent variable via the mediator (Sobel, 1982). However, the Sobel test assumes that the indirect effect is normally distributed, and this assumption may not always hold, particularly when sample size is small (Bollen & Stine, 1990; Preacher & Hayes, 2004). Some researchers have suggested that a bootstrapping approach may be more appropriate for estimating the size and the significance of mediation effects (Bollen & Stine, 1990; Preacher & Hayes, 2004). Bootstrapping is an approach to statistical inference that involves selecting random samples with replacement from a data set, and analyzing each sample for the statistic for interest. The final estimate is the mean of the values obtained from each of the bootstrap samples. Because the data is resampled with replacement, a particular data point from the original data set could appear multiple times in a given bootstrap sample. Confidence intervals are taken directly from the range of sample estimates. The SPSS macro published by Preacher and Hayes (2004) was 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).

Consistent with the conclusions drawn from the Baron and Kenny criteria, neither the Sobel statistics nor the estimates based on the bootstrapping method supported the hypotheses that coping mediated the relationship between cognitive functioning and depression for the Active and Avoidant Coping analyses examined separately (see Table 4). For the Composite Coping analysis, the Sobel statistic suggested a trend towards significance ($Z = -1.78$; $p < .10$). According to the bootstrap estimates, the indirect effect of cognitive functioning on depression via coping is different from zero with 95% confidence (-2.16; LL 95% CI: -4.90; UL 95% CI: -0.12). Hence, the bootstrap estimates suggest that the mediation effect for Composite Coping is significant at the $\alpha = .05$ level. This is consistent with the conclusion drawn from the Baron and Kenny criteria. Figure 6 illustrates the nature of the mediation relationship.

Table 4. Mediation tests: Sobel statistics and bootstrap estimates of the indirect effect of Cognitive Task Index on Depression via Coping Indices.

Mediator Variable	Sobel Test		mean effect	Bootstrap estimates		
	Sobel's Z	p-level		SE	95% Confidence Interval Lower Limit	Upper Limit
Active Coping Index	-1.24	ns	-1.45	1.09	-4.07	0.06
Avoidant Coping Index	-1.5	ns	-1.41	0.99	-3.57	0.15
Composite Coping Index	-1.78	<.10	-2.16	1.27	-4.9	-0.12

Figure 6. 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 Composite Coping Index.



* $p < .05$; ** $p < .01$; *** $p < .005$

Discussion

The present study used a longitudinal design in order 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 the a priori hypotheses speculated that analyses would reveal support for coping in both moderation and mediation roles.

Coping as a moderator indicates that the relationship between cognitive dysfunction and depression is dependent on coping style. I 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 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 high risk for depression. Coping as a mediator suggests that the relationship between cognitive dysfunction and depression is due to cognitive dysfunction's effects on coping. In other words, cognitive functioning is a coping resource. Cognitive deficits impair the individual's ability to employ adaptive coping strategies, leaving them more likely to employ maladaptive coping strategies. That is, it is cognitive functioning's effect on coping style that is responsible for increased likelihood of depression. In order to operationalize coping, three different indices of coping behavior derived from the COPE were used (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.

In order to examine coping as a moderator and mediator of the relationship between cognitive functioning and depression, I evaluated four hypotheses, using separate models to test the three coping indices independently. Hypotheses 1 and 2 examined the independent effects of cognitive dysfunction and coping on depression. Hypothesis 1 was that an inverse relationship between cognitive functioning and depression would be demonstrated by a regression model using cognitive function at time 1 to predict depression at time 2. I found support for this hypothesis—the cognitive index at time 1 was responsible for 16% of the variance in depression at time 2. Hypothesis 2 was that an inverse relationship between adaptive coping and depression (and a positive relationship between maladaptive coping and depression) would be demonstrated by a regression model using coping at time 1 to predict depression at time 2. This hypothesis was evaluated for the three coping variables of interest. The active and avoidant coping indices at time 1 did not significantly predict depression at time 2. However, the composite coping index that took into account the use of adaptive relative to maladaptive coping, did significantly predict depression at time 2. This index at time 1 was responsible for 8% of the variance in depression at time 2. The fact that the composite coping index was a better predictor of depression than either of the indices that comprise it supports the utility of operationalizing coping in this way.

