The Pennsylvania State University

The Graduate School

College of the Liberal Arts

THE LONGITUDINAL RELATIONSHIP BETWEEN FATIGUE AND COGNITION: IS COPING STYLE A MODERATOR?

A Thesis in

Psychology

by

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Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Master of Science

May 2012

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ABSTRACT

Approximately 50 percent of patients with multiple sclerosis (MS) experience cognitive impairment, which adversely affects performance of daily activities. Although patients report that fatigue contributes to cognitive difficulties, results from previous empirical studies do not show a clear linear association. This study assesses coping style as a moderator of the relationship between fatigue and cognition in a longitudinal MS sample. 50 participants (39 female) with a clinical diagnosis of multiple sclerosis completed fatigue, coping, and cognitive measures and repeated the assessments three years later. Scores on the Fatigue Impact Scale at time 1 and measures of coping (COPE Active Factor, COPE Avoidant Factor, and a Composite Adaptive Coping Index of the difference between the Active and Avoidant Factors) at time 2 were modeled in regression analyses to predict performance on a battery of cognitive tests known to be sensitive to MS. The hypothesis of this study was that patients with reported high impact of fatigue on their functioning who generally use more adaptive coping strategies will have better cognitive functioning than patients who use less adaptive coping strategies, and patients with low impact of fatigue will have good cognitive functioning regardless of coping style. Results supported the hypothesis, showing that the Composite Adaptive Coping Index moderated the relationship between reported fatigue and performance on cognitive tests.

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Chapter 1

Introduction

Multiple sclerosis (MS) is a neurological disease, with pathophysiology including inflammation, demyelination and degeneration of axon fibers, and formation of lesions in the central nervous system (Compston & Coles, 2008). MS affects approximately 2.5 million people worldwide (Drew, Starkey, & Isler, 2009), 300,000 in the United States (Anderson, Ellenberg, Leventhal, Reingold, Rodriguez, & Silberberg, 1992), and occurs twice as often in women than in men. Common symptoms include physical difficulties like muscle weakness, gait and balance problems, and incontinence, as well as problems like fatigue, sleep disturbance, depression, anxiety, and cognitive impairment. Typical onset of MS occurs in early adulthood, without significantly shortening the lifespan, which gives special importance to patients' ability to negotiate distressing symptoms.

Cognitive difficulties are a particularly insidious result of MS, affecting about 50 percent of patients and contributing to an inability to perform daily activities (Rao, Leo, Bernardin, & Unverzagt, 1991a; Rao, Leo, Ellington, Nauertz, Bernardin, & Unverzagt, 1991b). Identification of factors that influence cognition, and treatments related to those factors, will greatly benefit this population. Patients often report that fatigue, which affects as many as 75 to 95 percent of those with MS (Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Lerdal, Celius, Krupp, & Dahl, 2007), impacts cognitive difficulties. However, empirical studies of the relationship between fatigue and cognition show mixed results (Diamond, Johnson, Kaufman, & Graves, 2008; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009; Parmenter, Denney, & Lynch, 2003). This type of inconsistency suggests that the lack of a robust effect may be due to the existence of moderators of the relationship between the two variables (Arnett, Barwick, & Beeney, 2008).

Although about half of people with multiple sclerosis will develop cognitive impairment, there are no clear methods for improving cognition. Many of these individuals develop the disease in early adulthood and are in need of treatments that will allow them to continue performing daily activities and lead a fulfilling life. The multiple sclerosis research literature has few longitudinal studies of psychological variables or studies of risk factors and moderators. Identification of risk and protective factors for cognitive impairment could greatly improve quality of life for people with multiple sclerosis. Fatigue and coping style are two variables that may be related to the development of cognitive impairment and are amenable to treatment- physical activity and medications alleviate fatigue for many people with MS, while psychotherapeutic techniques can teach active coping strategies and stress management. This study examines the relationship between fatigue and cognition over a three year period, and proposes that coping style will moderate the relationship. In particular, patients with high fatigue who have an overall adaptive coping style are predicted to experience better cognitive functioning than those with an overall less adaptive coping style.

Multiple Sclerosis Disease Characteristics

Diagnosis, pathophysiology, and clinical features

Multiple sclerosis is a degenerative neurological disease characterized by lesions which form in the brain and spinal cord as a result of inflammation, demyelination and remyelination of axons, and depletion of glial cells forming the myelin sheath (Compston & Coles, 2008). Loss of myelin around axons slows neural transmission and contributes to the physical, cognitive, and emotional consequences of the disease. Although diagnosis still relies mostly on clinical features, laboratory tests now supplement the diagnostic process. Neuroimaging detects some axon plaques, evoked potential studies indicate abnormal activation patterns, and cerebrospinal fluid and blood tests measure the levels of white blood cells and proteins associated with MS (Awad, Hemmer, Hartung, Kieseier, Bennett, & Stuve, 2010; Polman, Reingold, Edan, Filippi, Hartung, Kappos, Lublin, Metz, McFarland, O'Connor, Sandberg-Wollheim, Thompson, Weinshenker, & Wolinsky, 2005). A diagnosis of MS takes into account lesion locations, timing of exacerbations, and disease progression (Polman et al., 2005).

Patients with MS display a wide variety of possible symptoms. Common symptoms include pain, muscle weakness, movement and balance problems, incontinence, heat sensitivity, fatigue, sleep disturbance, and sexual dysfunction. Additional symptoms may include cognitive impairment, depression, anxiety, and other forms of psychological distress (Miller, 2001).

Periods of increased disease activity, commonly referred to as exacerbations or relapses, may be interspersed with periods of relative recovery or stability of symptoms. MS typically follows four different course types (relapsing-remitting, primary progressive, secondary progressive, progressive-relapsing), each characterized by rate of decline and some with a pattern of exacerbations or remissions (McDonald, Compston, Edan, Goodkin, Hartung, Lublin, McFarland, Paty, Polman, Reingold, Sandberg-Wollheim, Sibley, Thompson, van den Noort, Weinshenker, & Wolinsky, 2001). A relapsing-remitting course type involves distinct, alternating periods of exacerbations and recovery. People with primary progressive MS show a gradual and steady decline in functioning, while those with a secondary progressive course show an early period of relapse-remission followed by a steady progression of disability that occurs even between exacerbations. People with MS rarely follow a progressive-relapsing course, with steady decline in functioning from the beginning, interspersed with exacerbations and no remissions.

Etiology and epidemiology

The pathogenic etiology of multiple sclerosis is unclear, although clinicians and researchers commonly conceive of MS as a disease of neuroimmunology. Dysfunction of regulatory processes of the immune response could allow autoreactive cells to cross the blood-brain barrier and cause inflammation (Compston & Coles, 2008).

Sex, genes, and geographic location have been reported as indicators of risk for MS. Worldwide, MS has a higher incidence among females than males, and recent research shows that the ratio has been increasing over the past few decades (Koch-Henriksen & Sorensen, 2010). Epidemiological data shows a familial risk for MS, with a concordance rate for monozygotic twins at about 40 percent, compared to a rate of three percent for fraternal twins and non-twin siblings (Cook, 2001). Environmental factors also play a large part in the development of MS, but the precise contributing factors are unclear. Prevalence rates may vary by geographic location, with higher latitudes showing increased rates, and by genetic or ethnic ancestry (Cook, 2001). Fewer incidences of MS occur in Asian and South American populations than in European and North American groups, and diagnoses are rarely made in Black Africans. Environment during childhood is a major risk factor for MS; risk remains low for people born in countries where MS is uncommon if they move to more high risk regions after age 15.

