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COMPREHENSIVE EXAMINATION OF FACTORS CONTRIBUTING TO EMPLOYMENT STATUS IN MULTIPLE SCLEROSIS

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ABSTRACT

Objective: Unemployment is common among individuals with Multiple Sclerosis (MS) and is associated with significant socioeconomic burden. Several MS-related factors have been found to be associated with unemployment status including fatigue, depression, cognitive problems, and motor difficulties. However, few studies have examined these factors collectively in predicting employment. The present study aimed to explore these variables together in predicting employment status in MS. Patients and Methods: Fifty-three individuals with MS participating in a research study of cognitive, emotional, and social factors related to MS were examined. Construct scores were created using factor analysis that represented cognition, fatigue, depression, and motor function. These construct scores, along with age and measures of disease burden, were explored as predictors of unemployment status (not working, working) via logistic regression. Models of mediation were also investigated. Results: A model including construct scores of motor function, cognition, depression, and fatigue significantly distinguished those who are unemployed from employed. However, only the cognitive, motor, and fatigue construct scores were found to be significantly associated with unemployment individually. Results of a mediation analysis indicated that the cognitive and fatigue construct scores significantly mediated the relationship of disability (EDSS) on work status. More specifically, processing speed and memory mediated the relationship of overall disability on work status. Conclusion: Cognitive function and fatigue mediate the effect of MS disability on employment status. Interventions targeting cognitive difficulties and fatigue in MS may be effective in helping individuals to maintain employment.

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Introduction

Overview

Multiple sclerosis (MS) is an autoimmune disorder marked by chronic inflammation of the central nervous system (CNS). It has a complex etiology involving both genetic susceptibility and exposure to factors in the environment. The immune systems of individuals with MS mistakenly identify myelin, the fatty insulation surrounding axons, as 'non-self' and thus attack and destroy the substance. The qualitative nature of symptoms depends upon the location of the damage and can include muscle weakness, loss of sensation, mental and physical fatigue, visual impairment, sexual dysfunction, cognitive decline, and depression (Arnett, Barwick, & Beeney, 2008; Frank & Elliott, 2000). Recent studies suggest that less visible symptoms like chronic fatigue and mood disruptions can be more distressing than visible symptoms such as physical limitations (White, White, & Russell, 2008). However, all symptoms of MS can be limiting. Unfortunately, there is no known cure for MS; current treatment involves regular use of disease-modifying agents or, when necessary, weekly steroid injections to depress the immune system (The National MS Society, 2015). Therefore, individuals when diagnosed with MS face a long, often expensive, disease course. To make matters worse, unemployment, secondary to disease symptoms, is common among individuals with MS. Currently there is no consent among the existing literature about what symptoms are most predictive of unemployment status. Generally vocational advice given by health professionals is based on measures of gross overall disease burden (Pompeii, Moon, & McCrory, 2005), which provides little room for interventions to target symptoms specifically contributing to unemployment. With these considerations

in mind, this study proposes to comprehensively examine four common symptom clusters associated with unemployment in MS- cognition, fatigue, depression, and motor skills, in addition to age and measures of overall disability, to identify which symptoms most proximately contribute to unemployment.

Pathophysiology of MS

MS is marked by dysfunctional activity in the immune system. Individuals with MS tend to present certain histocompatibility leukocyte antigen (HLA) class II receptors, due to genetic predisposition, on their antigen presenting cells (Sospedra & Martin, 2005). These particular HLA class II receptors are structurally more likely to expose proteins that are similar to myelin basic protein as 'non-self' to immune system components. Susceptible genes coding for the HLA are thought to account for 10%-60% of the genetic risk of MS (Haines et al., 1998). In MS, CD4+ T cells become particularly activated by HLA class II receptors and thus become reactive against self. These auto-reactive T-cells often become further activated by an infection. The purported mechanism of the infection is that it acts either in a 'molecular mimicry' way or a 'by-stander activation' way or both (Sospedra & Martin, 2005). In 'molecular mimicry,' the infectious antigen shares a similar structure to a 'self' myelin peptide and thus activates T-cells to myelin as well as the infectious agent. In 'bystander activation,' the general immune response to the infection creates a cytokine profile that activates already present myelin auto-reactive T-cells (a result of the genetic profile of the HLA receptors) (Sospedra & Martin, 2005). Additionally, this infection is thought to compromise the integrity of the blood brain barrier (Schoenberg & Scott, 2011).

The auto reactive T-cells bind to the endothelium of the compromised blood brain barrier and enter it through cerebrovascular endothelial cells. Once inside the CNS, the T-cells react with the myelin protein surrounding the axon of the neurons. This reaction creates a release of inflammatory mediating cytokines (specifically IFN-γ, IL-23, TNF- α, LT, as well as others) and chemokines (RANTES, IP-10, IL-8,) which activate local immune cells (such as microglia) and recruit additional immune components to the area, including B-cells, antibodies, complement, monocytes, and mast cells (Sospedra & Martin, 2005). The recruited B-cells become activated by the already present T-cells in the area and thus release auto-antibodies. The majority of the damage from this point on is caused by the formation of an inflammatory lesion around the CNS tissue by the newly recruited white blood cells (Sospedra & Martin, 2005). Formation of inflammatory lesions is clinically called an attack or flare up. During an attack or flare up, myelin is attacked and communication between neurons in the CNS is severely compromised secondary to decreases in axonal insulation. Long-term compromise of neural communication can eventually lead to neural death. The combination of both decreased efficacy of communication between neurons and intermittent neural death is responsible for the observed symptoms of MS.

Diagnosis and Prevalence

The first symptoms of MS usually occur in early adulthood between the ages of 20 and 40 (Schoenberg & Scott, 2011). More than 50% of the time, presenting symptoms include sensory disturbance of the limbs (e.g., numbness or tingling), visual disturbances (e.g., partial or complete vision loss), or motor disturbances (e.g., loss of coordination or

clumsiness) (Murray, 2005). The most commonly used diagnostic criteria for MS were developed by McDonald et al. in 2001 and involve confirmation of clinical attacks (as indicated by symptoms) and clinical lesions in the brain or spinal cord (as indicated by MRI) disseminated in space and time. Additional information such as the proportion of the inflammatory antibody IgG in the cerebral spinal fluid (CSF) can also be used in making diagnostic decisions.

MS has four clinical patterns of disease activity know as course types. The four course types include: relapsing remitting, secondary progressive, primary progressive, and progressive relapsing. The majority of MS cases begin as the relapsing remitting course type, which is distinguished from the other course types by acute, unpredictable attacks that remit or completely resolve after a period of time. About 80% of relapsing remitting cases convert to a secondary progressive course type with time, making it the second most common disease course. Secondary progressive courses are similar to relapsing remitting courses with the exception that individuals experience neurological decline between their attacks that does not remit. Primary progressive MS is the third most common course type and affects about 10% of those with MS. This course is demarcated by steady neurological decline without clear attacks. Progressive relapsing is the least common course type and is similar to primary progressive MS in that it is also characterized by a steady neurological decline. However, in this course type the individual also suffers acute attacks (Schoenberg & Scott, 2011).