Hypothesis 3 was that coping at time 1 would moderate the effect of cognitive functioning at time 1 on depression at time 2, in a stress-buffering fashion. This hypothesis was supported for all three coping variables of interest. The composite coping and cognitive functioning interaction term accounted for 15% of the variance in depression at time 2. Support for this hypothesis suggests that, as hypothesized, low levels of adaptive coping and high levels of maladaptive coping put individuals with cognitive dysfunction at high risk for developing

depression. On the other hand, an adaptive coping style protects individuals with cognitive deficits from experiencing depressive symptoms. Individuals with low levels of cognitive impairment reported very little depression regardless of the type of coping style they used. This is consistent with the stress-buffering model put forth by Finney and colleagues (1984). The effects of coping are only evident when the individual is experiencing high levels of cognitive dysfunction—i.e. at high levels of stress (Finney et al., 1984). When adaptive coping strategies are employed, stress caused by cognitive disability has substantially less impact.

Hypothesis 4 was that coping at time 2 would mediate the relationship between cognitive functioning at time 1 and depression at time 2. Again, all three coping indices were examined to evaluate this hypothesis. Only the composite coping variable was a significant mediator of the relationship between cognitive dysfunction and depression. Analyses revealed that the indirect effect of cognitive functioning on depression via coping was significant at the .05-level, supporting partial mediation of the composite coping index on the relationship between cognitive dysfunction and depression. As discussed above, the implication of this finding is that cognitive functioning is a coping resource, and hence cognitive deficits result in a diminished ability to use adaptive active coping strategies. Such deficits may result in individuals relying on maladaptive coping. The relative increase in the use of maladaptive coping, in conjunction with low levels of adaptive coping, may lead to an increase in depression symptoms. Because, the direct effect of cognitive functioning on depression remained significant when accounting for the indirect effect via coping, partial mediation, and not full mediation, was supported. This partial mediation relationship indicates that cognitive functioning has a significant direct effect on depression, and also a significant indirect effect on depression, via its effect on coping.

The results of the present study contribute significantly to the understanding of cognitive dysfunction, coping, and depression in patients with MS. Firstly, this study replicates 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 behavior relative to the outcome of interest—depression. Furthermore, the longitudinal design has allowed for rigorous evaluation of the hypothesis that coping mediates the relationship between cognitive dysfunction and depression in patients with 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 also 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 project is the unique way that coping style is operationalized. In addition to examining active coping as an index of adaptive coping strategies, and avoidant coping as an index of maladaptive coping strategies, the present study also considered 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 WOC (Folkman & Lazarus, 1988) or the COPE (Carver et al., 1989). There are obvious strengths of this approach. Carver and colleagues

provide 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 in order 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 functional portrait of the individual's coping on the whole. A precedent is developing 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 prior 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 or 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 in order 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.

The rationale behind using the composite coping index follows from the idea that individuals would arrive at similar composite coping scores in different ways—i.e. 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 based on the assumption that relative levels of active and avoidant coping should be more meaningfully related to depression than either factor in isolation.

Examination of a selection of individual cases supports that individuals in this sample do in fact, arrive at similar composite coping scores in different ways. For example, two participants from the study sample received a composite coping z-score near -3.20 (-3.20 and -3.24), indicating that these participants are 3.2 standard deviations below the mean composite coping score. However examining these individuals' active and avoidant index scores reveals two very different profiles. One participant scored .57 standard deviations above the mean for active coping and 3.81 standard deviations above the mean for avoidant coping. In other words, this individual was near average for our sample in use of active coping strategies, and very much above average for our sample in use of avoidant strategies. The other participant, however, scored 2.53 standard deviations below the mean for active coping and .67 standard deviations above the mean for avoidant coping. This is nearly the opposite of the other participant's profile; this participant was very much below average in the use of active coping strategies, and slightly above average in the use of avoidant strategies. Despite these disparate coping profiles, these two participants reported similar levels of depression at time 1, with combined CMDI mood and evaluative t-scores of 62.07 and 64.37 respectively. As might be expected, due to their low composite coping scores, these individuals scored more than one standard deviation above the mean depression score for the study sample.

Other support for the utility of composite coping comes from the examination of participants who received the same active or avoidant index score, but may have scored very differently on the other index. For example, two participants received active coping index scores

1.60 standard deviations above the mean for the sample. However, one participant scored above the mean for avoidant coping, whereas the other participant scored slightly below the mean. This might explain the discrepancy between these participants' time 2 depression scores. The participant with relatively high reported use of avoidant strategies scored more than 1 standard deviation higher in depression symptoms than the participant who reported relatively low use of avoidant coping. Despite the fact that both participants reported high use of active coping strategies, the relatively high use of avoidant strategies may have put the one participant at higher risk for depression.