Cognition in Multiple Sclerosis

Empirical research consistently shows a relationship between a multiple sclerosis diagnosis and development of cognitive impairment (Arnett, Higginson, Voss, Randolph, & Grandey, 2002; Cerezo Garcia, Martin Plasencia, Aladro Benito, Balseiro Gomez, & Rueda Marcos, 2009; Drew et al., 2009; Figved, Benedict, Klevan, Myhr, Nyland, Landro, Larsen, & Aarsland, 2008), with a prevalence of impairment estimated at 50 percent (Amato, Ponziani, Siracusa, &

Sorbi, 2001; Rao et al., 1991a). Cognitive impairment in multiple sclerosis may result from primary and secondary disease processes. Psychophysiology studies show a relationship between cognitive impairment and abnormal brain synchronicity, neurodegeneration, and other neuropathology (Arrondo, Alegre, Sepulcre, Iriarte, Artieda, & Villoslada, 2009). Several studies (Benedict, Bruce, Dwyer, Weinstock-Guttman, Tjoa, Tavazzi, Munschauer, & Zivadinov, 2007; Cerezo Garcia et al., 2009; Holtzer & Foley, 2009) show a specific association between multiple sclerosis and impaired performance on executive functioning tasks, which measure the broad category of cognition commonly conceptualized as encompassing attention, working memory, mental flexibility, problem-solving, and processing speed, among other functions. Many neuropsychological measures of cognition were designed to address abilities necessary for real tasks of everyday living, and research generally supports that these measures are ecologically valid (Cerezo Garcia et al., 2009; Kalmar, Gaudino, Moore, Halper, & Deluca, 2008; Lincoln & Radford, 2008; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994).

Some of the common physical and psychological consequences of multiple sclerosis, such as decreased physical activity, depression, and fatigue may also lead to development of cognitive impairment. For example, concurrent depression in patients with multiple sclerosis contributes to impairments in cognition, although the incidence of cognitive impairment occurs beyond that which researchers attribute to depression (Denney, Sworowski, & Lynch, 2005;

Diamond et al., 2008). Additional research will provide insight into the role of other secondary factors in MS.

Fatigue in Multiple Sclerosis

For many people with multiple sclerosis, fatigue emerges early in the course of the disease and persists over time (Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009). Fatigue is considered the most commonly reported symptom of MS, and twenty-eight percent of patients with MS report fatigue as one of their worst symptoms (Krupp et al., 1988; Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). The Multiple Sclerosis Council for Clinical Practice Guidelines defines fatigue as a lack of energy, physical feeling of tiredness, and exhaustion. Patients with MS often report that their fatigue is a major source of stress in their lives, interfering with the ability to engage in physical and social activities, like employment, and contributing to feelings of negative affect and psychological distress (Strober & Arnett, 2005). Research has not clearly identified the cause of fatigue in MS. Fatigue may be a primary result of the neurophysiological changes that are associated with MS since it worsens during periods of exacerbations, but there is no clear association between fatigue and disease course type or observable neurophysiology in imaging studies. Some research suggests that fatigue may be a secondary symptom associated with other common consequences of MS, such as physical disability, sleep disturbance, and depression (Krupp, 2003).

Fatigue is multidimensional, often conceived as including physical, mental, emotional, and social aspects (Bol et al., 2009; Fisk, Ritvo, Ross, Haase, Marrie, & Schlech, 1994b). Several empirical studies associate fatigue with physical and cognitive problems, as well as psychological symptoms like depression and anxiety. In all of these cases, the relationship between fatigue and other symptoms is unclear. The most consistent findings are a relationship between physical activity and physical fatigue and a relationship between fatigue and depression (Skerrett & Moss-Morris, 2006). Efforts to distinguish fatigue and depression in multiple sclerosis (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003; Mohr, Goodkin, Likosky, Beutler, Gatto, & Langan, 1997; Pittion-Vouyovitch, Debouverie, Guillemin, Vandenberghe, Anxionnat, & Vespignani, 2006; Randolph, Arnett, Higginson, & Voss, 2000) may provide important information about the nature of MS symptoms, their impact on quality of life, and development of appropriate interventions. When diagnosing depression in MS, clinicians must differentiate vegetative and non-vegetative symptoms. Vegetative symptoms of depression, such as sleep disturbance and changes in eating habits, may relate more to fatigue than depression in patients with MS.

Fatigue is hard to quantify; measures of the symptom are usually subjective but may also be based on performance, such as after an extended period of testing or other physical or mental exertion. Measures of fatigue sometimes differentiate between subcomponents like cognitive and physical fatigue. Cognitive fatigue refers to feelings of mental exhaustion and fogginess, while physical fatigue relates to a bodily experience of weakened muscles. Research sometimes distinguishes between state fatigue in the present moment and chronic fatigue that has been characteristic of the patient over a specified period of time. Researchers measure present state fatigue by self-report or induce it through experimental means. Epidemiological studies indicate that 70 percent of patients with MS who experience fatigue report that their fatigue is stable over time (Lerdal et al., 2007). Clinical interventions, including pharmacological agents and prescriptive physical activity, may relieve symptoms of fatigue in chronic illness like multiple sclerosis (Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007).

Relationship between Fatigue and Cognition in Multiple Sclerosis

Fatigue, as a significant source of stress for MS patients, could contribute to the development of cognitive impairment. Sustained negative somatic experiences and arousal can lead to biochemical and structural changes in the brain (Eriksen, Murison, Pensgaard, & Ursin, 2005), which in turn may cause cognitive impairment. While patients commonly report that their fatigue impairs cognitive abilities (Middleton, Denney, Lynch, & Parmenter, 2006), empirical studies show inconsistent results. Cross-sectional analyses show a mix of positive (Diamond et al., 2008; Krupp & Elkins, 2000; Parmenter et al., 2003) and negative findings (Morrow et al., 2009; Schwid, Petrie, Murray, Leitch, Bowen, Alquist, Pelligrino, Roberts, Harper-Bennie, Milan, Guisado, Luna, Montgomery, Lamparter, Ku, Lee, Goldwater, Cutter, & Webbon, 2003). These studies employ a variety of methods for measuring fatigue and its influence on cognition. One approach is to administer self-report questionnaires of general fatigue levels (i.e. Diamond et al., 2008), while another approach is to assess state fatigue at its reported highest and lowest point of the day (i.e. Parmenter et al., 2003). Furthermore, some experiments (i.e., Johnson, Lange, DeLuca, Korn, & Natelson, 1997) induce state fatigue by requiring participants to spend several hours completing a cognitive test battery prior to reporting fatigue. This research also varies in its use of multidimensional measures of fatigue like the Fatigue Impact Scale (FIS), which assesses physical, cognitive, and social fatigue, or more unitary measures of fatigue like the Fatigue Severity Scale (FSS), which focuses on physical fatigue.

Morrow and colleagues (2009) did not find significant results in cross-sectional and longitudinal analysis of the FSS and a battery of neuropsychological tests. The authors concluded that there is little empirical support for a linear relationship between fatigue and cognition in MS. The mixed results in this literature may partly relate to measurement differences, but the results also suggest the presence of moderating variables that previously have not been considered.

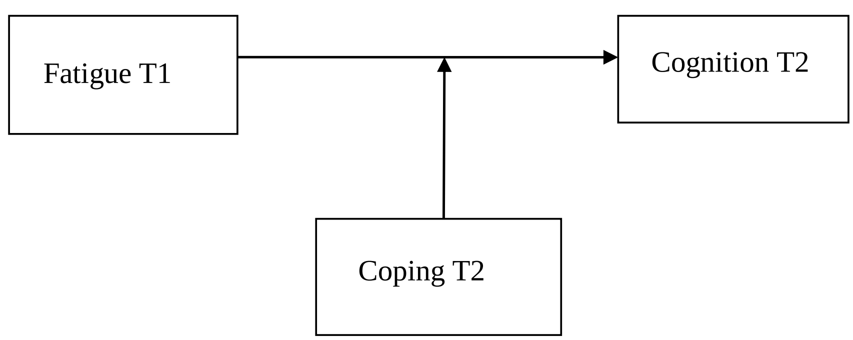
Some researchers have proposed an overlap in the constructs of cognitive fatigue and cognition, suggesting that cognitive fatigue is the subjective experience of impaired cognitive function. However, empirical research shows little correlation between MS patients' perceived and actual cognitive performance (Sherman, Rapport, & Ryan, 2008) and previous research does not consistently show a linear relationship between induced cognitive fatigue and cognitive performance (Bailey, Channon, & Beaumont, 2007; Paul, Beatty, Schneider, Blanco, & Hames, 1998). The experience of fatigue, which may be malleable, need not imply actual cognitive impairment. Further research of fatigue, especially chronic fatigue, and cognition will help to clarify their relationship.