MS is disproportionally more common in women than men by a factor of two to three (Schoenberg & Scott, 2011). Onset of MS in women is estimated to occur 5 years earlier than onset in men (Murray, 2005). MS occurs predominantly in the Caucasian

population and is most common in individuals of northern European decent. Interestingly, individuals who spent their childhoods in northern latitudes are at a higher risk of developing MS. Depending on the racial composition and latitude of the country, the prevalence of MS ranges from 2 to 150 affected per 100,000 individuals (Schoenberg & Scott, 2011). It is estimated that more than 400,000 individuals in the Unites States and 2.5 million world-wide have MS. Two-hundred new cases are diagnosed every day in the United Sates (Healthline, 2015).

Symptoms

Chronic symptoms of MS fit loosely into four categories: fatigue, cognitive decline, physical/motor difficulties, and mood disturbances

Fatigue is the most common symptom of MS and is thought to be a problem for over 80% of individuals with the disease. A seminal study on fatigue in MS found that 28% percent of individuals with MS report fatigue as their worst symptom. This same study also found that more than half of those reporting fatigue as a symptom of MS experience it at the moderate to severe level. Unlike fatigue in healthy individuals, research suggests that fatigue in MS feels substantially different and limits the individual from participating in daily activities (Krupp & Christodoulou, 2001). Although, recent research suggests that fatigue is likely the result of neurophysiological changes associated with MS (Krupp, 2003; Krupp & Christodoulou, 2001), no clear etiology for fatigue has been determined. Thus, fatigue could be secondary to other MS symptoms like depression and motor difficulties.

The lifetime prevalence rate for depression in individuals with MS is around 50%; this figure is striking when compared to the 17% depression lifetime prevalence rate of the general population (American Psychiatric Association, 2013; Patten & Metz, 1997; Sadovnick et al., 1996). According to a review conducted in 2008, the risk for depression increases at the onset of MS and about 10% of the variance in depression can be attributed to overall disease burden as the disease progresses (Arnett, Barwick, et al., 2008). The remaining variance is likely explained by MS symptoms such as pain, cognitive difficulties, fatigue, and motor difficulties moderated by lifestyle factors such as coping style, social support, and stress levels.

About half of individuals with MS experience decline in cognitive functioning as the disease progresses (Amato, Ponziani, Siracusa, & Sorbi, 2001; Beatty & Aupperle, 2002; Schoenberg & Scott, 2011), with some research suggesting that cognitive decline can start to occur even early on in this disease course (Amato et al., 2001). Neuropsychological domains most commonly afflicted include memory, working memory, and processing speed. Memory problems have been reported in 40-60% of individuals, with explicit memory for recent events being reported as the most troublesome (Rao, 1995). Slowed processing speed is the most commonly found neuropsychological deficit in MS and is thought to, on some level, underlie other cognitive difficulties in MS. Specifically, impaired working memory in MS is thought to be particularly related to slowed processing speed (Schoenberg & Scott, 2011). Difficulties with executive functioning, attention, and language functions in MS are also well-accepted. Evidence for a moderate relationship between neuroanatomical measures

(e.g., lesion load and atrophy) and cognitive decline has also been determined (Benedict et al., 2006; Schoenberg & Scott, 2011).

Motor symptoms are often the most obvious symptoms of MS due to their outward visibility. Individuals with MS often experience difficulty with gross motor movement (e.g. walking and balance), fine motor skills (e.g., writing or typing), and oral-motor sequences (e.g., talking) (Beers et al., 2003). One study found that nearly half of the individuals surveyed for their study owned or rented an assistive device during the course of their MS to aid with their mobility (Finlayson, Guglielmello, & Liefer, 2001). Traditionally, overall disability is measured by examining difficulties primarily in the motor domain (Rao, 1990b).

Unemployment in MS

Unemployment is common among individuals with MS and is associated with significant socioeconomic burden. The relationship between MS and unemployment has been well documented, with the rate of unemployment in MS falling between 22% and 80% (Busche, Fisk, Murray, & Metz, 2003). This large range is most likely due to variation in disability of the study samples and year of publication (with individuals in recent studies presumably having access to more effective disease modifying medication). A recently published large-scale study found that employment rates in an MS population are affected up to 8 years prior to diagnosis, compared to a control population, and continue to drop steadily after diagnosis is confirmed (Jennum, Wanscher, Frederiksen, & Kjellberg, 2012). Results from a longitudinal study found that only 50% of individuals with MS were employed at baseline; additionally, after about two-and-a-half years, 22%

of those previously employed became unemployed (Busche et al., 2003). Unfortunately, once an individual becomes unemployed they may struggle to regain full-time employment for fear of losing their vital disability benefits. This predicament is known as the disability trap (Turkewitz & Linderman, 2012).

The mean age range of unemployment among individuals with MS ranges from about 49 - 52 (O'Connor, Cano, Ramio i Torrenta, Thompson, & Playford, 2005; Smith & Arnett, 2005). Overall it appears that individuals with MS leave their jobs somewhere in their late 40s to early 50s. Peak earning years are late 50s for college graduates and early 40s for non-college graduates (Monk-Turner, 1995). This suggests that many individuals with MS are leaving the workforce prior to or during the time when most are at their earning peak. Obvious sequelae of this juxtaposition are financial issues concerning saving for retirement, supporting children, and/or supporting aging parents. It has been documented that employment status and household income are closely related to quality of life measures in individuals with MS (Aronson, 1997; Glanz et al., 2012; Miller & Dishon, 2006). Further research on possible areas of intervention that might keep individuals with MS employed longer is clearly needed

Predictors of Unemployment in MS

Several demographic and illness-related factors have been found to be associated with employment status in MS including disease duration, course type, age, years of education, sex, and general disability (Glad, Nyland, Aarseth, Riise, & Myhr, 2010; Glanz et al., 2012; Gronning, Hannisdal, & Mellgren, 1990; Honarmand, Akbar, Kou, & Feinstein, 2011; Larocca, Kalb, Scheinberg, & Kendall, 1985; Smith & Arnett, 2005).

Other MS symptom-related factors have also been found to predict employment status including fatigue (Smith & Arnett, 2005; Uccelli, Specchia, Battaglia, & Miller, 2009), depression (Glad et al., 2010; Glanz et al., 2012; Honarmand et al., 2011), motor difficulties (Julian, Vella, Vollmer, Hadjimichael, & Mohr, 2008), and cognitive problems (Covey, Shucard, Shucard, Stegen, & Benedict, 2012; Rao et al., 1991). More specifically regarding cognitive problems, tests of processing speed, verbal fluency, working memory, and long-term memory are typically lower in unemployed versus employed individuals with MS (Honarmand et al., 2011; Morrow et al., 2010; Strober et al., 2012).