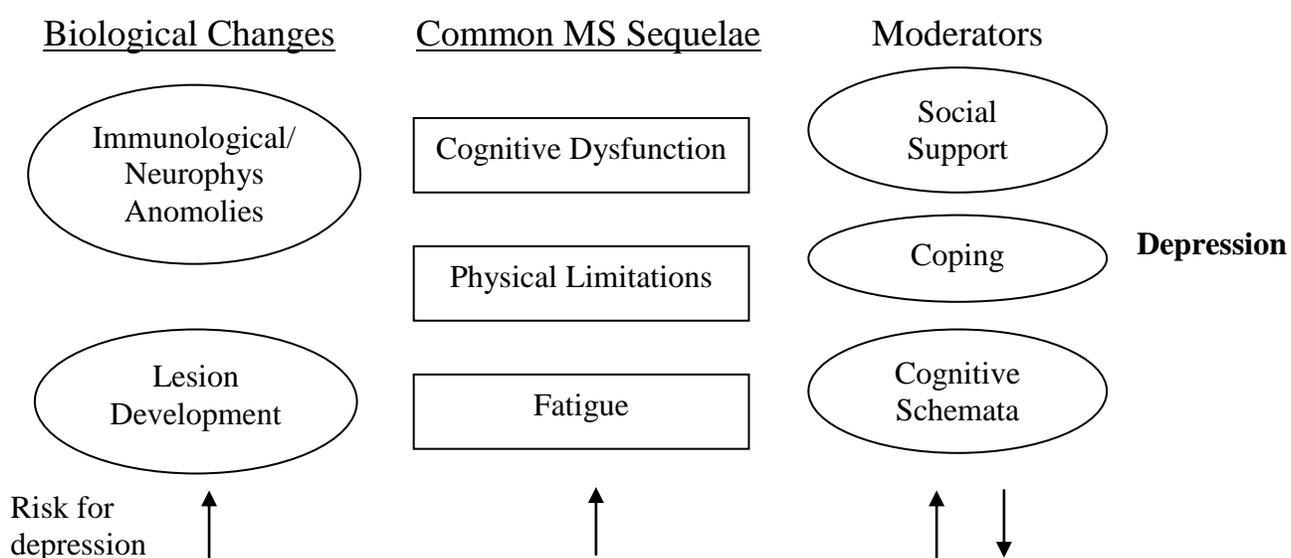
Similarly, two other participants both received avoidant coping scores .86 standard deviations above the mean for this sample. One participant scored 1.5 standard deviations below the sample mean for active coping, whereas the other was more than .5 standard deviations above the mean for active coping. Again, this might explain the difference between reported depression in these two participants at time 2. The participant who reported relatively low active coping, scored more than 2 standard deviations higher on the depression index than the participant who reported relatively high use of active coping strategies. This latter participant's use of active coping may have mitigated some of the deleterious effects of this individual's relatively high use of avoidant coping strategies.

Contributions to a Model of Depression in Multiple Sclerosis

Arnett and colleagues have proposed a theoretical model that integrates the literature regarding depression in MS in a way that provides testable hypotheses for future work (Arnett, Barwick, & Beeney, 2008). Their model attempts to address the increased risk for depression in MS patients following MS diagnosis by considering biological changes related to the MS disease

process, common sequelae of MS, and possible moderators that may buffer the effects of MS symptoms on depression (see figure 7). Arnett and colleagues review the literature on biological correlates of depression in MS patients. Studies examining lesion burden, brain atrophy, and immunological anomalies have reported an association between these disease variables and depression, however, these factors explain a relatively limited proportion of the variance in depression (Bakshi, Czarnecki et al., 2000; Berg et al., 2000; Fassbender et al., 1998; Feinstein et al., 2004; W. G. Honer, T. Hurwitz, D. K. Li, M. Palmer, & D. W. Paty, 1987; Pujol et al., 2000; Pujol et al., 1997; Reischies, Baum, Brau, Hedde, & Schwindt, 1988; Zorzon et al., 2001). Several MS sequelae have been examined regarding their relationships with depression. Fatigue, physical disability, cognitive dysfunction, and pain, have all been shown to have an inconsistent relationship to depression (Arnett et al., 2008). Arnett and colleagues posit that these inconsistent relationships suggest the possible presence of moderator variables. In their model, Arnett et al. propose that social support, coping, and cognitive schema may moderate the relationships between MS symptoms and depression.

