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Cognitive Reserve Attenuates the Effect of Disability on Depression in Multiple Sclerosis

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Abstract

Objective: The current study explored the moderating role of cognitive reserve on the relationship between disability and depression in a sample of individuals in which brain pathology is thought to contribute to depression (multiple sclerosis; MS).
Method: Fifty-four individuals with MS were examined. Depression was measured using the Beck Depression Inventory-Fast Screen (BDI-FS). In addition to collecting demographic (education) and disease burden (Expanded Disability Status Scale; EDSS) related variables, participants completed a neuropsychological test battery and psychosocial questionnaires. Cognitive reserve (CR) was conceptualized in two ways: Fixed CR and Malleable CR. Fixed CR was measured using years of education and crystallized intelligence (Shipley Vocabulary). Malleable CR was operationalized as a composite of measures from the Cognitive Heath Questionnaire (CHQ). Two regressions on depression (BDI-FS) examining either type of cognitive reserve, EDSS, and their interactions were explored. Results: The interaction between EDSS and both conceptualizations of cognitive reserve were significant, $t(50) = -2.60$, $p = .013$, PRE = .12 (Fixed CR); $t(47) = -2.02$, $p = .049$, PRE = .08 (Malleable CR). Simple effects testing revealed the same pattern regardless of the type of cognitive reserve examined; EDSS predicted depression only in those with low cognitive reserve.
Conclusions: Cognitive reserve moderates the relationship between disability and depression in MS; disability does not appear to influence depression in those with high cognitive reserve.

Keywords: Multiple sclerosis; Depression; Intelligence

Introduction

Cognitive Reserve

The construct of cognitive reserve developed from the repeated clinical observation that there is no consistent one-to-one relationship between degree of brain pathology and its functional manifestations (Stern, 2002). For example, two individuals with identical brain pathology may functionally look very different in their cognitive abilities, motor functioning, and day-to-day functioning depending on their level of cognitive reserve. Support for the validity of the cognitive reserve construct has been found in neurodegenerative populations including Alzheimer's disease (AD; Stern, 2002), Parkinson's disease (PD; Hindle, Martyr, & Clare, 2014), chronic traumatic encephalopathy (CTE; Alosco et al., 2016), and multiple sclerosis (MS; Sumowski et al., 2013).

Cognitive reserve is, inherently, the moderator between measures of damage from disease and functional outcomes of this damage. Typically, damage is assessed through either structural images of the brain, passage of time (the assumption being that damage occurs in neurodegenerative diseases over time), or clinical measures of neurological disability (Feinstein, Lapshin, O'Connor, & Lanctôt, 2013; Stern, 2002). Measures of functional outcome vary as well. In the AD literature, the traditional functional outcome is whether diagnostic criteria for dementia are met (Stern, 2002). Recently, additional

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neuropsychological measures that capture more nuanced aspects of functioning, such as processing speed or memory performance, have become popular functional measures as well (Amato et al., 2013; Fairjones, Vuletich, Pestell, & Panegyres, 2011). There is no standard way of measuring cognitive reserve, but measures of intelligence, vocabulary/literacy, education, and occupational attainment are common (Stern, 2009). More recently, measures of cognitively enriching lifestyle factors have become popular proxies for cognitive reserve, as these are thought to be less affected by factors outside of the individual's control (in contrast to factors like genetics and socio-economic status in childhood, etc.) and thus more easily adjusted. Such lifestyle factors include time spent engaging in cognitively stimulating activities (e.g., Crossword puzzles) as well as additional stimulating leisure activities such as aerobic exercise and socializing (Sandroff, Schwartz & DeLuca, 2016; Scarmeas & Stern, 2003; Stern, 2009). In order to capture the variety of ways in which cognitive reserve has been conceptualized, this study will utilize both a traditional/fixed (e.g., vocabulary) measures of cognitive reserve as well as a lifestyle/malleable (e.g., engaging in cognitively stimulating activities) measure of cognitive reserve.