With all this said, research on cognition and depression has produced inconsistent findings. Regarding cognition, though most studies have found it to be associated with employment status, some have not (Smith & Arnett, 2005). Additionally, significant relationships between executive function and employment have sometimes been shown to be mediated by fatigue (Covey et al., 2012). Depression research has also yielded inconsistent findings, with one study finding the opposite result of what has been typical, with the employed group having higher depression scores than the unemployed group (Smith & Arnett, 2005). Some of these inconsistencies may be due to different operationalizations of these factors across studies. Additionally, it is possible that these inconsistencies can be explained by variations across studies in the factors that were statistically controlled in researchers' models. It is evident that a more comprehensive look at these four key MS symptom-related factors (i.e., depression, cognition, fatigue, and motor functioning) in predicting employment status is needed, as they very likely covary with each other and overall disease burden. Notably, no research examining which

symptoms mediate the relationship between demographic (e.g., age) and illness related variables (e.g., EDSS and disease duration) on employment status exists. Given that demographic and illness related variables are not realistic points of intervention (i.e., individuals cannot change their age or how long they have had MS), identification of more proximal predictors of unemployment is needed.

To my knowledge, there are no published studies that have examined these four key symptoms together, as constructs, in predicting employment status. Therefore, the present study aims to create construct scores for depression, cognition, fatigue, and motor symptoms and explore these construct scores, along with demographic and illness related variables, in predicting employment status in MS.

Using these goals as a guide the proposed study will evaluate the following hypotheses:

1) Construct scores for cognition, fatigue, depression, and motor functioning as a group, will significantly predict employment status.
2) Age and measures of disease burden (disease duration and EDSS) will predict employment status.
3) The predictive relationship of age and measures of disease burden (EDSS and disease duration) on employment status will be mediated, in parallel, by the construct scores of cognition, motor function, fatigue, and depression.

Methods

Procedure

This study involves the retrospective analysis of data collected during a longitudinal investigation of cognitive, emotional, and social factors related to MS. A psychosocial interview was administered at the beginning of the testing session in order to collect demographic information. Cognitive tasks, motor tasks, and measures of fatigue and depression were administered by a clinical psychology doctoral student within one three to four hour session. Frequent breaks were offered throughout the testing session to counter the effects of fatigue.

Analyses for this project were run exclusively on data collected during the second phase of the study, which occurred between 2004 and 2008 (Arnett, 2005), and thus are cross-sectional in nature.

Participants

Participants were recruited from neurologists and MS society newsletters in greater Pennsylvania. A positive diagnosis of Multiple Sclerosis, based on the 2001 McDonald et al. criteria, by a board-certified neurologist was the only inclusion requirement for this study. Prior to enrolling in the research study, potential participants were administered a structured telephone interview to screen them for eligibility. Individuals were excluded for any of the following: a) significant history of alcohol or drug abuse (e.g., history of/or current consumption of 4 to 6 drinks daily for 1 year) b) nervous system disorder other than MS (e.g, stroke, encephalitis); c) sensory impairment that would significantly interfere with testing (e.g., loss of vision); d) developmental

history of learning disability (LD) or attention deficit hyperactivity disorder (ADHD); e) significant medical condition, other than MS, that could interfere with cognitive or motor function (e.g., Myocardial infarction); f) relapse or corticosteroid use within four weeks of participation in the study; or g) physical or neurological impairment that would make testing impossible (e.g., if participant was bed bound or physically unable to move hands, speak, etc.). Neurological disability was evaluated using the Expanded Disability Status Scale (EDSS). The study was approved by the Institutional Review Board at The Pennsylvania State University and all participants signed an informed consent form prior to partaking in the study.

Fifty-nine individuals with MS (10 males and 49 females) were examined. Six participants were excluded from analyses because they indicated that their unemployment status was due to factors unrelated to their MS. Thus 53 participants (8 males and 45 females) were included in all of the regression analyses. There were 30 individuals with a relapsing-remitting course type, 17 with secondary progressive, 3 with primary progressive, and 3 with progressive relapsing course types. Thirty-three individuals were employed at the time of the study and 20 were currently unemployed. Of the 20 unemployed individuals, 13 were on disability, 4 were not on disability, and 3 were missing information about whether they were receiving disability. Four participants were not included in some analyses because data from four individual tasks were lost due to experimental error. See Table 1 for more information on participant demographics.

Table 1. Participant characteristics of people living with MS by employment status.

Demographic Characteristic	**Employed N= 33**	**Unemployed N= 20**	**Total Sample N= 53**
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	48.0 (8.0)	57.8 (8.5)	51.7 (9.4)
Education (years)	14.8 (2.1)	14.3 (2.1)	14.7 (2.1)
EDSS	3.8 (2.0)	5.0 (2.0)	4.2 (2.1)
Disease Duration (years)	12.5 (7.3)	19.1 (8.8)	15.0 (8.5)
	Percent	Percent	Percent
Percent Female	78%	95%	85%
Course Type			
Relapsing Remitting	64%	45%	57%
Secondary Progressive	24%	45%	32%
Primary Progressive	6%	5%	5.5%
Progressive Relapsing	6%	5%	5.5%
Percent on Disability	0%	65%	25%

Measures

Neuropsychological measures from Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-N), the Minimum Assessment of Cognitive Function in MS (MACFIMS), and the Multiple Sclerosis Functional Composite (MSFC) were selected to be included in the analyses to establish construct scores for cognitive and motor functions. The Judgment of Line Orientation (JLO) (from the MACFIMS) and the Selective Reminding Test (from the BRB-N) were not administered in this study and thus were not included in analyses. All other tests from the aforementioned batteries were included. Maximum Repetition Rate (MRR), Finger Tapping Test (FTT), and the Grooved Pegboard Test were also included in analyses in order to capture a broad range of motor function. Self-report measures of depression and fatigue, validated for use in MS, were selected to be included in analyses to establish construct scores for depression and fatigue.

Reliability measures (e.g., test-rest, internal consistency, or alternate form) from initial or updated validation studies are reported with their respective measures.

Cognitive Measures.

Digit Symbol - Coding [subtest from WAIS-III(Wechsler, 1997)]. Digit Symbol Coding is a processing speed subtest from the Wechsler Adult Intelligence Scale-IV. The examinee is instructed to attend to a 'coding key', which presents nine symbols paired with nine digits (i.e., 1, 2, 3, etc.). With the key present, the examinee is given a list of digits and instructed to draw the symbol associated with each digit as rapidly as possible. Scores are calculated by tallying the number of correct substitutions in 120 seconds. Digit

Symbol Coding has good test-retest reliability with a reliability coefficient of .86 (Wechsler, 2008).