Figure 7. Model of Depression in MS.



The results of the present project support Arnett and colleagues' (2008) model by demonstrating that coping does in fact moderate the relationship between cognitive dysfunction and depression longitudinally. As noted earlier, prior work has already demonstrated this relationship cross-sectionally (Arnett et al., 2002). The results of the present study underscore the importance of replicating the other moderation relationships reported in the literature, and cited in support of the model, with longitudinal data.

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. While several research studies have looked at the role of coping in adjustment to chronic illness (Aikens et al., 1993; 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. Findings like those reported presently offer guidelines for interpreting self-reported coping in a clinically relevant way. This work, along with other research (Aikens et al., 1993; 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 demonstrate that this relationship is robust longitudinally—i.e. maladaptive coping style precedes depression.

Administering the COPE in clinical settings could help identify individuals who are at risk for developing depression. Talk therapy interventions designed to teach more adaptive coping strategies may be an effective preventative treatment for these individuals.

Research has examined the efficacy of cognitive behavioral therapy (CBT) for depression in depressed patients with MS (D. Mohr, 1999; D. C. Mohr, A. C. Boudewyn, D. E. Goodkin, A. Bostrom, & L. Epstein, 2001; D.C. Mohr, Hart, & Goldberg, 2003; D. C. Mohr et al., 2000). The results of a meta-analysis that examined the efficacy of different depression treatments in MS patients found that anti-depressant medication and psychosocial interventions that focus explicitly on increasing adaptive coping are more effective than supportive or insight-oriented psychotherapy (D. Mohr, 1999). The most common coping-focused psychosocial intervention is CBT. A form of CBT administered to MS patients in a study by Mohr and colleagues (2001) included behavioral activation and cognitive restructuring as outlined in traditional CBT manualized treatments for depression (Beck, Ruch, Rush, Emery, & Shaw, 1979). This treatment also taught specific skills relevant to coping with typical problems faced by MS patients, such as the management of fatigue, pain, mild cognitive impairment, sexual dysfunction, and stress (D. C. Mohr, A. C. Boudewyn, D. E. Goodkin, A. Bostrom, & L. Epstein, 2001). This adapted CBT was found to be superior to supportive group psychotherapy in a randomized clinical trial (D. C. Mohr, et al., 2001).

Given that CBT is a therapeutic orientation that focuses on adaptive coping and skill building, it is likely that CBT's efficacy for treating depression in MS is in large part due to direct effects on coping behaviors. The present findings, in conjunction with the therapy outcome literature cited above, support this claim. However, the results of the present study also suggest that clinical interventions may be further improved by what we know about coping in

MS. Examination of the subscales and items that make up the active and avoidant factors of the COPE offers more concrete definitions of adaptive and maladaptive coping, which could inform treatment. Furthermore, the present findings underscore that the relative use of active and avoidant strategies is clinically relevant—highlighting the importance of addressing both types of coping behaviors in treatment. Finally, the longitudinal nature of the present study suggests that pre-emptive interventions targeting individuals with maladaptive coping styles could prevent the development of depression in MS patients. This could be particularly useful for individuals with high levels of cognitive impairment who are at high risk of developing depression when coping is poor.

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 employing active coping strategies as a result of their disability. There are important clinical implications of this finding. As a result of cognitive dysfunction, depressed clients with neuropsychological deficits may be different from depressed clients without neurological 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. In order to increase treatment efficacy, therapists may need to augment traditional CBT interventions for depression in order to make them more accessible to cognitively compromised clients.

Such a CBT intervention has been employed in the context of traumatic brain injury. The results of the present study suggest that many of the principles recommended for treating adjustment to brain injury may apply to the treatment of depression in MS patients. Hibbard and colleagues suggest that cognitive therapy may be ideal for brain-damaged individuals in that it is

behaviorally oriented, time-limited, active and directive, and focused on current problems. However, the authors go on to suggest that certain modifications to traditional CBT should be made for use in this population—for example, a greater emphasis on behavioral techniques, expansion of positive social interactions, modeling of assignments by both the patient and the therapist, simplification of tasks, establishment of a therapeutic alliance with a spouse or relative that may help the patient complete home work assignments, and a focus on challenging and correcting cognitive distortions exhibited in session (Hibbard, Rendon, Charatz, & Kothera, 2005).