Coping

When challenged by stress, people commonly respond by employing a set of coping strategies. The description and classification of coping strategies may distinguish adaptive and maladaptive types of coping, that is, explain which strategies best allow the individual to overcome stress and return to a healthy or desired state. Coping results from a conscious process for management of stress, as opposed to subconscious defense mechanisms (Somerfield & McCrae, 2000). Multiple conceptions of coping exist in the psychological literature, including a stage model of stress and coping developed by Lazarus and a model of behavioral self-regulation developed by Carver and Scheier. Lazarus identified stages of the coping process and two major types of coping. Problem-focused coping describes the process of taking action to alter a stressor and emotion-focused coping describes the process of trying to reduce the negative emotions associated with a stressor (Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen, 1986). Coping researchers frequently refer to this theory in discussion of strategies displayed by a population of interest e.g., (Lynch, Kroencke, & Denney, 2001; Montel & Bungener, 2007). In early research, problem- and emotion-focused coping served as a comprehensive description of coping, but this conception may oversimplify the range of possible coping strategies. Furthermore, problem- and emotion-focused coping do not represent unitary constructs distinguishing adaptive and maladaptive coping, and thus may not provide the most utility for predicting positive and negative outcomes (Aldwin, Folkman, Schaefer, Coyne, & Lazarus, 1980; Scheier, Weintraub, & Carver, 1986; Somerfield & McCrae, 2000).

Carver and colleagues (Carver, Scheier, & Weintraub, 1989) designed the self-regulation model as a theoretically and empirically derived model of coping. In this model, active coping refers to a set of typically adaptive strategies for taking action, planning a response, seeking social support, suppressing attention to competing activities, and exercising restraint from acting prematurely, while avoidant coping is comprised of typically less adaptive strategies associated with denial, focus on and venting of emotions, and behavioral and mental disengagement from goal attainment. An individual may not uniformly employ active or avoidant coping strategies to deal with stress. A composite assessment of active and avoidant coping may provide the best model of overall coping style. Theoretically, coping moderates or mediates the relationship between stress and illness. According to cognitive theories of stress, interpretation of physiological symptoms like fatigue as a sign of declining ability will adversely affect performance on functional tasks, possibly due to its effects on self-efficacy or neurobiological changes resulting from a sustained stress response (Bandura, 1986; Cioffi, 1991; Eriksen et al., 2005). People with multiple sclerosis may vary in their experience of fatigue and the way that they handle fatigue, particularly chronic fatigue, as a form of stress. Use of an overall more adaptive coping style may reduce stress and protect a highly fatigued person from experiencing cognitive problems, but use of an overall less adaptive coping style may lead to increased cognitive impairment. With these considerations, in mind, this study assessed the role of coping as a moderator in the relationship between fatigue and cognition (Figure 1).

Figure 1. Longitudinal relationship between fatigue and cognition, with coping as a moderator



Hypotheses

The main hypotheses for this study are:

1. Fatigue self-report scores at time 1 will predict cognitive performance at time 2. As fatigue increases, cognitive performance will decrease.

2. Coping style at time 2 will moderate the longitudinal relationship between fatigue at time 1 and cognition at time 2. Coping will provide a buffering effect on the inverse relationship between fatigue scores and cognitive performance.

In summary, the study predicts that in general those with poor outcomes- below average cognitive performance relative to others in the sample- will score higher on fatigue and score lower on composite adaptive coping, lower on active coping, or higher on avoidant coping. Conversely, those with better cognitive outcomes who have higher fatigue scores will score higher on composite adaptive coping, higher on active coping, or lower on avoidant coping. Since fatigue acts as a predictive stress in the model, the study also hypothesizes that participants with lower fatigue will have good outcomes, above average cognition, regardless of coping style.

Previous studies of fatigue and cognition do not specify a developmental relationship between the variables or only look at fatigue as a predictor of cognition. In order to further assess directionality in the longitudinal relationship between fatigue and cognition, the study also analyzed cognition as a predictor of later fatigue. Given the directionality of the above hypothesis, it was expected that cognitive performance at the first time point would not predict fatigue assessed at the second time point. It was further anticipated that coping and cognition would not interact to predict fatigue.

Chapter 2

Method

Participants and Data Collection

This study involved the retrospective analysis of data collected during a longitudinal investigation of cognitive and emotional functioning of people with multiple sclerosis in the Northwest region of the United States (Arnett, 2005; Arnett, Higginson, Voss, Bender, Wurst, & Tippin, 1999). Local neurologists and a local MS society chapter recruited participants for the study. Exclusion criteria included history of alcohol or drug abuse, a nervous system disorder other than MS, pre-morbid history of learning disability, severe motor or visual impairment that could interfere with cognitive testing, and inability to receive evaluation at the testing center. Each participant received a diagnosis of definite or probable MS, based on published criteria (Lublin & Reingold, 1996), from a board-certified neurologist. A patient received a diagnosis of probable MS if not meeting full criteria for clinical features or lab tests for MS. None of the participants were experiencing a clinical exacerbation of disease symptoms at the time of evaluation. Participants completed a comprehensive neuropsychological test battery and received written and verbal feedback as compensation. Participants were assessed twice over an interval of three years. All participants gave informed consent in accordance with institutional guidelines.

Seventy-nine participants completed the first time point of the study and 53 completed the second time point. Three participants were excluded from analysis due to missing data on primary psychological measures. The final sample of 50 participants included 38 females and had mostly relapsing-remitting (41 percent) and secondary progressive (18 percent) course types. Additional participant characteristics are reported in Table 1.

Table 1. Demographic and clinical characteristics

	Mean (SD) in years
Age	49.36 (7.7)
Education	15.18 (2.34)
Diagnosis Duration	10.40 (6.06)
	n (Percent)
Sex	
Females	38 (76%)
Males	12 (24%)
Disease Course	
Relapsing-remitting	31 (41%)
Primary Progressive	5 (7%)
Secondary Progressive	13 (17%)
Progressive-relapsing	1 (1%)

Measures

Fatigue

The Fatigue Impact Scale (FIS) measures the subjective extent to which fatigue has been a problem for physical, cognitive, and psychosocial functioning over the past month (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994a). Ratings on the 40 items range from 0= “No problem” to 4 = “Extreme problem”. Individual items describe the examinees’ experience with the reference statement “Because of my fatigue…” The physical fatigue subscale, consisting of ten items, includes the item, “I have to be careful about pacing my physical activities.” The cognitive fatigue subscale, consisting of ten items, includes the item, “I have difficulty paying attention for a long period of time.” The social fatigue subscale, consisting of 20 items, includes the item, “I am not able to provide as much emotional support to my family as I should.” Initial validation of the FIS showed good internal consistency reliability for the overall FIS (Cronbach’s alpha = 0.98) and the three subscales (all Cronbach’s alpha > 0.87) (Fisk et al., 1994b). The baseline FIS measure is the predictor variable for this study.

Cognitive Index

Cognitive functioning was measured with performance on a battery of neuropsychological tests, which previous studies show are sensitive to cognitive changes associated with multiple sclerosis (Arnett et al., 1999; Higginson, Arnett,

& Voss, 2000; Rabinowitz & Arnett, 2009). These tests primarily assess executive functions, including attentional capacity, working memory, and information processing speed. The Cognitive Index was created by averaging participants' standardized scores on five cognitive tests. A positive Cognitive Index score indicates above average performance in relation to the sample. The Cognitive Index from time 2 is the outcome variable in the longitudinal analysis.

