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Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis

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Abstract

According to the cognitive reserve hypothesis, neuropsychological expression of brain disease is attenuated among persons with higher education or premorbid intelligence. The current research examined cognitive reserve in multiple sclerosis (MS) by investigating whether the negative effect of brain atrophy on information processing (IP) efficiency is moderated by premorbid intelligence. Thirty-eight persons with clinically definite MS completed a vocabulary-based estimate of premorbid intelligence (Wechsler Vocabulary) and a composite measure of IP efficiency (Symbol Digit Modalities Test and Paced Auditory Serial Addition Task). Brain atrophy was estimated from measurements of third ventricle width using high-resolution anatomical brain magnetic resonance imaging (magnetization-prepared rapid gradient echo). In a hierarchical regression analysis controlling for age and depressive symptomatology, brain atrophy predicted worse IP efficiency ($R^2 = .23$, $p = .003$) and cognitive reserve predicted better IP efficiency ($R^2 = .13$, $p = .013$), but these effects were moderated by an Atrophy × Cognitive Reserve interaction ($R^2 = .15$, $p = .004$). The negative effect of brain atrophy on IP efficiency was attenuated at higher levels of reserve, such that MS subjects with higher reserve were better able to withstand MS neuropathology without suffering cognitive impairment. Results help explain the incomplete and inconsistent relationship between brain atrophy and IP efficiency in previous research. (*JINS*, 2009, *15*, 606–612.)

Keywords: Multiple sclerosis, Cognitive reserve, Cognition, Processing speed, Brain atrophy, Intelligence

INTRODUCTION

Neuropsychological expression of brain disease is frequently incomplete. For instance, persons without clinical dementia prior to death can meet the neuropathological criteria for Alzheimer's disease (AD) on autopsy (Crystal et al., 1988; Katzman et al., 1988; Price & Morris, 1999). To explain this variability in the clinical expression of neurologic disease, the cognitive reserve hypothesis states that persons with higher premorbid intelligence or educational attainment can withstand more severe neuropathology before suffering cognitive impairment (Stern, 2002). For instance, elders with higher cognitive reserve can withstand a greater degree of parietal hypometabolism on positron emission tomography (a proxy of AD progression) before developing dementia (Alexander et al., 1997; Stern et al., 1992). Others have reported interactions between cognitive reserve and estimates of AD neuropathology [e.g., neurotic plaques (Bennett et al., 2003), fibrillar β-amyloid (Roe et al., 2008)], such that persons with higher reserve are able to withstand more severe AD neuropathology before suffering cognitive impairment. The evidence for cognitive reserve in AD is extensive (for review, see Stern, 2006) and has since been extended to other neurologic populations, including stroke (Elkins et al., 2006), lead exposure (Bleecker et al., 2007), and age-related white matter ischemic changes (Dufouil et al., 2003). To date, however, there is still little-to-no research on cognitive reserve in multiple sclerosis (MS).

MS is a chronic neurologic disease characterized by central nervous system white matter lesions and cerebral atrophy. In addition to the sensorimotor symptoms commonly associated with the disease, more than 50% of MS patients also suffer cognitive impairment (Benedict et al., 2006b; Peyser et al., 1990; Rao et al., 1991), especially information processing (IP) inefficiency (for review, see Chiaravalloti & DeLuca, 2008). Despite this, very little is known about risk and protective factors for cognitive impairment in MS. Some

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researchers have reported higher educational attainment among MS patients without cognitive impairment (e.g., Bonnet et al., 2006), but only one study has shown that cognitive reserve moderates the negative effect of MS on cognition (Sumowski et al., in press). Sumowski et al. reported an interaction between MS diagnosis and cognitive reserve, such that the negative effect of MS diagnosis on IP efficiency was attenuated at higher levels of cognitive reserve. More specifically, persons with MS showed impaired IP efficiency relative to matched healthy controls at lower levels of reserve, but this performance discrepancy narrowed as cognitive reserve increased and disappeared completely at higher levels of reserve. The current research moves beyond the dichotomous characterization of MS disease as present or absent using a magnetic resonance imaging (MRI) estimate of brain atrophy as a continuous measure of MS disease severity. The purpose of the current research was to investigate whether cognitive reserve moderates the deleterious effect of MS disease severity (i.e., brain atrophy) on IP efficiency.