Symbol Digit Modalities Test [SDMT; (Smith, 1982)]. The SDMT is a test of visual processing speed, attention, and memory. It is presented in two conditions: oral and written. In both conditions the examinee is instructed to attend to a 'coding key,' which presents nine symbols paired with nine single digits. With the key present, the examinee is given a set of symbols and instructed to either say or write (depending on the condition) the corresponding digit as rapidly as possible. Scores are calculated by tallying the number of correct substitutions given in 90 seconds. The SDMT has good test-retest reliability with the written condition demonstrating a Pearsons' r of .80 and the oral condition demonstrating an r of .76 (Strauss, Sherman, & Spreen, 2006).

Paced Auditory Serial Addition Task [PASAT; (Gronwall, 1977)]. The PASAT is a speeded serial addition task that is used to assess information processing speed, attention, and working memory. Examinees are aurally presented with a list of single digits and instructed to add pairs of numbers so that each digit is added to the digit that immediately preceded it. In the current study the digits were presented at both 2- second and 3-second intervals in differing conditions. Scores are calculated by adding the correct additions out of a possible 60. The measure of interest in this study is the sum of the correct possible additions in both conditions. The PASAT has high internal reliability with a Cronbach's alpha for the four PASAT trials of .90 (Crawford, Obonsawin, &

Allan, 1998). Test-retest reliability after sort retest intervals is also high (r>.9) (Strauss et al., 2006).

California Verbal Learning Test, 2nd edition [CVLT-II; (Delis & Kramer, 2000)]. The CVLT is a measure of verbal memory and learning. Examinees, in the first 5 trials, are aurally presented with a list of 16 words (List A) and ask to recall as many of they can. Examinees are then presented with a single alternative (List B) list of 16 words and ask to recall as many as possible. A short-delay free recall and cued-recall are administered for list A. After 20 minutes, a long-delay free recall and cued -recall are administered for list A. For this study the measures of interest are the raw cumulative number of correct words recalled in trials 1 through 5 as well as the long delay cued recall. Test-retest reliability is high for the five immediate recall trials (r =.80-.89) (Delis & Kramer, 2000; Strauss et al., 2006)

10/36 Spatial Recall Test [10/36 SRT; (Rao, 1990a)].The SRT is a measure of visual-spatial memory. Examinees are presented with a 6 X 6 checkerboard with 10 markers placed in a specific pattern. Examinees are asked to remember the pattern, and after 10 seconds of looking at the pattern are asked to replicate the pattern on a blank checkerboard. The test is repeated three times with the same pattern. After a 20-25 minute delay, the examinee is asked to recreate the pattern again on a blank checkerboard. The total number of correct responses during the 3 learning trials, as well as the delayed trial, are the variables of interest in this study. The SRT demonstrates poor

internal consistency reliability with the learning trials exhibiting an interclass correlation coefficient (ICC) of .5 and the delay trial exhibiting an ICC of .57 (Portaccio et al., 2010)

Brief Visuospatial Memory Test- Revised [BVMT-R; (Benedict, 1997)]. The BVMT-R is a measure of visual learning and memory. The examinee is presented with six simple geometric designs and asked to remember the shapes; after 10 seconds of looking at the designs, the examinee is asked to draw the designs on a blank page. This process is repeated 3 times using the same six simple geometric designs. After a 30-minute delay the examinee is asked to draw the designs from memory on a blank page. The total correct replications across the first three learning trials, as well as the total recall at the delayed recall trial, are the variables of interest for this study. The BVMT-R has adequate to high test-retest reliability with individual trial reliability coefficients ranging from .60-.84. The reliability coefficient for the total recall score is good, falling at .80 (Benedict, 1997).

Controlled Oral Word Association Test [COWAT; (Benton & Hamsher, 1989)]. The COWAT is a measure of verbal fluency. Examinees are presented aurally with a letter and asked to generate as many words as they can that begin with that letter. The CFL (i.e., letters C, F and L) version was used in the present study. The variable of interest is the total number of correct words generated in 60 seconds across all three letter cues. The test–retest reliability of the COWAT total word score is good with a reliability coefficient of .84 (Ross et al., 2007).

***Animal Naming* (Strauss et al., 2006).** The Animal Naming test is another measure of verbal fluency. Examinees are presented aurally with the semantic cue "animals" and asked to generate as many animals as they can. The variable of interest for this study is the total number of correct animals given in 60 seconds. Measures of category fluency are generally found to have good test-retest reliability at the .7-.79 level (Strauss et al., 2006).

Delis Kaplan Executive Function System- Sorting Task [D-KEFS-Sorting Task; (Delis, Kaplan, & Kramer, 2001)]. The sorting task sub-test from the D-KEFS is a measure of problem-solving, concept formation, and cognitive flexibility. The examinee is asked to sort 6 cards into two groups of 3 using as many different schemas (e.g., sort by color, sort by font, sort by sematic cue, etc.) as they can. The variable of interest is the total number of correct sorts. Internal consistency reliability (split-half) for correct sorts is adequate, with the reliability coefficient falling between .70 and .79. However, test-retest reliability is low (<.59) (Strauss et al., 2006).

Motor Measures.

Grooved Pegboard (Kløve, 1963; Matthews & Klove, 1964). The Grooved Pegboard is a measure of fine motor coordination and speed. Examinees are instructed to insert grooved metal pegs into a metal board as quickly as they can. The pegs must be rotated appropriately before they are capable of being inserted into the board. The task is completed separately with the left (with pegs being inserted from right to left) and then right hand (with pegs being inserted from left to right). The time it takes to complete the

task is recorded. The mean time across hands to complete the task is the variable of interest in this study. Test- retest reliability for the Grooved Pegboard is good, with reliability coefficients ranging from .67 to .86 in healthy samples (Strauss et al., 2006).

Finger Tapping Test [FTT; (Reitan, 1969)]. The FTT is a measure of manual motor speed. Examinees are instructed to place their index finger on a specially designed "tapper" and tap as fast as they can with that finger for 10 seconds. A counter attached to the "tapper" records the number of taps. This procedure is done with both the dominant and non-dominant hand. Five consecutive trials resulting in scores within 5 taps of each other are required before the test is considered completed. The mean number of taps in 10 seconds across hands is the variable of interest in this study. Moderate to high test-retest reliability has been reported for the FTT with reliability coefficients ranging from .58 to .93 in both healthy control subjects and patient populations (Strauss et al., 2006).