Affective Reading Span Test

The Affective Reading Span Test measures working memory capacity. Participants read sentences while trying to hold a target word in memory, with a new target word after each sentence. For the purposes of this study, the key outcome index was the total number of words recalled, regardless of affective content.

Paced Auditory Serial Addition Task

The Paced Auditory Serial Addition Task measures attention and information processing speed (Gronwall, 1977). In this administration, participants listened to an audio tape of strings of numbers, with digits presented every three seconds. Participants added each digit to the one immediately preceding it. Scores were determined by the total number of correct additions out of a possible 60.

Symbol Digit Modalities Test

The Symbol Digit Modalities Test assesses attention and processing speed in a task requiring an oral response (Smith, 1968). Participants received a key of nine symbols, each with a corresponding digit underneath. The participants moved through a sequence of symbols and verbalized the appropriate number. Performance was based on the total number of correct responses in a 90 second period.

Tower of Hanoi

The Tower of Hanoi, administered on a computer, measures planning ability and strategy formation (Leon-Carrion, Morales, Forastero, Dominguez-Morales, Murillo, Jimenez-Baco, & Gordon, 1991). Participants saw three linearly positioned pegs on a screen. Initially, five disks are stacked in increasing size on the far right peg. Using the computer mouse, participants moved the disks in a way that results in the same pattern on the far left peg. The task consists of two blocks, with four trials each, administered approximately 30 minutes apart. Participants received instructions to complete the blocks as fast and in as few moves as possible. Scores were based on the amount of time and number of moves per trial from both blocks.

Visual Elevator

Visual Elevator, a subtest from the Test of Everyday Attention, was designed as an ecologically valid measure of speeded attention, cognitive flexibility, and working memory (Robertson et al., 1994). The Visual Elevator involves a series of visually presented elevators. The elevator starts on the first floor and moves one floor at a time according to the direction of intermittently presented arrows. Participants were required to say aloud the floor on which the elevator was located when presented with an elevator picture or say the direction the elevator was moving when presented with an arrow. The elevator switches directions a total of 40 times across ten trials. Participants received a score based on time per switch for correct trials.

Coping

Carver, Scheier, and Weintraub (1989) designed the COPE as a theoretically and empirically valid assessment of strategies that impede or contribute to adaptive coping. The instructions are as follows:

> *We are interested in how people respond when they confront difficult or stressful events in their lives. There are lots of ways to try to deal with stress. This questionnaire asks you to indicate what you generally do and feel, when* you *experience stressful events. Obviously, different events bring out somewhat different responses, but think about what you* usually *do when you are under a lot of stress.*

Participants rated 60 items by using a range from 1 = “I wouldn’t do this at all” to 4 = “I would do this a lot”. This study employed items from six scales in the COPE, and each scale includes four items. In the initial validation of the COPE, factor analysis showed that three scales formed a factor related to Active Coping: the Active Coping scale, Planning scale, and Suppression of Competing

Activities scale. These scales were seen as describing adaptive forms of coping, based on coping theory and similarity to other coping scales. The Active Coping scale includes items assessing the propensity to actively engage in steps toward overcoming a stressor. The Planning scale describes the process of thinking about the best strategies to deal with a problem. Suppression of Competing Activities includes items indicating focus on the stressor and suppression of attention to extraneous events.

In the initial validation study, three scales formed a factor related to Avoidant Coping: Behavioral Disengagement, Mental Disengagement, and Denial. These scales were thought to assess maladaptive coping strategies. The Denial scale assesses refusal to acknowledge the stressor or acting as if the stressor does not exist. The Mental Disengagement scale includes items describing use of distraction to avoid thinking about the stressor. The Behavioral Disengagement scale describes reduction of efforts to handle a stressor and giving up on attempts to obtain goals that the stressor obstructs.

To create potentially more unitary scales, in the present study Active and Avoidant Coping Factors were created through a factor analysis of participants' scores on items from the six scales identified by Carver and colleagues (1989). Items were subjected to a principal components analysis with varimax rotation to restrict correlation of factors. The number of factors to extract was fixed at two. The study retained items loading onto a factor at 0.4 or greater. Overall, the composition of the factors was consistent with *a priori* predictions, forming one factor largely consisting of items from the Active Coping, Planning, and

Suppression of Competing Activities scales, and another factor largely consisting of items from the Behavioral Disengagement, Mental Disengagement, and Denial scales. The exceptions were one Avoidant Coping item (Behavioral Disengagement, item 51) that loaded positively on one factor and negatively on the other, and two Active Coping items (Active Coping and Suppression of Competing Activities, items 15 and 58) that loaded negatively on the Avoidant Coping Factor but did not load on the Active Coping Factor. The raw data for these latter two items were re-coded so that the items would load positively on the Avoidant Coping Factor. For each factor, item scores were summed, and then the resulting raw factor scores were converted to Z-scores.

An individual can employ a combination of active and avoidant strategies and will not necessarily score high on one measure and low on the other. Using methods outlined in previous research (Rabinowitz & Arnett, 2009), a Composite Adaptive Coping Index was created to model overall coping style. The Avoidant Factor Z-scores were subtracted from the Active Coping Factor Z-scores to create a single coping score for each participant. The Composite Adaptive Coping Index provides a holistic construct of adaptive coping that is not captured by the Active or Avoidant Coping Factors alone.

Data Analysis

A longitudinal design allows for analysis of the developing relationship between the predictor and outcome variables, and the effects of other variables that may influence that relationship.

The model (Figure 1) placed the coping moderator variable at time 2, with the idea that the individual's coping style is important at the time of performance on cognitive testing. Nevertheless, coping theory posits that strategies for managing stress may be dispositional, and the COPE was designed to assess a stable pattern of coping (Carver et al., 1989). Thus, the coping variable could theoretically be placed at time 1 or time 2, and it is expected that the measures at both time points will be highly correlated.

This study analyzed moderation effects of active, avoidant, and composite adaptive coping on the longitudinal relationship between fatigue and cognition with the multiple linear regression forced entry method. Covariates were entered in the first step of the regression, followed by main and interaction terms in sequential steps. All significance tests used an alpha level of 0.05.

The analysis included 50 participants who completed at least 50 percent of the items on the FIS and the Active and Avoidant scales from the COPE. Calculations of Cognitive Index scores included means for participants who had data on at least three of the five cognitive measures, and who were missing less than 50 percent of the items on those measures. Three participants were excluded due to missing data.

Pearson correlation coefficients were calculated for all psychological measures in the study.

Coping as a moderator of the relationship between fatigue at baseline and later cognitive functioning

Calculation of three separate regression models of moderation for each coping variable tested the hypothesis that coping at time 2 moderated the relationship between fatigue at time 1 and cognition at time 2. The dependent variable was the cognitive index at time 2. In order to test the main effect of fatigue as a distal predictor of cognition, the FIS at time 1 was entered in the second step of the regression, after the covariate, Diagnosis Duration, in step one. In the first analysis, the Active Coping Factor at time 2 was entered in the third step of the regression. The second analysis entered the Avoidant Coping Factor at time 2 as a moderator in the third step. The third analysis entered the Composite Adaptive Coping Index at time 2 in the third step. For each analysis, the fatigue by coping interaction term was entered in the fourth step of the regression. The steps for each analysis are summarized in Table 2. It was expected that participants with higher fatigue who used more adaptive coping strategies would have better performance on the cognitive index than participants who use less adaptive coping.

Table 2. Primary regression analyses: Fatigue Impact Scale and Coping Factors predict performance on the Cognitive Index Secondary Analyses

	Variable	Analysis 1	Analysis 2	Analysis 3
Step 1	Covariate	Diagnosis Duration, Time 2	Diagnosis Duration, Time 2	Diagnosis Duration, Time 2
Step 2	Independent predictor	FIS, Time 1	FIS, Time 1	FIS, Time 1
Step 3	Moderator	Active COPE, Time 2	Avoidant COPE, Time 2	Composite Adaptive Coping Index, Time 2
Step 4	Interaction term	FIS*Active COPE	FIS*Avoidant COPE	FIS*Composite Adaptive Coping

Note: The dependent variable for all analyses is the Cognitive Index, time 2.