Other work in the area of traumatic injury offers specific recommendations for dealing with cognitive limitations. Memory deficits may be addressed by requiring the patient to take notes, make audiotapes of sessions, or reviewing materials presented in each session. Attentional difficulties may be mitigated by highly structuring the session, using visual anchors, or multiple modes of presenting material. Repetition and slowed presentation could assist patients with speed of processing deficits. Additionally, asking structuring questions may help cognitively compromised individuals organize their thoughts (Whitehouse, 1994). The findings of the present study suggest that teaching clients to apply some of these cognitive aids outside of session, in coping situations, may be particularly beneficial. While this practical advice is certainly intuitively appealing, whether or not these techniques would improve treatment efficacy for depressed individuals with MS is an empirical question that is yet to be addressed.

It is possible that the demonstrated coping mediation effect would cease to be significant within the context of a therapeutic intervention. Learning and practicing coping skills in session may relieve much of the cognitive burden individuals face when coping with unfamiliar or unanticipated stressful situations. Hence, effective talk therapy could mitigate the effects of

cognitive deficits on coping ability. This may be one of the mechanisms by which CBT is an effective treatment for depression in MS.

Limitations

There are limitations of the present study that should be highlighted. The sample size is relatively small, with 55 subjects. Hence, the study may have been underpowered to identify small to moderate effects. This may explain why neither the active nor avoidant coping indices were 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 significant moderation effects were demonstrated for the active and avoidant coping indices, suggests that these effects are robust.

Another possible limitation of the present project is that depression was operationalized on a continuous scale using the CMDI, as opposed to using a diagnostic interview to distinguish between sub-threshold 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 sub-threshold 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.

There are also limitations to the way that coping and cognitive dysfunction were operationalized. While there is support in the literature for the notion that active coping leads to

more positive psychosocial outcomes and that avoidant coping leads to negative psychosocial outcomes (Arnett et al., 2002; Carver et al., 1989), it is important to keep in mind that these coping factors were not explicitly designed to be indices of adaptive and maladaptive coping *per se*. Additionally, there are two factors from the COPE that were not examined at all in the present analyses: one factor related to seeking social support, and another factor that is comprised of seemingly adaptive emotion-focused coping strategies. While less is known about these two coping factors, it is clear that these other coping behaviors must be considered in future work. A better understanding of how emotion focused coping and seeking social support operate in the context of active and avoidant coping would surely enrich an operationalization of clinically relevant coping behaviors.

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 prior 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 prior 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. A case could be made for expanding the cognitive index to include a comprehensive battery of measures spanning more domains of functioning. It is possible that cognitive dysfunction broadly—across a wide variety of domains—leads to depression via increased stress and decrements in cognitive resources needed for effective

coping. Conversely, however, it is also possible that the cognitive index in the present study is too broad, and a more specific operationalization of cognitive skills may be more robustly related to depression and coping in MS. Perhaps cognitive functioning should be operationalized differently for moderation and mediation analyses. It is plausible that cognitive domains in which deficits lead to the most stress are different from those cognitive domains most relevant for adaptive coping. Future work on the relationship between cognitive dysfunction and coping should address these issues.

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. Future work should aim to extend these findings by examining the efficacy coping-based interventions for the treatment of depression in MS. While there are studies that have evaluated CBT therapy in depressed individuals with MS (D. Mohr, 1999; D. C. Mohr et al., 2001; D.C. Mohr et al., 2003; D. C. Mohr et al., 2000), this work has not explicitly measured coping, or evaluated coping as a mediator or moderator of therapeutic change.

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 individuals with MS. 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 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.

These findings may also have implications for other patient groups. For example, some research suggest that similar issues may be relevant for individuals with traumatic brain injury with regards to the effects of cognitive dysfunction on coping (Krpan et al., 2007) and possible clinical implications of cognitive deficits (Hibbard et al., 2005; Whitehouse, 1994).

Furthermore, the results of the present study may potentially have broader implications regarding the role of cognitive skills and coping behaviors in effective emotion regulation. These findings suggest that, at least in this patient group, cognitive functions are a significant emotion-regulation resource. It follows that cognitive and intellectual resources may have a significant impact on emotion regulation efficacy in the general population as well. This speculation may offer a mechanism by which talk therapy is an effective treatment for emotional disorders—learning and practicing coping skills in the context of therapy may relieve much of the cognitive burden that individuals face when coping with unfamiliar or unanticipated stressful situations. The results of the current study raise important and clinically relevant questions about coping, cognitive functioning, and emotional consequences in chronic disease and mental illness patient groups. The extent to which the present findings may or may not extend to other populations is an empirical question that should be addressed by future research.

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