9 – Hole Peg Test (Mathiowetz, Weber, Kashman, & Volland, 1985). The 9-Hole Peg Test is a measure of fine motor skill and dexterity. The examinee is asked to insert all 9 smooth pegs into a pegboard and subsequently remove them as quickly as possible. The task is completed with both the dominant and non-dominant hand. The variable of interest in this study is the mean time to complete the task across hands. The 9-Hole Peg Test has both good inter-rater (r=.93) and intra-rater reliability (r=.96 to.98) (Solari, Radice, Manneschi, Motti, & Montanari, 2005). Although it has good test-retest reliability for the right hand (r=.69), it has relatively poor reliability for the left hand (r=.43) (Mathiowetz et al., 1985).

The Timed 25 – Foot Walk [Subtest from MSFC; (Fischer, Rudick, Cutter, & Reingold, 1999)]. The Timed 25-Foot Walk is a test from the Multiple Sclerosis Functional Composite that measures leg function and mobility. Examinees are instructed to walk the length of a marked 25-foot course as quickly as possible. The course is completed twice. The variable of interest in this study is the mean time to complete the course across trials. The 25-Foot Walk has good inter-rater (r=.99) and intra-rater reliability (r=.98) (Solari et al., 2005).

Maximum Repetition Rate of Syllables and Multisyllabic Combination [MRR; (Kent, Kent, & Rosenbek, 1987)]. The MRR is common measure of oral motor speed. Examinees are instructed to repeat the monosyllables "pa" "ta" and "ka" as quickly as they can after taking a breath. The syllables "pa" "ta" and "ka" are administered in separate trials. A fourth trial is administered in which the examinee is asked to repeat the sequence "pa-ta-ka" as quickly as they can in one breath. The variable of interest in this study is the mean number of phonemes produced per second across all four trials. The MRR shows good internal consistency reliability with the four trials correlating positively (.58 to .83) with each other in a MS population (Arnett, Smith, Barwick, Benedict, & Ahlstrom, 2008).

Depression Measures.

Beck Depression Inventory-II [BDI-II; (Beck, Steer, & Brown, 1996)]. The BDI-II is a commonly used self-report measure of depression. It consists of 21 items in which the examinee picks one statement per item that best describes the way they have

been feeling over the past 2 weeks. If multiple statements apply, the one assigned a higher value is chosen. Each item has 4 statements assigned a value 0 through 3, with higher scores indicating higher depression symptomology. Internal consistency reliability for the BDI-II is high with a Pearson's r between odd and even items of .86. The BDI-II also shows good convergent validity with a clinical rating of Depth of Depression by a psychiatrist (Beck, Ward, & Mendelson, 1961).

Chicago Multiscale Depression Inventory [CMDI; (Nyenhuis & Luchetta, 1998); (Nyenhuis et al., 1995)]. The CMDI is a 50–item, self-report questionnaire designed to evaluate depressive symptoms in individuals with neurological and other medical conditions including MS. The CMDI can be broken down into 3 subscales: mood, evaluative, and vegetative. Each subscale is represented by 14 words or phrases in the larger questionnaire. Examinees are asked to read each word or phrase and rate on a scale of 1 ("not at all") to 5 ("extremely") how well each describes them during the past week. Internal consistency reliability for the CMDI is high with coefficient alphas for each subscale ranging from .77 to .91. Although the subscales only correlate with each other moderately, 0.30 to 0.59, this is expected because the scale was developed to assess the different (though related) dimensions of depression. The CMDI shows good convergent validity with other measures of depression, with the CMDI total score correlating .68 with the Beck Depression Inventory and .77 with Profile of Mood States Depression inventory. For this study only the Evaluative and Mood subscales were used in analyses because they are thought to be the most accurate means of examining

depression in MS. The vegetative sub-scale is excluded due to the high overlap of vegetative and MS symptoms (Nyenhuis & Luchetta, 1998).

Fatigue Measures.

Fatigue Impact Scale [FIS; (Fisk et al., 1994)]. The FIS is a 40-item self-report measure of the extent to which fatigue affects quality of life. The FIS evaluates the examinee's perception of functional impairment due to fatigue in three domains: cognitive functioning, psychosocial functioning, and physical functioning. Examinees are asked to rate a statement starting with "Because of my fatigue…" on a scale of 0 ("no problem") to 5 ("extreme problem") as to how much fatigue has caused them problems in certain domains of life (i.e., "I feel less alert.") Internal consistency reliability for the FIS is high, with Cronbach's alphas for the overall FIS of .98, and for the three subscales of >.87. The FIS shows good validity by its ability to distinguish divergent patient groups (MS and Chronic Fatigue) based on its summary scores and individual item responses (Fisk et al., 1994).

Fatigue Severity Scale [FSS; (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989)]. The FSS is self-report questionnaire designed to evaluate fatigue severity in individuals with medical and neurological disorders, including MS. Examinees are asked to rate on a 7 point Likert scale (1= strongly disagree, 7= strongly agree) how well 9 statements about fatigue describe them (e.g., "my motivation is lower when I am fatigued"). Internal consistency reliability for the FSS is high, with a Cronbach's alpha of

.88. The FSS shows good validity by its ability to distinguish divergent patient groups (MS, Lupus, and Healthy Controls) based on its scores (Krupp et al., 1989).

Data Analysis

Missing Data. Missing data on five measures were imputed using a Winsorisation technique in order to accommodate for individuals unable to perform these measures due to their MS symptoms (e.g., a wheelchair bound individual on a task that involved walking). These individuals were given a score one unit worse than the poorest score on that measure within the sample (e.g., if the poorest score within the sample on the Timed 25-Foot Walk test was 44 seconds, a wheelchair bound individual would get a score of 45 seconds on that task). Tasks in which this technique was used include: Grooved Pegboard, 9-Hole Peg Test, PASAT, FTT, and the Timed 25-Foot Walk. Six cases were imputed for the Timed 25-Foot Walk. One case (the same individual) was imputed for Grooved Pegboard, 9-Hole Peg Test, and FTT. One case was imputed for the PASAT. Other missing data appeared to be missing completely at random and was treated as such; no other imputations were made.

Construct Scores. Two methods were utilized to create scores to represent the underlying constructs of cognition, motor function, fatigue and depression. Both methods involved running four Principal Component Analyses (PCA), one for each hypothesized construct, with all available measures for each construct included. The first method created ***composite scores*** that were theory driven and empirically supported. All measures included in the composites were equally weighted. The second method created

factor scores that were empirically driven. Measures included in the factor scores were weighted by how strongly they correlated with the primary factor. See succeeding sections for specifics on how these construct scores were created.