Secondary Analyses

Cognitive functioning as a predictor of later fatigue, and coping as a moderator of the relationship

In order to further assess the longitudinal relationship between fatigue and cognition and approach causality, this study also analyzed the reverse relationship to that outlined in the primary analyses. Calculation of three separate regression models for each coping variable tested whether coping at time 2 moderated a relationship between cognition at time 1 and fatigue at time 2. The dependent variable was fatigue at time 2. EDSS, disability score, significantly correlated with fatigue and was entered as a covariate in the first step. In order to test the main effect of cognition as a distal predictor of fatigue, the Cognitive Index at time 1 was entered in the second step of the regression. In the first analysis, the Active Coping Factor at time 2 was entered in the third step of the regression; in the second analysis, the Avoidant Coping Factor at time 2 was entered in the third step of the regression; and in the third analysis, the Composite Adaptive Coping Index at time 2 was entered third. For each analysis, the cognition at time 1 by coping at time 2 interaction term was entered in the fourth step. Table 3 summarizes the steps for each of these analyses. These analyses tested whether participants’ baseline cognitive performance predicted their later fatigue, and whether their coping style moderated the relationship.

Table 3. Secondary regression analyses: The Cognitive Index and Coping Factors predict performance on the Fatigue Impact Scale

	Variable	Analysis 1	Analysis 2	Analysis 3
Step 1	Covariate	EDSS, Time 2	EDSS, Time 2	EDSS, Time 2
Step 2	Independent predictor	Cognitive Index, Time 1	Cognitive Index, Time 1	Cognitive Index, Time 1
Step 3	Moderator	Active COPE, Time 2	Avoidant COPE, Time 2	Composite Adaptive Coping Index, Time 2
Step 4	Interaction term	Cognitive Index*Active COPE	Cognitive Index*Avoidant COPE	Cognitive Index*Composite Adaptive Coping

Note: The dependent variable for all analyses is the Fatigue Impact Scale, time 2.

Cognitive change

The main hypothesis proposed that fatigue and its interaction with coping would significantly predict later cognitive performance. However, baseline cognition would most likely be the best predictor of later cognition, and the real world importance of other variables could lie in their unique contribution to the effect. In other studies, initial cognitive performance is consistently the best predictor of later cognitive performance, including when accounting for practice effects (Duff, Beglinger, Moser, Paulsen, Schultz, & Arndt, 2010). The study also included post-hoc analysis of cognitive performance at the first time point as a predictor of cognitive performance at the second time point. It was hypothesized that initial cognitive performance would account for a significant amount of variance, but the main findings of the relationship between fatigue, coping, and cognition would also still be significant.

Cognition at time 1 was entered in the first step of the regression model along with diagnosis duration. As in the main analysis, baseline FIS was entered in second step, the COPE measured at time 2 was entered in the third step, and the interaction term was entered in the fourth step. As in other analyses, separate regression models analyzed the three different coping measures- the Active Coping Factor, Avoidant Coping Factor, and Composite Adaptive Coping Index. Table 4 summarizes the steps for these analyses.

Table 4. Secondary regression analyses: The Cognitive Index at baseline predicts later performance on the Cognitive Index

	Variable	Analysis 1	Analysis 2	Analysis 3
Step 1	Covariate	Diagnosis Duration, Time 2; Cognitive Index, Time 1	Diagnosis Duration, Time 2; Cognitive Index, Time 1	Diagnosis Duration, Time 2; Cognitive Index, Time 1
Step 2	Independent predictor	FIS, Time 1	FIS, Time 1	FIS, Time 1
Step 3	Moderator	Active COPE, Time 2	Avoidant COPE, Time 2	Composite Adaptive Coping Index, Time 2
Step 4	Interaction term	FIS*Active COPE	FIS*Avoidant COPE	FIS*Composite Adaptive Coping

Note: The dependent variable for all analyses is the Cognitive Index, time 2.

Chapter 3

Results

Main Analyses

Participant means scores on measures of interest are reported in Table 5. Pearson correlations between the measures are reported in Table 6. The FIS showed good internal consistency reliability for the overall FIS (Cronbach's alpha = 0.98) and the three subscales (all Cronbach's alpha ≥ 0.95).

Table 5. Participant scores on fatigue, coping, and disability measures

	M (SD)
FIS, Time 1	61.24 (34.93)
COPE Active items, Time 2	2.90 (0.68)
COPE Avoidant items, Time 2	1.88 (0.59)
EDSS	4.64 (1.60)

Note: FIS = Fatigue Impact Scale; EDSS = Expanded Disability Status Scale.

Table 6. Correlations between psychological and disease variables

	FIS, T1	FIS, T2	Active COPE	Avoidant COPE	Composite Adaptive Coping Index	Cognitive Index, T1	Cognitive Index, T2	Diagnosis Duration	EDSS
FIS, T1	1								
FIS, T2	.81**	1							
Active COPE	-.11	-.21	1						
Avoidant COPE	.44**	.42**	-.41**	1					
Composite Adaptive Coping Index	-.33*	-.37**	.84**	-.84**	1				
Cognitive Index, T1	-.26	-.22	.36*	-.47**	.50**	1			
Cognitive Index, T2	-.35*	-.34*	.35*	-.56**	.54**	.86**	1		
Diagnosis Duration	-.03	.01	-.24	.06	-.18	-.31*	-.30*	1	
EDSS	.32*	.52**	-.09	.08	-.10	-.27	-.28*	.22	1

*Note: **Correlation significant .01 level; *Correlation significant .05 level*

The results for all main regression analyses are summarized in Table 7. In the multiple regression analysis, diagnosis duration, the covariate, accounted for 8.8 percent of the variance in cognitive functioning ($\Delta F = 4.63$, $p < 0.05$). Fatigue level at baseline predicted performance in cognitive functioning at time 2 ($\Delta F = 7.73$, $p < 0.01$), accounting for 12.9 percent additional variance. The main effect of Active Coping at time 2 reached a trend level of significance ($\Delta F = 3.98$, $p = 0.05$), independently predicting 6.2 percent of the variance in cognitive performance; however, the interaction between fatigue and Active Coping was not significant ($\Delta F = 2.43$, $p > 0.05$).

In the Avoidant Coping analysis, the main effect of Avoidant Coping was significant ($\Delta F = 13.7$, $p < 0.05$), predicting 13.7 percent of the variance in cognitive functioning, and the interaction effect of fatigue and Avoidant Coping reached a trend level ($\Delta F = 3.66$, $p = 0.06$), accounting for 4.5 percent of the variance. Figure 2 shows the nature of the trend level interaction between the FIS and Avoidant Coping. Separate regression lines were calculated for the first and third quartile scores of the Cognitive Index.

The main and interaction effects of the Composite Adaptive Coping Index at time 2 were significant in predicting cognitive performance, accounting for 16 and 7.7 percent of independent variance, respectively (main effect $\Delta F = 11.8$, $p < 0.005$; interaction effect $\Delta F = 6.34$, $p < 0.05$). Figure 3 shows the nature of the interaction between the FIS and the Composite Adaptive Coping Index. Separate regression lines were calculated for the first and third quartile scores of the Cognitive Index.

Table 7. Longitudinal model primary regression analyses: main and interaction effects

		β	ΔR²	ΔF	p
Step 1	Diagnosis Duration	-0.22	0.09	4.63	<0.05
Step 2	FIS, T1	-1.25	0.13	7.73	<0.01
Step 3	Active COPE, T2	-0.10	0.06	3.98	0.05
Step 4	FIS, T1*Active COPE, T2 interaction	0.98	0.04	2.43	n.s.
Step 1	Diagnosis Duration	-0.28	0.09	4.63	<0.05
Step 2	FIS, T1	0.55	0.13	7.73	<0.01
Step 3	Avoidant COPE, T2	0.03	0.18	13.7	<0.005
Step 4	FIS 1*Avoidant COPE, T2 interaction	-1.04	0.05	3.66	n.s. (0.06)
Step 1	Diagnosis Duration	-0.22	0.09	4.63	<0.05
Step 2	FIS, T1	-0.20	0.13	7.73	<0.01
Step 3	Composite Adaptive COPE, T2	-0.12	0.16	11.8	<0.005
Step 4	FIS, T1*Composite Adaptive COPE, T2 interaction	0.62	0.08	6.34	<0.05

Note: The dependent variable for all analyses was the Cognitive Index, time 2; "n.s." = not significant.