Cognitive Reserve in Multiple Sclerosis

MS causes a variety of symptoms including pain, muscle weakness, fatigue, depression, and cognitive impairment (Kister et al., 2013). The literature examining cognitive reserve in MS has focused almost exclusively on cognitive functioning as the functional outcome measure. Several studies have demonstrated that proxies of cognitive reserve moderate the relationship between measures of disease burden and cognitive performance in MS (Amato et al., 2013; Benedict, Morrow, Guttman, Cookfair, & Schretlen, 2010; Martins Da Silva et al., 2015; Modica et al., 2016; Sumowski et al., 2013). Benedict and colleagues (2010) found that cognitive reserve (measured by level of education and performance on the National Adult Reading Test) moderated decline in information processing speed in individuals with MS over a 5-year period. Amato and colleagues (2013) found that an index of cognitive reserve calculated by education, IQ, and time spent in premorbid leisure time activities moderated the relationship between cortical volume and memory/processing speed tasks cross-sectionally. Sumowski and colleagues (2013) found that cognitive reserve, measured by assessing early life cognitively enriching leisure activities, moderated the relationship between lesion load and cognitive performance even after controlling for education level, brain reserve, and the interaction of lesion load and brain reserve. Overall, it is clear that the construct of cognitive reserve has validity within the MS population. However, the majority of literature examines whether cognitive reserve moderates the relationship between measures of disease burden and neurocognitive sequelae of MS. Whether the cognitive reserve construct functions similarly when examining neuropsychiatric sequelae of MS pathology is currently unknown. If cognitive reserve is conceptualized as more efficient use of brain resources to maintain normal functioning, this logic should also apply to other aspects of behavior controlled by the brain, like mood and emotion.

Depression as the Functional Outcome Measure

Depression in MS is about as common as cognitive symptoms. More importantly, depression impacts individuals' daily functional ability, is often associated with poorer cognitive functioning, and can worsen disease progression through increased fatigue and decreased adherence to potentially disease modifying behaviors (e.g., medication adherence and exercise) (Arnett, Barwick, & Beeney, 2008; Arnett, Higginson, & Randolph, 2001; Brown et al., 2009; Bruce, Hancock, Arnett, & Lynch, 2010; Patel, Walker, & Feinstein, 2018). Thus far, cognitive reserve literature in MS has not examined neuropsychiatric sequelae of MS, such as depression, as the functional outcome. Depression has been an exclusionary criterion, statistically controlled for, or simply not considered in the general MS cognitive reserve literature. We posit that there may be merit in conceptualizing depression status as the functional outcome variable. The risk for depression increases at the onset of MS, and there is typically a medium to large effect size of disease burden (e.g., EDSS) and measures of brain integrity (e.g., white matter lesion load) on depression status in MS (Arnett et al., 2008; Bakshi et al., 2000). However, there is no one-to-one relationship between disease burden/brain pathology and depression, suggesting a potential role for a construct such as cognitive reserve. Furthermore, preliminary evidence shows that cognitive reserve may play a protective role against neuropsychiatric sequelae of other diseases including apathy in human immunodeficiency virus (HIV) and depression in moderate/severe traumatic brain injury (TBI) (Salmond, Menon, Chatfield, Pickard, & Sahakian, 2006; Shapiro, Mahoney, Peyser, Zingman, & Verghese, 2013). With these considerations in mind, the goal of the current study was to examine whether cognitive reserve moderates the relationship between disease burden and depression in MS. Cognitive reserve was operationalized in two ways including a traditional/fixed measure based on vocabulary skills and years of education, as well as a lifestyle/malleable measure based on time spent engaging in stimulating leisure time activities including cognitive stimulation, socializing, and

physical exercise. We hypothesize that both operationalizations of cognitive reserve will moderate the relationship between disease burden and depression in MS.

Methods

Procedure

This study involved an analysis of data collected as part of a longitudinal investigation of cognitive, emotional, and social factors related to MS. Analyses for this project were run exclusively on data collected during the third phase of the study and thus are cross-sectional in nature.

Participants

Participants were recruited from the greater Pennsylvania area. A positive diagnosis of MS by a board-certified neurologist based on Polman and colleagues (2010) revised McDonald criteria was the only inclusion requirement. Individuals were excluded for any of the following: (a) significant history of substance abuse; (b) nervous system disorder other than MS; (c) sensory impairment that could interfere with testing; (d) developmental history of learning disability or attention deficit hyperactivity disorder; (e) significant medical condition, other than MS, that could interfere with cognitive or motor function; (f) relapse or corticosteroid use within 4 weeks of participation in the study; or (g) physical or neurological impairment that would make testing impossible. The study was approved by the Institutional Review Board at The Pennsylvania State University, and all participants signed an informed consent form prior to starting the study. All procedures were performed in compliance with relevant laws and institutional guidelines.

Fifty-four individuals with MS (16 males and 38 females) were examined. Course types included relapsing-remitting ($n = 39$), secondary progressive ($n = 12$), and primary progressive ($n = 3$). The mean age of the sample was 52.6 and the mean disease duration was 16.0 years, meaning that this sample can best be conceptualized as a chronic MS population who are unlikely to be dealing with the initial emotional consequences of adjusting to the disease. Sixteen individuals (30% of the sample) met criteria for clinical depression (i.e., BDI-FS score ≥ 4). This prevalence level is typical of what is found when depression is screened in samples of individuals with MS (e.g., Patel & Feinstein, 2017; Strober & Arnett, 2015). Thirty-nine individuals (72% of the sample) reported taking disease modifying therapies (DMTs). More information on demographic variables, illness-related variables, and other major variables examined in this study (depression, cognitive reserve, etc.) is available in Table 1.