Composite Scores. Principal Component Analyses (PCA) were conducted in order to establish which tests to include in the following composites: cognitive, motor, fatigue, and depression. The PCAs were run using varimax rotation, 25 maximum iterations for convergence, and principle components extractions when eigenvalues were greater than 1. The following tests were included in the PCAs: Cognitive Composite: Digit Symbol Coding-correct in 120s, SDMT- Written total correct in 90s, SDMT-Oral total correct in 90s, PASAT 2s correct + 3s correct, CVLT-II total trial 1-5, CVLT-II long delayed cued recall, 10/36 SRT total correct immediate recall, 10/36 SPT total correct delayed recall, BVMT-R score on trials 1-3, BVMT-R delayed recall, COWAT-number of correct words generated across all three trials, Animals Naming - number of correct animals generated, D-KEFS sorting test- number of correct sorts; Motor Composite: Grooved Pegboard-mean time across hands, FTT-mean taps per trial across hands, Nine Hole Peg Test-mean time across hands, 25 Foot Walk- average time, MRR-pa-ta-ka combined mean phonemes per second; Depression Composite: CMDI-Evaluative, CMDI-Mood, BDI-II total; Fatigue Composite: FIS-Psychosocial, FIS-Cognitive, FIS-Physical, FSS-total. Three more factor analyses were run in order to parse out the cognitive composite into three sub composites representing the cognitive domains of memory, processing speed, and executive functioning. It was decided a priori that all test indices with component loadings on the first factor greater than .40 would be retained in

the respective composites (Hair, Anderson, Tatham, & Black, 1998). Items were transformed in order to be in the same direction before testing internal consistency. Cronbach's alpha was assessed to confirm the internal consistency of the indices entered into each composite. A cutoff score of .70 was used (Streiner, 2003). Remaining tests' *z* scores were combined into a mean *z* score for each composite.

Only one component was extracted for the motor, fatigue, and depression constructs with all measures included in the respective analyses loading on the sole factors at a level greater than 0.4. Measures included in these three composites demonstrated internal reliability scores greater than 0.7. Multiple components were extracted from the cognitive construct analysis, however the majority of them loaded at a level greater than 0.4 on the principle component. Thus, those measures were included in the final composite. Measures included in final composites can be found in Table 2.

Table 2. Tests included in composite scores based on results from the principal component analysis and internal consistency reliability calculations. The tests are equally weighted within each composite.

Composite:	**Tests included in composite:**
Motor	Grooved Pegboard - mean time across hands, FTT - mean taps per trial across hands, 9-HPT - mean time bilaterally, 25-Foot Walk - mean time, MRR- pa-ta-ka combined mean phonemes per second
Depression	CMDI-Evaluative, CMDI-Mood, BDI-II total
Fatigue	FIS-Psychosocial, FIS-Cognitive, FIS-Physical, FSS-total
Cognition	Digit Symbol - Coding total correct in 120s, SDMT- Written total correct in 90s, PASAT 2s correct + 3s correct, CVLT-II total correct trials 1-5, CVLT-II long delayed cued recall COWAT- number of correct words generated across all three trials Animals Naming - number of correct animals generated, D-KEFS total correct sorted
Cognition Sub- Composites:	
Processing Speed	Digit Symbol Coding correct in 120s, SDMT- Written total correct in 90s, SDMT- Oral total correct in 90s
Executive Function	COWAT grand total across 3 phonetic cues, Animal Naming number correct, D-KEFS total correct sorted, PASAT 2s correct + 3s correct
Memory	SRT recall total correct immediate recall, SRT recall total correct delayed recall, CVLT-II total correct trials 1-5, CVLT-II long delayed cued recall, BVMT-R total correct trials 1 through 3, BVMT-R delayed recall score

Abbreviations: FTT, Finger Tapping Test; 9-HPT, 9 Hole Peg Test; MRR, Maximum Repetition Rate of Syllables and Multisyllabic Combination; CMDI, Chicago Multiscale Depression Inventory; BDI-II, Beck's Depression Inventory-II; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Task; CVLT-II, California Verbal Learning Test, 2nd edition; COWAT, Controlled Oral Word Association Test; D-KEFS, Delis - Kaplan Executive Function System; SRT, 10-36 Spatial Recall Test; BVMT-R, Brief Visuospatial Memory Test- Revised.

Factor Scores. PCAs were conducted in order to create factor scores for the following constructs: cognitive, motor, fatigue, and depression. The PCAs were run using varimax rotation, 25 maximum iterations for convergence, and principal components extractions when eigenvalues were greater than 1. Unlike the composite scores analyses, factor scores were saved for each component extracted in this analyses. The following tests were included in the PCAs: Cognitive Factor: Digit Symbol Coding-correct in 120s, SDMT- Written total correct in 90s, DSMT-Oral total correct in 90s, PASAT 2s correct + 3s correct, CVLT-II total trial 1-5, CVLT-II long delayed cued recall, 10/36 SRT total correct immediate recall, 10/36 SRT total correct delayed recall, BVMT-R score on trials 1-3, BVMT-R delayed recall, COWAT-number of correct words generated across all three trials, Animals Naming - number of correct animals generated, D-KEFS sorting test- number of correct sorts; Motor Factor: Grooved Pegboard-mean time across hands, FTT-mean taps per trial across hands, Nine Hole Peg Test-mean time across hands, 25 Foot Walk- average time, MRR-pa-ta-ka combined mean phonemes per second; Depression Factor: CMDI-Evaluative, CMDI-Mood, BDI-II total; Fatigue Factor: FIS-Psychosocial, FIS-Cognitive, FIS-Physical, FSS-total.

Only one component was extracted for the motor, fatigue, and depression constructs. Thus only one factor score was saved for each of these constructs. Four components were extracted from the cognition construct. However, inspection of the scree plot indicated that the majority of variance was explained by only one factor. Thus, the PCA was run again for this construct forcing it to converge on one factor. The factor score from this analysis was saved for the cognition factor. Measures and their corresponding weights included in the factor scores can be found in Table 3.

Table 3. Tests included in factor scores based on results from the principal component analysis. The tests are weighted by the factor loading within each factor.

Factor:	Tests included in factor:	Factor loading
Motor	Grooved Pegboard - mean time across hands	.895
	FTT - mean taps per trial across hands	.631
	9-HPT - mean time bilaterally	.884
	25-Foot Walk - mean time	.667
	MRR- pa-ta-ka combined mean phonemes per second	.482
Depression	CMDI-Evaluative	.930
	CMDI-Mood	.936
	BDI-II total	.852
Fatigue	FIS-Psychosocial	.911
	FIS-Cognitive	.732
	FIS-Physical	.881
	FSS-total	.727
Cognition	Digit Symbol - Coding total correct in 120s	.863
	SDMT- Oral total correct in 90s	.843
	SDMT- Written total correct in 90s	.824
	PASAT 2s correct + 3s correct	.738
	CVLT-II total correct trials 1-5	.728
	CVLT-II long delayed cued recall	.570
	COWAT-number of correct words generated across all three trials	.630
	Animals Naming - number of correct animals generated	.640
	D-KEFS total correct sorted	.561
	SRT total correct immediate recall	.744
	SRT total correct delayed recall	.643
	BVMT-R score of trials 1-3	.681
	BVMT-R delay recall	.554

Abbreviations: FTT, Finger Tapping Test; 9-HPT, 9 Hole Peg Test; MRR, Maximum Repetition Rate of Syllables and Multisyllabic Combination; CMDI, Chicago Multiscale Depression Inventory; BDI-II, Beck's Depression Inventory-II; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Task; CVLT-II, California Verbal Learning Test, 2nd edition; COWAT, Controlled Oral Word Association Test; D-KEFS, Delis - Kaplan Executive Function System; SRT, 10-36 Spatial Recall Test; BVMT-R, Brief Visuospatial Memory Test- Revised.