Figure 2. Interaction graph for the trend-level moderating effect of Avoidant Coping on the relationship between the Fatigue Impact Scale (FIS) at time 1 and the Cognitive Index at time 2

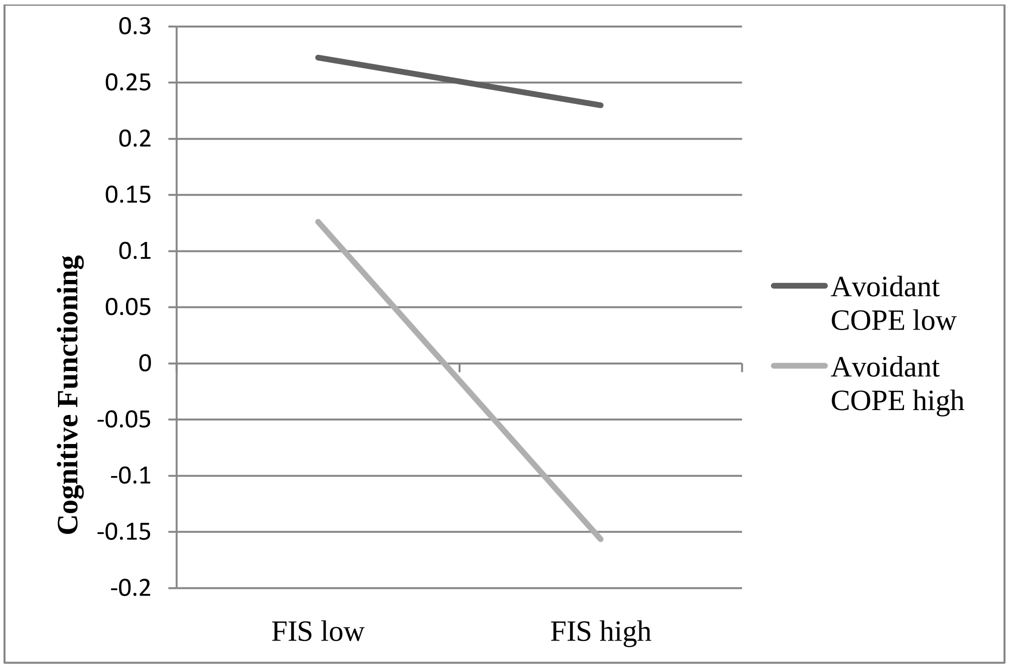
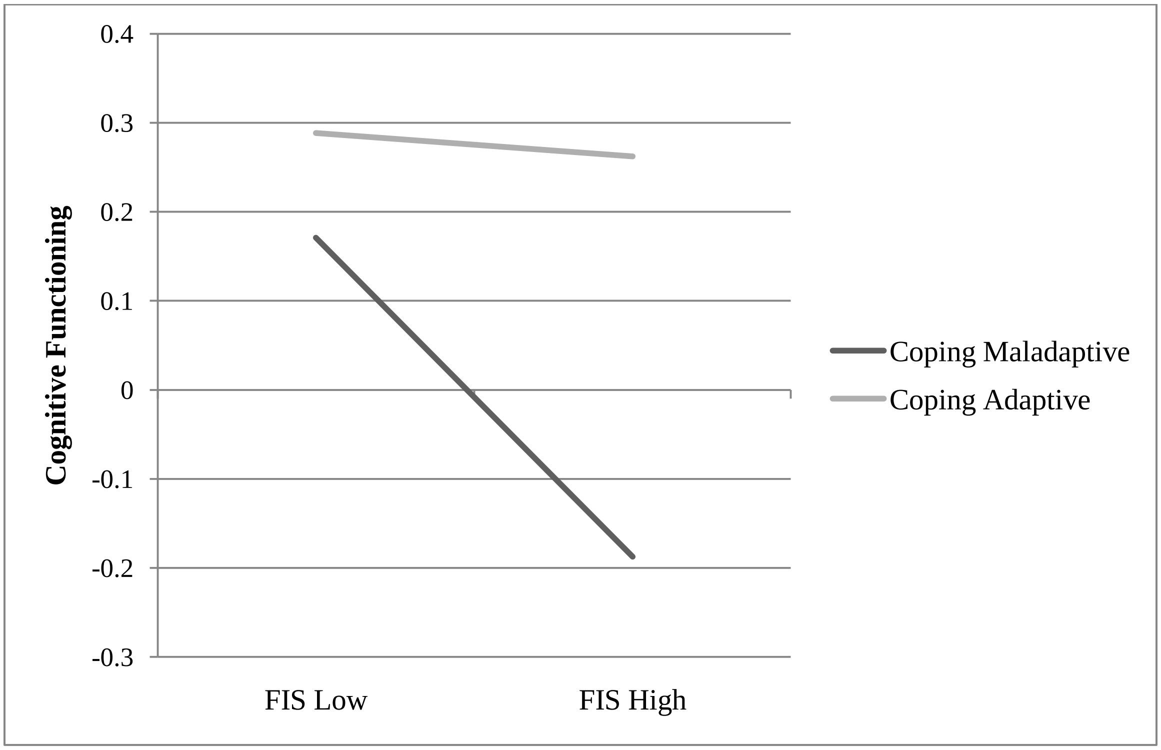


Figure 3. Interaction graph for the significant moderating effect of the Composite Adaptive Coping Index on the relationship between the Fatigue Impact Scale (FIS) at time 1 and the Cognitive Index at time 2



Case Studies

The relationship between the variables displayed in the main group-level analysis appears in the profiles of individual participants. For example, one participant had a high raw score of 113 on the Fatigue Impact Scale, more than a standard deviation above the mean, and the participant used mostly maladaptive coping strategies, with a Composite Adaptive Coping Index Z-score more than three standard deviations below the mean, -3.74. This participant’s cognitive functioning was poor relative to the group, with a Cognitive Index Z-score more than one standard deviation below the mean, -1.36. In contrast, another participant had a similarly high raw FIS score of 117, but the participant’s adaptive coping was more than two standard deviations above the mean, 2.19. This participant’s cognitive performance was just above average, 0.46. Thus, two participants who both reported a high impact of fatigue had very different performance on the cognitive tests, which was moderated by their relative use of adaptive or maladaptive coping strategies.

The group findings can also be illustrated in two participants who reported low fatigue. One participant who had a relatively low raw FIS score of 25 and favored the use of adaptive coping strategies, with Composite Adaptive Coping Index Z-score of 3.37, had a cognitive score just above average, 0.64. In comparison, a participant who had a similar low raw FIS score of 21 but used much less adaptive coping, scoring -1.81 on the Composite Adaptive Coping Index, still had a similarly above average cognitive performance score of 0.75. Thus, for individual participants who reported low impact of fatigue, they typically displayed above average cognition regardless of whether they used adaptive or maladaptive coping strategies.