MRI estimates of brain atrophy are currently the best predictors of IP efficiency in MS (for review, see Bermel & Bakshi, 2006). Despite this, brain atrophy only explains about 25–45% of the variance in IP efficiency (Benedict et al., 2004, 2006a; Christodoulou et al., 2003; Houtchens et al., 2007; Sanfilipo et al., 2006). Similar to the aforementioned clinicopathological research in AD, the relationship between MS brain atrophy and cognition appears both incomplete and inconsistent across samples. Also similar to AD, the neuropsychological expression of MS brain disease may be moderated by cognitive reserve. As such, we expect an interaction between brain atrophy and cognitive reserve in the current study, such that MS subjects with higher cognitive reserve will be more resistant to atrophy-related decrements in IP efficiency. Such a finding would advance our current understanding of MS-related cognition by identifying cognitive reserve as a protective factor against cognitive impairment. This finding may also help explain variability in previous research on brain atrophy and cognition and inform future investigations of brain–behavior relationships in MS.

METHOD

Participants

Persons aged 18–55 years with a diagnosis of clinically definite MS (McDonald et al., 2001) were recruited from local MS clinics and the North Jersey Chapter of the National MS Society. Subjects were only excluded if they had had an exacerbation in the past 4 weeks; were currently taking corticosteroid medication; or had a history of serious psychiatric diagnosis (e.g., schizophrenia, bipolar), substance abuse, diagnosed learning disability, or neurologic condition other than MS. Given the high prevalence of depression among MS patients (for review, see Siegert & Abernethy, 2005), persons with depression after MS diagnosis were included, and depressive symptomatology was quantified with the Beck Depression Inventory, Second Edition (BDI-II; Beck et al., 1996). In total, the study sample consisted of 33 women and 5 men aged 27–54 years (44.0 ± 7.5, mean ± *SD*) with 12–20 years of education (mean 15.9 ± 2.3). Depressive symptomatology on the BDI-II, which was included as a regressor in the subsequent analyses, was minimal (mean 12.0 ± 8.0), with elevations due mostly to somatic and vegetative symptoms consistent with MS. Disease duration ranged from 1 to 29 years (mean 10.1 ± 7.1), and MS course included relapsing–remitting (30), secondary progressive (6), and primary progressive (2). Mild overall gait disturbance was observed with the Hauser Ambulation Index (Hauser et al., 1983; mean 2.1 ± 2.2). The institutional review boards at the UMDNJ and the Kessler Foundation Research Center granted approval for the study. Informed consent was obtained from all subjects prior to participation.

Materials and Procedure

IP efficiency

IP efficiency refers to the speed and accuracy of cognitive processes and was evaluated in the current study with the two most validated tasks of processing speed/working memory in MS research and practice: the oral version of *Symbol Digit Modalities Test* (SDMT; Smith, 1982) and the two-trial version of the *Paced Auditory Serial Addition Task* (PASAT; Cutter et al., 1999). The SDMT and PASAT are the primary measures of processing speed/working memory within the Brief Repeatable Battery of Neuropsychological Tests in MS (Rao & the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990) and the Minimal Assessment of Cognitive Function in Multiple Sclerosis (Benedict et al., 2002). During the SDMT, subjects use a symbol-digit reference key to rapidly provide the digits associated with a series of symbols. The PASAT requires fast and accurate calculation of single digits presented every 3 s (trial 1) or 2 s (trial 2) from an audio recording. Raw scores for all tasks were converted to z scores based on published normative data from healthy controls (Benedict et al., 2006b), and the two trials of the PASAT were averaged to form one total PASAT z score. The SDMT and PASAT z scores were correlated ($r = .64$, $p < .001$) as expected based on previous research (Benedict et al., 2006b), and the scores were averaged to create a single IP efficiency z score to be used in subsequent analyses.