Hypothesis Testing

Construct Scores. Bivariate correlations were conducted to determine how similar, as measured by Pearson's r, the corresponding construct scores were (e.g., how strongly did the cognition composite score and cognition factor score correlate, etc.). As seen in Table 4 composite and factor scores were highly correlated. To be parsimonious, only one set of construct scores were used in the following hypothesis testing analyses. Although factor scores are thought to represent a purer measure of the underlying constructs, as they are created from derivatives of the original measures, they may be less ecologically valid than the composite scores. Therefore, composite scores were chosen over factor scores because they are comprised of the original measures and thus could be easily re-created in a clinical setting.

Table 4. Correlation and significance values of corresponding construct scores.

Construct	Pearson's r	*p*-value
Cognitive Composite and Cognitive Factor	0.950	<.0001
Motor Composite and Motor Factor	0.993	<.0001
Fatigue Composite and Fatigue Factor	0.999	<.0001
Depression Composite and Depression Factor	1.000	<.0001

Hypothesis 1. The four composite scores (cognitive, motor function, fatigue, depression) were entered as a group into a logistic regression with unemployment status (1, 0) as the dependent variable. The Hosmer-Lemeshow test of goodness of fit was run to ensure adequate fit of each model to the data.

Hypothesis 2. Age, disease duration, and EDSS were individually entered into logistic regressions with unemployment status (1, 0) as the dependent variable. The Hosmer-Lemeshow test of goodness of fit was run for each logistic regression to ensure adequate fit of each model to the data.

Hypothesis 3. A bootstrapping mediation analysis was conducted using the PROCESS procedure for SPSS (Hayes, 2014) with unemployment status (1, 0) as the outcome variable. Distal predictors of employment (age, disease duration, and EDSS) found to be significant from hypothesis 2 were individually entered as the independent variables, while composite scores (cognitive, motor, depression, and fatigue) found to be significant from hypothesis 1 were entered, as a group, as the mediator variables. Model number 4, 1000 bootstrap samples, and a 95% bias-corrected confidence interval were used as the parameters for this analysis.

Results

Logistic Regression

A model including composites of motor function, cognition, depression, and fatigue distinguished those who are unemployed from employed, χ^2 (4) =13.8, p=.008, Nagelkerke R^2=.334. However, none of the composites were found to be significant

associates of unemployment after controlling for all other variables in the model. A model including composites of motor function, depression, fatigue, and the three cognitive sub-composites also distinguished those who are unemployed from employed, χ^2 (6) =17.9, p=.007, Nagelkerke R^2=.422. Again, none of the composites were found to be significant associates of unemployment after controlling for all other variables in the model. However, in this model the processing speed cognitive sub-composite trended towards significance, OR= 0.234 [.05, 1.1]. The lack of individually significant associates of unemployment in these models is likely a covariance problem. Specifically, the motor and cognitive composites and the depression and fatigue composites are highly correlated, R=.537 p<.001; R=.524, p<.001. Therefore analyses examining the individual effects of each composite were run.

Individually the composites for motor, cognition, and fatigue significantly associated with unemployment, OR= 0.31 [.13, .76]; OR= 0.32 [.13, .79]; OR= 2.90 [1.22, 6.90], respectively. The depression composite did not significantly associate with unemployment suggesting depression symptoms do not contribute to unemployment in MS. See Table 5 for more details on these regression analyses.

Table 5. Summary of logistic regression models evaluating factors distinguishing unemployed from employed patients with MS.

Predictor Variable	**OR**	**95% C.I. for OR**	***p***
Analysis 1: All Four Symptoms-Related Composites			
Cognitive Composite	0.50	0.18 - 1.40	.19
Motor Composite	0.44	0.14 - 1.33	.15
Fatigue Composite	2.73	0.77 - 9.70	.12
Depression Composite	0.78	0.34 - 1.83	.57
Analysis 2: Cognitive Composite			
Cognitive Composite	0.32	**0.13 - 0.79**	**.01**
Analysis 3: Motor Composite			
Motor Composite	0.31	**0.13 – 0.76**	**.01**
Analysis 4: Fatigue Composite			
Fatigue Composite	2.90	**1.22 - 6.90**	**.02**

Notes: Bold text indicates statistical significant at $\alpha < .05$. In the case of the Cognitive and Motor composites, values reflect better cognitive and motor functioning in employed individuals. With the Fatigue composite, the value reflects higher fatigue in unemployed individuals. N= 20 for unemployed, N=33 for employed.

Given that fatigue has been shown to mediate the relationship between measures of cognition and employment status (Covey et al., 2012), fatigue was examined as a covariate. Even after including fatigue as a covariate, both the cognitive (OR= 0.37 [.15, .92], p=.032) and motor composites (OR= 0.37 [.15, .95], p=.039) remained significant associates of unemployment status. The influence of fatigue in both aforementioned cases became non-significant when including the cognitive or motor composite, suggesting that motor and cognitive problems may mediate the effect of fatigue on unemployment. A bootstrapping mediation analysis corroborated this finding; the motor and cognitive composites, as a group, were found to mediate the relationship between the fatigue composite and unemployment (total indirect effect=.4593, 95% CI [.042, 1.30]). The reverse mediation relationships (i.e., the fatigue composite as the mediator) were non-significant.

As cognitive functioning is a heterogeneous construct, the cognitive sub-composites were further explored in order to examine which aspects of cognition contribute to unemployment. When run as a group, the three cognitive sub-composites significantly distinguished those who are unemployed from employed, χ^2 (3) =11.7, p=.008, Nagelkerke R^2=.287. The processing speed sub-composite remained a significant associate even after controlling for all other cognitive variables (memory and executive function) in the model (OR= 0.26 [.07, .93], p=.039) indicating that it may be the strongest cognitive predictor of unemployment. The processing-speed sub-composite remained significant (OR=.20 [.044, .891] when fatigue was added as a covariate to this model.

Goodness of fit

All Hosmer-Lemeshow tests of goodness of fit were non-significant, indicating that all models previously reported had adequate fit.