Secondary Analyses

Predicting fatigue

Three separate multiple regression analyses tested the possibility that cognitive performance at time 1 predicted fatigue at time 2. Cognition at time 1, coping at time 2, and an interaction term of those two variables were included as predictors of fatigue at time 2 in the regression model and were entered in separate steps. Disability score measured at time 2 was included in the first step of the model as a covariate. Results of the analyses showed that disability predicted a significant amount of variance in time 2 fatigue ($\Delta F = 17.44$, $p = 0.00$, $\Delta R^2 = 0.27$). Time 1 cognition was entered in the second step of the model. Results did not show a significant main effect of cognition ($\Delta F = 0.50$, $p > 0.05$, $\Delta R^2 = 0.01$) in predicting fatigue. The time 2 coping variables were entered in the third step of separate analyses, and the interaction terms for time 2 coping and time 1 cognition were entered in the fourth step of each analysis. There was a significant main effect of the Composite Adaptive Coping Index in predicting fatigue ($\Delta F = 7.43$, $p < 0.01$, $\Delta R^2 = 0.10$) but there was not a significant interaction effect of adaptive coping and time 1 cognition ($\Delta F = 0.01$, $p > 0.05$, $\Delta R^2 = 0.00$). In the analysis of Avoidant Coping there was a significant main effect ($\Delta F = 11.13$, $p < 0.01$, $\Delta R^2 = 0.14$) but not an interaction effect with cognition ($\Delta F = 0.11$, $p > 0.05$, $\Delta R^2 = 0.00$). With Active Coping neither the main effect of coping ($\Delta F = 1.31$, $p > 0.05$, $\Delta R^2 = 0.02$) nor the interaction effect with cognition was significant ($\Delta F = 0.06$, $p > 0.05$, $\Delta R^2 = 0.00$). The results are summarized in Table 8.

Table 8. Longitudinal model secondary regression analyses for predicting fatigue: main and interaction effects

		β	ΔR^2	ΔF	p
Step 1	EDSS	0.50	0.27	17.44	0.00
Step 2	Cognitive Index, T1	-0.15	0.01	0.50	n.s.
Step 3	Active COPE, T2	-0.15	0.02	1.31	n.s.
Step 4	Cognitive Index, T1*Active COPE, T2 interaction	0.11	0.00	0.06	n.s.
Step 1	EDSS	0.52	0.27	17.44	<0.01
Step 2	Cognitive Index, T1	-0.01	0.01	0.50	n.s.
Step 3	Avoidant COPE, T2	0.44	0.14	11.13	<0.01
Step 4	Cognitive Index, T1*Avoidant COPE, T2 interaction	0.14	0.00	0.11	n.s.
Step 1	EDSS	0.51	0.27	17.44	<0.01
Step 2	Cognitive Index, T1	0.10	0.01	0.50	n.s.
Step 3	Composite Adaptive COPE, T2	-0.37	0.10	7.43	<0.01
Step 4	Cognitive Index, T1*Composite Adaptive COPE, T2 interaction	0.02	0.00	0.02	n.s.

Note: The dependent variable for all analyses was the Fatigue Impact Scale (FIS), time 2; "n.s." = not significant.

Cognitive change

In a set of regression analyses, cognition at time 1 was included as a covariate in a model using fatigue at time 1, coping at time 2, and their interaction to predict cognitive performance at time 2. Diagnosis duration at time 2 was also included as a covariate in the model. The two covariates accounted for a significant amount of the variance in time 2 cognition ($\Delta F = 68.7$, $p < 0.00$, $\Delta R^2 = 0.75$). The main effect of time 1 fatigue did not reach statistical significance, but it reached a trend level significance ($\Delta F = 3.71$, $p = 0.06$, $\Delta R^2 = 0.02$). With time 1 cognition, time 2 diagnosis duration, and time 1 fatigue in the model, none of the coping variables had a significant main effect in predicting cognitive performance, nor did the interaction term of fatigue and coping. The results are summarized in Table 9.

Table 9. Longitudinal model secondary regression analyses for cognitive change: main and interaction effects

		β	ΔR^2	ΔF	p
Step 1	Diagnosis Duration; Cognitive Index, T1	-0.04; 0.78	0.75	68.70	0.00
Step 2	FIS, T1	-0.65	0.02	3.71	n.s. (0.06)
Step 3	Active COPE, T2	-0.15	0.00	0.24	n.s.
Step 4	FIS, T1*Active COPE, T2 interaction	0.53	0.01	2.12	n.s.
Step 1	Diagnosis Duration; Cognitive Index, T1	-0.07; 0.72	0.75	68.70	0.00
Step 2	FIS, T1	0.16	0.02	3.71	n.s. (0.06)
Step 3	Avoidant COPE, T2	0.01	0.02	3.65	n.s.
Step 4	FIS 1*Avoidant COPE, T2 interaction	-0.38	0.01	1.12	n.s.
Step 1	Diagnosis Duration; Cognitive Index, T1	-0.06; 0.72	0.75	68.70	0.00
Step 2	FIS, T1	-0.12	0.02	3.71	n.s. (0.06)
Step 3	Composite Adaptive COPE, T2	-0.12	0.01	2.00	n.s.
Step 4	FIS, T1*Composite Adaptive COPE, T2 interaction	0.29	0.02	3.31	n.s.

Note: The dependent variable for all analyses was the Cognitive Index, time 2; "n.s." = not significant.

Chapter 4

Discussion

Hypothesis 1: Fatigue self-report scores at time 1 will predict cognitive performance at time 2. As fatigue increases, cognitive performance will decrease.

This study evaluated the relationship between self-reported fatigue and performance on a battery of cognitive tests in a community sample of people with multiple sclerosis. The study contributes to an understanding of how secondary factors influence the progression of cognitive problems in MS, showing a significant relationship with a moderate effect size between fatigue and cognitive performance three years later. The results support the study's first hypothesis, replicating some previous empirical research and clinical reports of a linear relationship between fatigue and cognition, while countering studies that did not find the effect. While a cross-sectional analysis would show only a correlation between variables at a single time point, the longitudinal study provides temporal separation of the variables for additional evidence of the possible development of cognitive impairment in people with multiple sclerosis who are highly affected by fatigue.

The result appears unidirectional- cognitive performance did not predict later fatigue levels. High fatigue may act as a source of stress that challenges patients' ability to manage daily activities, leading to progressive functional impairments, including cognitive impairment. The measure employed by this study, the Fatigue Impact Scale, specifically addressed the effect of fatigue in physical, cognitive, and psychosocial domains. With its three subscales, the FIS may provide a more comprehensive assessment of the multidimensional nature of fatigue than other measures, like the Fatigue Severity Scale, which assesses only physical and cognitive fatigue. Since the FIS assesses the impact of fatigue on functioning rather than the severity, one might surmise that the measure could confound with a coping variable. However, correlation analysis showed minimal overlap between the FIS and the Composite Adaptive Coping Index, with only 11 percent shared variance ($r = 0.33$). Impact of fatigue and the ability to deal with stress seem to be largely independent, and formed the basis for analysis of coping as a moderating variable. Additional research may help to clarify the specific mechanism by which fatigue may lead to cognitive impairment in MS, although much research shows that psychological variables, including depression and anxiety, influence cognitive functioning. Fatigue, acting as a multifaceted source of stress, may be more likely to have widespread effects on cognition than a specific effect on a single cognitive domain. Future studies may explore the susceptibility of different cognitive domains to fatigue effects.

Five tests were included in the Cognitive Index in order to provide a more comprehensive examination of cognition than use of performance on a single test as the outcome. These tests are sensitive to different cognitive changes that occur with MS. People with MS not only show variability in the experience of any cognitive problem, but also variability in the specific types of cognitive problems (i.e., memory or information processing speed) that develop. Analyzing results of a single test could impede detection of cognitive problems throughout the sample. Limited analytic power may have contributed to the mixed results found in previous studies.

Hypothesis 2: Coping style at time 2 will moderate the longitudinal relationship between fatigue at time 1 and cognition at time 2. Coping will provide a buffering effect on the inverse relationship between fatigue scores and cognitive performance.