Brain atrophy

High-resolution three-dimensional images of the brain were created for all subjects from magnetization-prepared rapid gradient-echo (MP-RAGE) scans performed in a 3.0 T Siemens Allegra scanner (Siemens Medical Solutions USA, Inc., Malvern, PA). As third ventricle width (TVW) has been identified as the best MRI predictor of cognition among MS patients in previous research (e.g., Benedict et al., 2006a), we measured TVW to estimate brain atrophy in the current study. First, the acquired MP-RAGE images were realigned to the anterior commissure (AC)–posterior commissure (PC)

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line and were resampled to 0.5-mm^3 voxels to improve the precision of the TVW measurement. Similar to published procedures (e.g., Benedict et al., 2006a), two independent raters identified the axial slice where the third ventricle was most visible, manually marked the left and right boundaries of the ventricle on this slice, and calculated the distance in millimeters between these points to determine the TVW. As TVW is unrelated to adult intracranial volume (Gyldensted, 1977), TVW was not indexed on brain size in either the current or the previous research (e.g., Benedict et al., 2006a). The intraclass correlation for interrater reliability across all 38 subjects was very high (r = .96), with only a small average difference between raters (R1 − R2 = 0.32 mm; Bland & Altman, 1986). Test–retest intrarater reliability for a subset of 19 subjects after 1 week yielded very high intraclass correlations for both raters (rs > .98). Four differences in measurement greater than 1 mm were resolved through joint reanalysis and consensus. Differences of 1 mm or less were averaged. The final TVW measurement was highly correlated with each rater's individual measurements (rs = .99).

Cognitive reserve

Vocabulary knowledge is frequently used to estimate premorbid intelligence because it is resistant to decline secondary to neurologic insult (Lezak, 2004) and is therefore often used as a proxy of cognitive reserve (for review, see Stern, 2006). Other proxies of reserve in AD research include educational attainment and occupational complexity as these data are readily available and are independent of AD neuropathology. In MS, however, the much younger age of onset increases the chances that MS disease impacts patients' level of education and type of occupation. Given that 19% of our sample was diagnosed between ages 19 and 25 years, neither education nor occupation was included as reserve variables. This is because education and career development are often not complete at such young ages. Cognitive reserve was thus estimated with the Vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Raw scores were converted to norm-referenced *T* scores, which were then transformed into *z* scores for ease of presentation.

Statistical analysis

This study investigates whether cognitive reserve moderates the relationship between brain atrophy and IP efficiency. After calculating descriptive statistics and Pearson intercorrelations for key variables, a hierarchical linear regression was performed to predict IP efficiency *z* scores. Controlling for age and BDI-II total score (block 1), brain atrophy [TVW (mm); block 2] and cognitive reserve (WASI Vocabulary *z* score; block 3) were entered into the model. Finally, and most importantly, an interaction term between brain atrophy and cognitive reserve was entered (block 4) to determine whether the impact of brain atrophy on IP efficiency differs as a function of cognitive reserve.

RESULTS

The mean IP efficiency *z* score was low average overall (mean −0.66 ± 1.1) but ranged from impaired (−2.5) to above average (1.2). The mean brain atrophy (TVW) of 4.95 ± 2.06 mm fell between published TVW means for relapsing–remitting and secondary progressive patients (Benedict et al., 2006a), which is consistent with the mixed MS course of our sample. Cognitive reserve *z* score was average overall (mean 0.44 ± 0.86) but ranged from below average (−1.1) to superior (2.5). There was essentially no relationship between cognitive reserve and brain atrophy (r = −.09, p > .5), thereby ruling out the possibility that vocabulary knowledge was affected by disease progression. This supports the use of vocabulary to estimate premorbid intelligence in MS. Cognitive reserve was also unrelated to age (r = .10, p > .5), gender [$t(36)$ = 0.17, p > .5], and disease course [relapsing–remitting *vs.* chronic progressive; $t(36)$ = 0.85, p > .1].