Mediation- EDSS

The EDSS, as expected based on prior work, significantly associated with unemployment status, OR= 1.37 [1.01, 1.86]. Results of a mediation analysis using 1,000 bootstrap samples indicated that, as a group, the cognitive, motor, and fatigue composites did not mediate the effect of EDSS on unemployment. However, as covariance and low power may have contributed to this null finding, the three aforementioned composites were examined independently as potential mediators. Both the fatigue (indirect effect=.10093, 95% CI [.0043, .3166]) and cognitive (indirect effect=.1012, 95% CI [.0020, .2983]) composites independently mediated in part the effect of EDSS on employment status. When further examined, both the processing speed (indirect effect=.1418, 95% CI [.0092, .3711]) and memory (indirect effect=.1011, 95% CI [.0071, .3566]) sub-composites independently mediated in part the effect of EDSS on employment status; however, the executive function sub-composite did not mediate this relationship. Additionally, the motor composite did not mediate the relationship between EDSS and employment.

Mediation- Disease Duration

Disease duration was significantly associated with unemployment status, OR= 1.11 [1.03, 1.18]. Results of the mediation analysis indicated that, as a group, the cognitive, motor, and fatigue composites did not mediate the effect of disease duration on unemployment. However, as covariance and low power may have contributed to this null finding, the three aforementioned composites were examined independently as potential mediators. Further analyses revealed that none of the composites or sub-composites mediated the relationship between disease duration and unemployment.

Mediation- Age

Age also significantly associated with unemployment status, OR= 1.16 [1.06, 1.26]. However, the Hosmer-Lemeshow test of goodness of fit was significant, indicating that this model had inadequate fit. Despite this finding, mediation analyses were conducted. Results of the mediation analysis indicated that, as a group, the cognitive, motor, and fatigue composites did not mediate the effect of age on unemployment. However, as covariance and low power may have contributed to this null finding, the three aforementioned composites were examined independently as potential mediators. Further analyses revealed that none of the composites or sub-composites mediated the relationship between age and unemployment.

Discussion

Results and Contributions from Current Study

Unemployment is common in MS, so the identification of constructs that contribute to unemployment is needed. Although a number of studies have examined predictors of employment status in isolation or evaluated a limited number of predictors, little published research has comprehensively examined this issue. The present study examined composite scores for depression, cognition, fatigue, and motor symptoms and explored these composites, along with measures of disease burden and age, in distinguishing employment status in MS. As a group, all four composites distinguished those who are unemployed from employed. However, individually only cognition, motor symptoms, and fatigue were significant individual associates. Surprisingly, depression was not a significant associate. In this sample, both cognition and motor function remained significant associates of unemployment after controlling for the effect of fatigue. In fact, results from a mediation analysis suggested that cognition and motor function mediate the effect of fatigue on unemployment. In other words, the results of these analyses suggest that increased fatigue leads to poorer cognitive and motor function, which in turn results in unemployment. However, as there is no universal order in which MS symptoms develop, and the absence of experimental manipulation with the current methods, true mediation cannot be definitively determined.

In agreement with the current literature, age, disease duration, and EDSS all independently predicted unemployment status. However, as none of these variables are realistic points of intervention, mediation analyses were conducted to determine more

proximal predictors of unemployment. Of the three distal predictors, only the effect of EDSS on unemployment was mediated in part by symptom composites. The effects of age and disease duration on employment status were not mediated by MS symptoms. These findings suggest that an older age and/or a longer disease duration results in unemployment, but not by way of increased MS symptoms.

Although the EDSS significantly associated with unemployment status, results from this study indicate that fatigue, slowed processing speed, and impairments in memory more proximately distinguish unemployment. Most physicians use the EDSS, a measure heavily weighted on by ambulation, to advise patients on when they should leave work (Pompeii et al., 2005). Results from the present study indicate that it may also be useful to utilize patients' fatigue level and cognitive functioning when making vocational suggestions, given that both appear to partially mediate the relationship between disability (i.e., EDSS) and employment status. Additionally, health care providers and vocational rehabilitation counselors could inform patients on techniques that help individuals with MS compensate for difficulties in these domains (i.e., repetition for memory impairment, allowing ample time to complete tasks for slowed processing speed, and increasing daily exercise and taking frequent breaks for fatigue) or guide them towards positions of employment that rely less on these domains. Recent research has found that improving physical fitness may also help improve cognitive functioning. (Beier, Bombardier, Hartoonian, Motl, & Kraft, 2014). According to the Americans with Disabilities Act Amendment Act of 2008, individuals with MS are entitled to certain work-place accommodations, should they disclose their disease, which may help compensate for difficulties in these areas as well.

Additionally, results from this study imply that impairments in memory and processing speed are more influential, at least on employment status, than measures of executive functioning. This suggests that measures of these two cognitive domains should be considered for inclusion in comprehensive measures of MS. Recent studies have suggested replacing the PASAT in the MSFC with the SDMT, and results from our study are consistent with these suggestions (Drake et al., 2010; Strober, Chiaravalloti, Moore, & DeLuca, 2014).

Perhaps most importantly, results from this study point to more specific possible areas for intervention. More research and clinical trials for cognitive rehabilitation in the areas of memory, processing speed and fatigue are needed. So far the literature is promising, with a recent literature review indicating that cognitive and neuropsychological training has measureable cognitive benefits in MS (Hämäläinen & Rosti-Otajärvi, 2014). Unfortunately, the generalizability of these benefits is questionable, further emphasizing the need for more research in this area to be conducted.

Limitations

A potential limitation of this study is the small sample size (n=53), a factor that may limit the ability to detect small effect sizes. Additionally, our study sample is predominantly (85%) female and thus its findings may not generalize to males. Furthermore, our sample is predominantly relapsing remitting (56%) patients, and thus our results may not generalize to other course types.

Reliability and validity of employment status may be diminished due to the fact that this variable is self-reported. Additionally, due to the small sample size, part-time

and full-time employed individuals were grouped in the 'employed' category. This may add error to our models, as some individuals in the 'employed' group may have cut down their working hours due to their MS symptoms. If a larger sample were available, analyses could be conducted with three working groups: full-time employed, part-time employed, and unemployed. An additional limitation of this study is that job type was not factored into our analyses. Predictors of employment likely depend on the attributes and skills needed for successful performance of any given job. Therefore, results from this study might be different if the sample size was large enough to accommodate breaking down job type into groups such as white collar versus blue collar or jobs with cognitive demands vs jobs with physical demands.

Conclusions

Employment status in MS is predicted by symptoms pertaining to cognition, fatigue, and motor skills but not depression. Fatigue and cognitive skills, specifically processing speed and memory, appear to mediate the relationship between overall disability and employment status. In other words, the severity of one's MS leads to poorer cognitive functioning and increased fatigue, and these symptoms in turn result in unemployment. Health care providers should assess fatigue and cognition when giving vocational advice as well as inform patients on techniques that help them compensate for difficulties with fatigue, memory problems, and processing speed deficits. Instruction of techniques to help compensate for these symptoms may help individuals with MS maintain employment.

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