The Active and Avoidant Coping Factors were created as psychometrically valid measures of coping styles. Only those items from the COPE subscales identified by Carver, Scheier, and Weintraub (1989) that loaded onto unitary active and avoidant coping constructs were included in the two factors for the study. Participants' overall coping style, as measured by a Composite Adaptive Coping Index, a composite of the Active and Avoidant Coping Factors, had a moderating influence on the inverse relationship between fatigue and cognitive performance. The result supports the second hypothesis of the study, modeled in Figure 1. Specifically, patients who reported that fatigue was having a large impact on physical, cognitive, and psychosocial functioning performed better on cognitive testing at the second time point if they used more active coping strategies, such as planning, than avoidant coping. These results agree with previous research showing that people who use more active coping and less avoidant coping strategies are better equipped to deal with stressors (e.g. Arnett et al., 2002; Rabinowitz & Arnett, 2009), and the study provides additional evidence that coping style buffers the negative effects of fatigue.

Although in the individual active and avoidant coping analyses neither coping style had a significant interaction with fatigue in predicting cognitive performance, avoidant coping reached a statistical trend level of significance. Use of avoidant strategies- denial, behavioral disengagement, and mental disengagement- could have a greater influence on development of cognitive impairment than use of active coping, perhaps by re-directing cognitive resources that are necessary to maintain functioning. The psychometric properties of the factors probably did not play a role in the stronger effect of avoidant coping, since the Active Factor was “purer”, consisting of more items that were characterized by Carver and colleagues as contributing to active coping.

On average, the magnitude of variance in cognitive performance accounted for by active and avoidant coping differed, with avoidant coping conferring a larger amount of variance; they did not simply have inverse effects. However, most participants reported use of some active and some avoidant coping strategies, with the proportion of each varying among individuals. Creation of the Composite Adaptive Coping Index allowed for quantification of overall coping style and the method of using the difference between standardized Active and Avoidant COPE Factor scores (Active minus Avoidant) was deemed the best way to measure adaptive coping. A ratio or multiple would change the magnitude of the relationship and the size of the sample limited power to conduct a regression analysis with a three-way interaction term for fatigue and active and avoidant coping. An index based on the difference score does not show the full distribution of coping styles in cases where individuals are high on both or low on both active and avoidant coping; in those cases participants would all have an index score equal to zero, along with participants who scored average on active and avoidant coping. However, there were no such cases in this sample of extreme scores in the same direction for both factors.

Looking at specific cases helps to reveal the nature of the Composite Adaptive Coping Index. Individuals with very different scores on the individual Active and Avoidant Coping Factors may have similar scores on the Composite Adaptive Coping Index. For example, one participant had an Active Factor Z-score of 0.13 and Avoidant Factor Z-score of 0.12; the Composite Adaptive Coping Index score for this individual was 0.01, an average score. In comparison, another participant scored 0.88 on the Active Factor and 0.84 on the Avoidant Factor, for a Composite Adaptive Coping Index score of 0.04; although the individual was nearly a standard deviation above average for each type of coping, the result was also an average composite index score.

The profile for individuals with the same composite score may look even more disparate. Two participants had similar scores of -2.73 and -2.79 on the Composite Adaptive Coping Index, which indicates overall use of mostly avoidant coping. In the first case, the individual scored more than one standard deviation below the mean on the Active Coping Factor and more than one standard deviation above the mean on the Avoidant Factor; in the second case, the individual scored more than two standard deviations below the mean on the

Active Factor and near the mean on the Avoidant Factor. While the underlying factor profiles may vary, the results of the study seem to indicate that the overall coping style is most important in predicting the outcome variable. In this study, the interaction of the FIS and the Composite Adaptive Coping Index predicted the outcome variable while the interaction of the FIS with the unitary coping factors did not. People who use adaptive coping seem more able to manage stress to the extent that they do not show impaired performance on objective tests of cognition. In the real world, this could translate to better functioning for this group at work and in their daily routine. In the secondary analysis, coping variables were used to predict fatigue. Interestingly, adaptive coping style again predicted a significant amount of variance in the outcome, which suggests that coping style may be a valuable predictor of functioning in people with MS.

Clinical Implications

The results of the study provide potentially beneficial information for understanding of the prognosis and improving the treatment of patients with multiple sclerosis. The progressive disease leads to cognitive impairment for a large proportion of individuals. The present study supports the idea that cognitive performance at one time best predicts future performance, and thus knowledge of current cognitive status may help to identify those at risk of cognitive impairment. However, currently no treatments exist that directly target cognition. Medications help to slow the development of neuropathology and could protect against cognitive impairment, but patients need additional means.

Increased attention to the importance of managing fatigue, one of the most commonly reported symptoms of MS, may be beneficial. Management of fatigue could include medication, exercise, or psychotherapy. In particular, psychotherapy that helps patients with a combination of increasing active coping strategies and decreasing avoidant coping strategies may lessen the impact of high levels of fatigue on cognitive functioning. In determining patients most at risk for developing cognitive impairments, which could lead to functional disability, clinicians may assess sources of patients' stress, like fatigue, and strategies for coping with stress. Patients who do not seem to manage stress well or have poor psychological health may be most at risk for developing debilitating impairments. Other conditions related to reactions to stress, like anxiety and depression, also seem likely to have similar effects on progression of functional abilities in neuropsychological disorders. Inclusion of coping and stress measures in assessment of individuals with clinical disorders could supplement reports of psychosocial risk and protective factors. The Ways of Coping questionnaire has been used clinically, but the COPE thus far has primarily been a research tool. Creation of validated norms for evaluation of clinical populations with the COPE could be a valuable clinical tool.

The Cognitive Index in the present study consisted of neuropsychological tests known as ecologically valid or sensitive to cognitive changes that occur in people with MS. Accordingly, the cognitive changes seen in the sample over the two time points potentially reflect observable changes in abilities that affect daily functioning. Observing changes in the group's cognitive functioning over the three year period allowed for the investigation of moderating risk and protective variables in the progression of disease impairment. Decreased cognitive functioning in multiple sclerosis has been associated with increased rates of depression, job instability, and other negative consequences on daily life (Rao et al., 1991a; Rao et al., 1991b). Especially given the typically normal lifespan of people with multiple sclerosis, each of these factors proves important in maintenance of quality of life.

Limitations

Although coping is a large area of research in clinical psychology, there remains disagreement about the best way to measure coping. The COPE attempts to narrow the focus of types of coping behavior and the frame of reference for a stressful event. Some researchers argue that the frame of a coping measure should be specific to the situation of interest. The dispositional frame of reference in the COPE, general response to stressful events, may call for a different type of coping than the hassles of living with a neurological illness. More specifically, in a study of fatigue as a form of stress, the best measure may be one that directly addresses how participants cope with fatigue. Creating a validated coping measure for every potential form of stress would be a challenge but may represent the ideal. Still a comprehensive measure such as the COPE provides a general picture of an individual’s way of dealing with a specific stressful event.

Of the 79 people who participated in the first time point of the study, 53 participated in the follow-up study and 50 of those met criteria for inclusion in this study. The group of participants who did not complete all parts of the study may not have been random. The most disabled participants may be most likely to not return or have difficulty completing all tasks, resulting in exclusion from analysis. As stated above, the primary measures in this study do not have standardized norms, and that hinders comparison of the scores of these participants to a wider population of people with MS or healthy individuals. Thus, one can only determine participants who are high or low on each of the measures relative to the other participants in the sample. Given an average EDSS score of 4.64, the sample as a whole had moderate disability. Additional research with a lower functioning sample, including participants who likely experience higher levels of fatigue and cognitive impairment and potentially different coping strategies, may reveal different relationships among the variables.

Conclusion

Taken together, the results of the study indicate that fatigue levels of people with multiple sclerosis are a significant predictor of their later cognitive performance. Those who reported a significant impact of fatigue on their functioning were more likely to show cognitive problems later on, but the reverse relationship did not hold true; cognitive performance did not predict impairment from fatigue. In addition, overall coping style was related to both fatigue and cognition, and coping style buffered the inverse relationship between those two variables. When assessing overall coping style, combined information about the use of adaptive and maladaptive strategies had the strongest predictive value, and those who used mostly adaptive coping strategies were likely to have better cognitive functioning. These results may help to inform both future research and clinical practice in identifying risk and protective factors for cognitive problems in this population.

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