There was a negative correlation between brain atrophy and IP efficiency (r = −.46, p < .01) such that IP efficiency declined as atrophy increased. Cognitive reserve was positively correlated with IP efficiency (r = .37, p < .05), with increased IP efficiency at higher levels of reserve. If higher cognitive reserve moderates the negative effect of brain atrophy on cognition, then the correlation between atrophy and IP efficiency should be stronger for patients with lower cognitive reserve relative to those with higher reserve. As a preliminary test of this hypothesis, we divided our sample into lower reserve (mean z = −0.28 ± 0.41) and higher reserve (mean z = 1.16 ± 0.51) using a median split. Atrophy was indeed more strongly associated with IP efficiency among subjects with lower reserve (r = −.79, p < .001) than those with higher reserve (r = −.16, p > .5). This pattern was more thoroughly investigated with multiple regression within which cognitive reserve was analyzed as a continuous variable.

The full regression model accounted for 52% of the variance in IP efficiency (Table 1). Neither age nor depressive symptomatology accounted for significant variance in block 1. There was a large negative effect of brain atrophy and a large positive effect of cognitive reserve on IP efficiency in blocks 2 and 3. These effects were moderated by a large Brain Atrophy × Cognitive Reserve interaction in block 4, indicating that the effect of atrophy on IP efficiency differs as a function of reserve. The predicted relationship between atrophy and IP efficiency for persons at three levels of reserve (low, normal, and high) is depicted in Figure 1. As illustrated, MS subjects with minimal atrophy (2.9 mm = −1 *SD*) produced normal IP efficiency regardless of cognitive reserve. At higher atrophy (7.0 mm = +1 *SD*), however, MS subjects with high cognitive reserve maintained performance within the average range (25th percentile), but those with normal reserve demonstrated mild impairment (5th percentile), and those with lower reserve showed severe impairment (1st percentile). As such, higher cognitive reserve allowed MS subjects to better withstand the increased cerebral demands associated with advancing disease (i.e., atrophy).

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Table 1. Summary of hierarchical regression predicting IP efficiency *z* score

	Model 1			Model 2			Model 3			Model 4		
Variable	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Constant	−1.03	1.14		0.11	1.08		0.46	1.00		1.28	0.93	
Age	0.01	0.02	0.05	0.02	0.02	0.11	0.01	0.02	0.06	0.01	0.02	0.06
BDI-II	0.01	0.02	0.05	−0.01	0.02	−0.09	−0.03	0.02	−0.23	−0.04	0.02	−0.27
Brain atrophy				−0.26	0.08	−0.51**	−0.26	0.08	−0.50**	−0.41	0.08	−0.79***
Cognitive reserve (CR)							0.49	0.18	0.39*	−0.78	0.44	−0.63
Brain Atrophy × CR										0.26	0.08	1.12**
Model R^2		.004			.236			.369			.518	
F for model		0.073			3.492*			4.824**			6.867***	
R^2 change		.004			.231			.133			.149	
F for change in R^2		0.073			10.292**			6.979*			9.857**	

*$p < .05$.
**$p < .01$.
***$p < .001$.

DISCUSSION

Cognitive reserve moderates the negative effect of MS brain pathology on cognition, with higher reserve protecting MS subjects from disease-related IP inefficiency. Stated differently, MS subjects with higher reserve are able to withstand more severe neuropathology before suffering cognitive impairment. This protective effect of reserve is not simply explained by greater IP efficiency in subjects with higher reserve across levels of disease (main effect of cognitive reserve); instead, higher reserve appears to actually lessen the impact of MS disease on cognition (interaction between atrophy and cognitive reserve). This attenuated effect of MS disease on cognition is consistent with previous cognitive reserve research in AD (e.g., Bennett et al., 2003).