Neuropsychological and Psychosocial Measures

Education. Years of education was collected as part of a semi-structured psychosocial interview administered by a doctoral student in clinical psychology. Standard scores were created based on the mean and standard deviation from this sample.

Crystallized intelligence. Crystallized IQ was assessed using the Shipley Institute of Living Scale (SILS; Zachary & Shipley, 1986). The SILS is designed to assess general intellectual functioning. It produces three summary scores: Vocabulary, Abstraction, and Total scores. Only the Vocabulary subscale was used in this study as this subscale is thought to best represent premorbid functioning (Franzen, Burgess, & Smith-Seemiller, 1997). Standard scores were created from available SILS norms that account for age.

Table 1. Demographic and illness-related information about the sample

	Mean	*SD*	Range
% Female	70.4	—	—
Age (years)	52.6	11.4	27–76
EDSS	4.4	1.7	0–8
Disease duration (years)	16.0	8.3	1.4–38.2
Fixed Cognitive Reserve (Standard Score)	102.0	11.5	71.2–122.7
Malleable Cognitive Reserve (Standard Score)	100.0	15.0	59.6–123.7
BDI-FS	3.1	3.8	0–19

Note: EDSS = Expanded Disability Status Scale. BDI-FS = Beck Depression Inventory-Fast Screen.

Cognitively healthy lifestyle factors. Cognitively healthy lifestyle factors were measured using the Cognitive Health Questionnaire (CHQ; Randolph et al., 2014). The CHQ is a 17-item questionnaire that measures various health-related behaviors relating to exercise, socializing, and cognitive exertion. Items cluster in three scales: exercise (e.g., "How much moderate physical exercise do you get in a typical week?"), socializing (e.g., "How often do you socialize with family members other than your partner in a typical week?"), and cognitive exertion (e.g., "How many times per week do you do something that makes you consider or remember new information?").

Cognitive reserve. To reflect the variety of ways in which cognitive reserve is operationalized across current literatures, cognitive reserve was conceptualized in two ways: fixed cognitive reserve (Fixed CR) and malleable cognitive reserve (Malleable CR). These terms are author-generated. Fixed CR was operationalized as the mean of the standard scores of years of education and the vocabulary subtest from the SILS. Malleable CR was measured as the standardized mean of three scales (cognitive exertion, physical exercise, and socializing) from the CHQ. These two operationalizations of cognitive reserve, although significantly positively correlated in this sample ($r = .28$, $p < .05$), represent distinct aspects of the overall construct of cognitive reserve as they only share approximately 7.5% of the same variance.

Neurological disability/disease burden. Neurological disability was evaluated using the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). We used the EDSS as it has been the most commonly used measure of neurological disability in the MS literature and is widely accepted as a core index of disease burden. In our study, we employed a modified self-report version of this scale. Although it has been more typical in this literature to use clinically based assessments of impairment due to MS, self-report instruments such as the measure we used have been shown to be have high levels of validity. For example, Solari and colleagues (1993) found high ($r = .84$) intraclass correlations between a patient self-administered version of the EDSS and neurologists' independent ratings.

Depression. The Beck Depression Inventory-Fast Screen (BDI-FS; Beck, Steer, & Brown, 2000) was used to assess depression. The BDI-FS is a commonly used self-report measure of depression created for use in medical populations. It consists of seven items thought to be unconfounded by medical illness. Examinees choose one statement per item that best describes the way they have been feeling over the past 2 weeks. Each item has four statements assigned a value 0 through 3, with higher scores indicating higher depression symptomology. A total score of four or above on the BDI-FS is considered clinically depressed (Strober & Arnett, 2015). The BDI-FS is ideal for use in populations such as MS, because it does not include neurovegetative symptoms that often overlap with MS symptoms (e.g., fatigue, sexual dysfunction, etc.); it has been validated for use in an MS population in at least two studies (Benedict, Fishman, McClellan, Bakshi, & Weinstock-Guttman, 2003; Strober & Arnett, 2015).

Data analyses

The Statistical Package for Social Sciences (SPSS) version 24 was used for all data analyses. We tested whether both conceptualizations of cognitive reserve moderated any observed association between neurological disability (EDSS) and depression. Fixed CR, Malleable CR, and EDSS were centered on their respective means for final analyses.