According to Stern et al. (2005), higher cognitive reserve is associated with elaborated and synaptically complex neural networks, which afford greater neurocognitive efficiency and capacity. As task demands increase and/or neurologic disease advances, persons with higher reserve should require fewer cerebral resources to perform the same cognitive tasks as persons with lesser reserve. [This is also consistent with the "neural efficiency hypothesis" (Neubauer et al., 2002).] MS is associated with cerebral inefficiency, as evidenced by greater cortical recruitment to perform the same cognitive tasks as healthy controls (Hillary et al., 2003; Sweet et al., 2006; Wishart et al., 2004), a pattern that becomes even more pronounced as brain atrophy increases (Morgen et al., 2007). Taken together, MS patients with lower reserve suffer the compounding effects of MS-related neurocognitive challenges in the context of lower premorbid neurocognitive efficiency and capacity, thereby explaining their increased risk for cognitive impairment in the current study. In contrast, MS patients with higher cognitive reserve are better able to withstand disease-related neurocognitive challenges because of greater premorbid neurocognitive efficiency and capacity. Consistent with this explanation, recent functional magnetic resonance imaging data from our laboratory indicate that MS subjects with higher cognitive reserve demonstrate greater cerebral efficiency during cognitive tasks (Sumowski et al., 2008). More specifically, the same patterns of cerebral activation that have discriminated between MS subjects and healthy controls in previous research (e.g., increased right prefrontal recruitment in MS subjects) also discriminate between MS subjects with higher and lower cognitive reserve (e.g., subjects with lower reserve require more right prefrontal recruitment to maintain cognitive performance).

Given the moderating effect of cognitive reserve on brain atrophy, the current results may help explain the incomplete and inconsistent relationship between brain atrophy and IP efficiency across previous research. As illustrated in Figure 1, the relationship between brain atrophy and IP efficiency differs as a function of reserve, with stronger associations at lower levels of reserve. In a similar way, the relationship between MS brain atrophy and IP efficiency in previous research

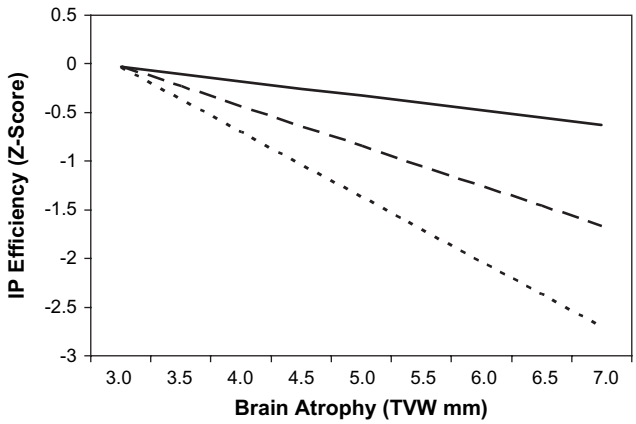

Fig. 1. Interaction between cognitive reserve and brain atrophy on IP efficiency. Predicted relationship between brain atrophy and IP efficiency for MS subjects with low cognitive reserve ($z = -1.0$; dotted line), normal cognitive reserve ($z = 0.0$; dashed line), and high cognitive reserve ($z = +1.0$; solid line). Age and BDI-II were held constant at sample means.

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may vary due to differences in cognitive reserve across samples. To investigate, we identified four recent studies that have (a) predicted SDMT and PASAT performance with MRI estimates of brain atrophy and (b) reported educational attainment for the sample analyzed (data on vocabulary were not available; Benedict et al., 2004; Christodoulou et al., 2003; Houtchens et al., 2007; Sanfilipo et al., 2006). When the SDMT and PASAT are averaged into one IP efficiency variable (as in the current study), brain atrophy across the current and four previous studies explains between 23 and 46% of the variance in IP efficiency. More importantly, there appears to be a large inverse relationship between the educational attainment of the samples and the amount of variance accounted for by brain atrophy (Figure 2). In other words, the effect of brain atrophy on IP efficiency is weaker in samples with higher cognitive reserve, which is consistent with our finding that cognitive reserve moderates the effect of atrophy on IP efficiency. As an important caveat, these data are based on a small number of studies with variable methods of estimating brain atrophy. Even still, future research examining the relationship between MS brain atrophy and cognition should investigate the interaction between brain pathology and cognitive reserve. Neglecting to consider this interaction could lead to exaggerated clinicopathological associations within lower reserve samples and suppressed associations within higher reserve samples.