Covariates. Demographic variables including age and sex as well as disease-related variables including disease duration and if the participant was taking DMTs were examined as potential covariates. None of these variable were significantly correlated with depression (BDI-FS) and thus were not retained as covariates in final analyses.

Analysis 1. Fixed CR, EDSS, and their interaction were entered into a hierarchical linear regression analysis with depression (BDI-FS) as the dependent variable.

Analysis 2. Malleable CR, EDSS, and their interaction were entered into a hierarchical linear regression analysis with depression (BDI-FS) as the dependent variable. Three individuals were missing data for Malleable CR, reducing the sample size for analysis 2 to 51 individuals.

Simple effects. Simple effect tests were run to clarify the pattern of significant interactions; the effect of disability on depression was tested at high and low (±1 *SD*) levels of each conceptualization of cognitive reserve.

Results

Analysis 1

A model including neurological disability (EDSS), Fixed CR, and the product of Fixed CR and neurological disability significantly predicted depression, $F(3,50) = 6.41$, $p = .001$, Percent Reduction in Error (PRE) = .28. The main effects of both disability ($t(50) = 2.02$, $p = .049$, PRE = .08) and Fixed CR ($t(50) = -2.64$, $p = .011$, PRE = .12) were significant. However, these main effects were qualified by a significant interaction between EDSS and Fixed CR, $t(50) = -2.60$, $p = .013$, PRE = .12. Simple effects testing revealed that disability predicted depression in those with low Fixed CR (1 *SD* below the mean), $t(50) = 3.33$, $p = .002$, PRE = .18, but not in those with high Fixed CR (1 *SD* above the mean), $t(50) = 0.65$, $p = .52$, PRE < .01. Overall, this result suggests that neurological disability influences depression only in those with low Fixed CR. See Fig. 1.

Analysis 2

A model including neurological disability (EDSS), Malleable CR, and the product of Malleable CR and neurological disability significantly predicted depression, $F(3,47) = 8.33$, $p < .001$, PRE = .35. The main effect of Malleable CR ($t(47) = -4.34$, $p < .001$, PRE = .27) was significant. There was no significant main effect of disability in this analysis when controlling for Malleable CR and the interaction term. The main effect of Malleable CR was qualified by a significant interaction between EDSS and Malleable CR, $t(47) = -2.02$, $p = .049$, PRE = .08. Simple effects testing revealed that disability predicted depression in those with low Malleable CR (1 *SD* below the mean), $t(47) = 2.2$, $p = .033$, PRE = .09, but not in those with high Malleable CR (1 *SD* above the mean), $t(47) = -0.65$, $p = .518$, PRE < .01. Overall, this result suggests that neurological disability influences depression only in those with low Malleable CR. See Fig. 1.

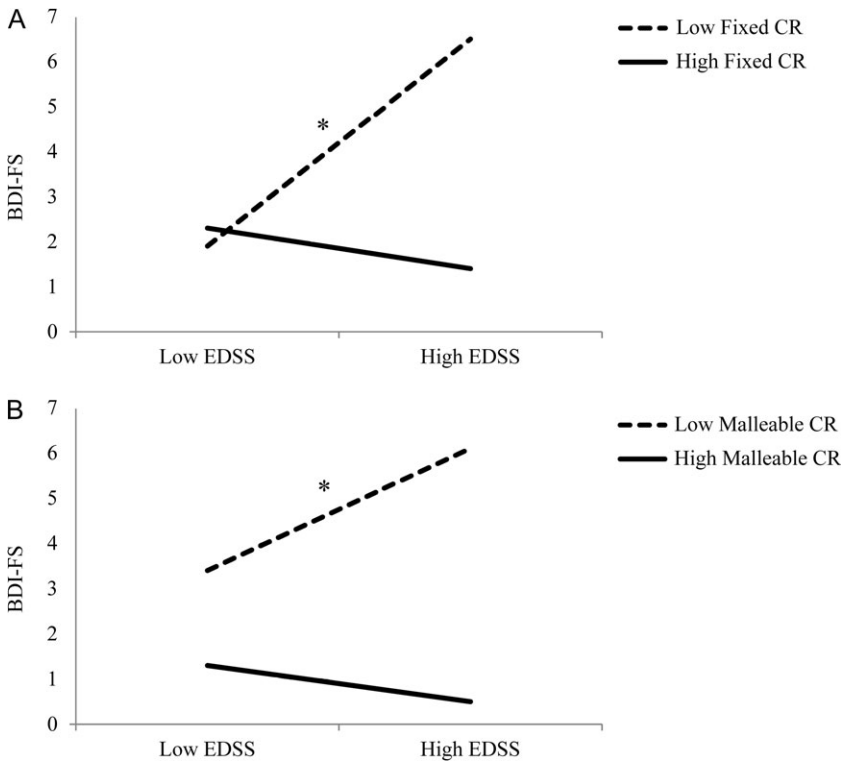

Fig. 1. Demonstrates how the relationship between disability (EDSS) and depression (BDI-FS) is moderated by level of (A) fixed cognitive reserve (Fixed CR) and (B) malleable cognitive reserve (Malleable CR). High and low cognitive reserve represents one standard deviation above and below the sample mean respectively. *indicates slope of designated line is significantly different from zero.

Discussion

Depression is common in MS. It often interferes with daily functioning and can exacerbate cognitive difficulties. There is sufficient support that depression is a functional outcome of MS pathology, evidenced through both its high prevalence rate and literature demonstrating a relationship between measures of disease burden and depression in MS. However, measures of disease burden fall short of fully accounting for depression in MS, leaving room for additional explanatory constructs like cognitive reserve. The present study examined whether two distinct operationalizations of cognitive reserve (Malleable CR and Fixed CR) moderated the relationship between disability and depression in individuals with MS. Irrespective of the form of cognitive reserve examined, results from this study demonstrated that higher disability predicts greater depression only in individuals who are low in cognitive reserve. Disability did not significantly correlate with depression among those who were high in either form of cognitive reserve. In other words, both forms of cognitive reserve may be protective against the effects of increased neurological disability on an individual's level of depression.

Cognitive reserve may serve as a point of intervention that could have beneficial effects not just on cognitive functioning but depression as well, both of which could improve an individual's overall daily functioning and quality of life. This study examined cognitive reserve in terms of education and vocabulary skills (Fixed CR) as well as engagement in stimulating leisure time activities (Malleable CR). Given that vocabulary skills and education level are generally set by adulthood, improving Malleable CR could be an important target of intervention for individuals with MS and depression. To illustrate, there is a rich literature demonstrating the positive effects of both social support and physical exercise on mental health in MS (Suh, Weikert, Dlugonski, Sandroff, & Motl, 2012). Despite this population having potential barriers to engaging in these activities such as physical or cognitive impairments, research shows that interventions (i.e. exercise training and behavioral interventions) for individuals with MS result in improvements not just in physical fitness but also cognition, quality of life, and depression (Motl & Sandroff, 2015; Pilutti, Dlugonski, Sandroff, Klaren, Motl, 2014). Additionally, depression in individuals with MS has been shown to account for 17% of the variance in determining one's engagement in leisure activity which was a significant predictor of cognitive functioning (Patel et al., 2018). This speaks to the intersection of depression and leisure activities and how treatment focusing on them could result in improvements in cognitive functioning.

Limitations

There are some limitations that arise when utilizing depression status as the outcome variable in a cognitive reserve model. There is no equivalent "rapid decline" in depression (such as from diagnosis of dementia to death in the AD literature), meaning that cognitive reserve in this conceptualization may never "run out" and thus, in some ways, is inherently different than the cognitive reserve developed from AD literature. In other words, we would not necessarily expect someone with advanced brain pathology due to MS to become severely and permanently depressed. The relationship between brain pathology and depression appears to be more complex than brain pathology and cognitive functioning. For example, loss of brain tissue will result in cognitive impairment and emotional dysfunction, but emotional dysfunction will not necessarily be associated with depressed mood.

Practical limitations of this study include its cross-sectional design, modest sample size, and use of a general self-report measure of neurologic functioning scale (EDSS) as opposed to a neuroanatomical index of disease burden. Furthermore, future studies would benefit from having a more equal mix of clinically depressed and not-depressed participants. Longitudinal work examining cognitive reserve as a moderator of neuropsychiatric sequelae of disease burden would be beneficial for better addressing the causal nature of this relationship and the role malleable cognitive reserve could play in interventions. Future research should also consider using a neuroanatomical index of disease burden, as well as larger sample sizes.

Conclusions

Previous research has indicated that cognitive reserve protects against the deleterious effects of MS disease burden on cognition; the results of the current study demonstrate how cognitive reserve may serve as a potential buffer against the negative emotional effects of neurological disability as well. Given that depression is a common problem (50% lifetime prevalence) among those with MS, and only responds to treatment in half of individuals who have it, continuing to find avenues to reduce the occurrence and severity of depression could greatly improve the daily functioning and quality of life of these individuals (Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001; Patten & Metz, 1997).

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Conflict of Interest

The authors do not have conflicts of interest to report.

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