The current results have potential clinical implications. Given that MS disease progression is unpredictable for any single patient, prediction of future cognitive impairment is often considered out of reach. According to our data, consideration of a patient's level of cognitive reserve may improve early identification of patients "at risk" for future cognitive decline. These patients could be directed to early intervention cognitive rehabilitation to learn and integrate compensatory strategies into their daily routines before cognitive impairment encumbers such learning (for review, see O'Brien et al., 2008). In fact, the clinical utility of cognitive reserve may be greater in MS than in diseases such as AD. An *in vivo* diagnosis of probable AD is based primarily on the cognitive criteria of dementia. As such, at AD diagnosis, any cognitive benefit from higher reserve has already been exhausted. Moreover, because persons with higher reserve can withstand more AD neuropathology before suffering dementia, they actually have more advanced AD at the time of diagnosis (Alexander et al., 1997; Bennett et al., 2003; Roe et al., 2008; Stern et al., 1992) and are therefore closer to death (Stern et al., 1995). In contrast, because a diagnosis of MS is based primarily on sensorimotor symptoms and neuroimaging (e.g., McDonald et al., 2001), there is little reason to expect MS patients with higher reserve to be diagnosed later in the course of their MS. Cognitive reserve at the time of diagnosis may prove to be a useful clinical indicator of the rate of future decline. This is particularly important given the relatively young age of MS diagnosis, which disrupts patients' lives at the beginning of their careers and the start of their families. Given the long course of the disease, the benefits of prediction and early intervention could potentially improve quality of life for decades.

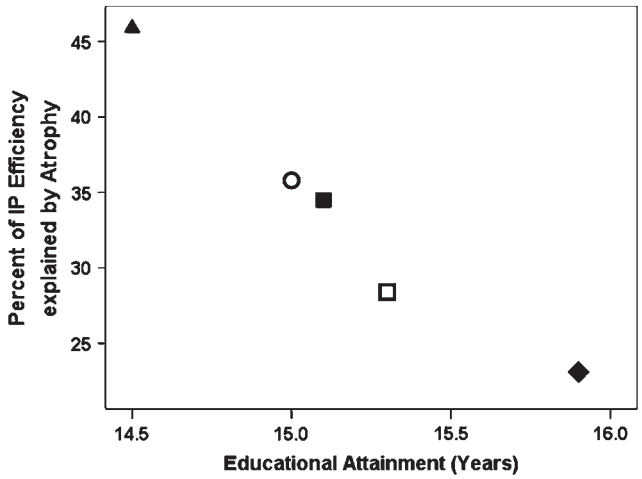

Fig. 2. The effect of brain atrophy on IP efficiency varies by samples' level of cognitive reserve. Scatter plot depicts the relationship between the years of educational attainment and the variance (R^2) in IP efficiency accounted for by brain atrophy across five studies. The current study is represented by a diamond, and the four previous studies are represented by a circle (Christodoulou et al., 2003), a solid square (Benedict et al., 2004), an open square (Sanfilipo et al., 2006), and a triangle (Houtchens et al., 2007).

We hope that the current study stimulates subsequent research on cognitive reserve in MS. For instance, prospective research with longitudinal data will help elucidate the effect of reserve as atrophy increases within the same patient. Also, although IP inefficiency is among the most prevalent MS-related cognitive deficits, future research should also examine the effect of reserve across several neuropsychological domains, including memory. Although the vocabulary-based estimate of reserve used in the current study is a strong proxy of cognitive reserve and therefore provides a necessary proof of principle, future research should investigate more malleable sources of cognitive reserve, which could become a focus of cognitive rehabilitation. For instance, premorbid participation in cognitive leisure activities uniquely and independently protects persons with AD from cognitive decline (Scarmeas et al., 2001; Verghese et al., 2003; Wilson et al., 2002). This remains to be examined in MS. Finally, we have discussed characteristics of MS that make cognitive reserve a clinically important consideration. We also believe that MS provides an ideal model for investigating cognitive reserve itself. Given that (a) MS diagnosis is independent of cognitive reserve, (b) MS diagnosis occurs prior to many age-related comorbid ailments (e.g., cardiovascular disease), and that (c) MRI permits *in vivo* documentation of disease progression, cognitive reserve researchers may consider MS as a model for investigating the protective effect of cognitive reserve from early to late adulthood.

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