Journal of the International Neuropsychological Society (2010), **16**, 829–835.

doi:10.1017/S1355617710000688

Cognitive reserve moderates decline in information processing speed in multiple sclerosis patients

RALPH H.B. BENEDICT,[1,2] SARAH A. MORROW,[1,2] BIANCA WEINSTOCK GUTTMAN,[1,2] DIANE COOKFAIR,[1,2] AND DAVID J. SCHRETLEN[3]

[1]Department of Neurology, Division of Cognitive and Behavioral Neurosciences, State University of New York at Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York
[2]Jacobs Neurological Institute, Buffalo, New York
[3]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

(RECEIVED January 19, 2010; FINAL REVISION June 2, 2010; ACCEPTED June 2, 2010)

Abstract

Cognitive reserve is widely recognized as a moderator of cognitive decline in patients with senile dementias such as Alzheimer's disease. The same effect may occur in multiple sclerosis (MS), an immunologic disorder affecting the central nervous system. While MS is traditionally considered an inflammatory, white matter disease, degeneration of gray matter is increasingly recognized as the primary contributor to progressive cognitive decline. Our aim was to determine if individual differences in estimated cognitive reserve protect against the progression of cognitive dysfunction in MS. Ninety-one patients assessed twice roughly 5 years apart were identified retrospectively. Cognitive testing emphasized mental processing speed. Cognitive reserve was estimated by years of education and by performance on the North American Adult Reading Test (NAART). After controlling for baseline characteristics, both years of education ($p = .013$) and NAART scores ($p = .049$) significantly improved regression models predicting cognitive decline. Symbol Digit Modalities Test (SDMT) performance showed no significant change in patients with > 14 years of education, whereas it declined significantly in patients with ≤ 14 years of education. We conclude that greater cognitive reserve as indexed by either higher premorbid intelligence or more years of education protects against the progression of cognitive dysfunction in MS. (*JINS*, 2010, *16*, 829–835.)

Keywords: Multiple sclerosis, Neuropsychology, Cognitive reserve, Brain

INTRODUCTION

Multiple sclerosis (MS), like other neurological diseases affecting the brain, causes impairment on a range of neuropsychological (NP) tests. Long considered primarily a physically disabling disease, many recent studies have shown mild to severe NP deficits in MS patients, especially on tests emphasizing either memory or the speed and efficiency of mental processing (Benedict et al., 2002; Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008; Rao, Leo, Bernardin, & Unverzagt, 1991). Recently, many studies have found that such deficits correlate with abnormalities on structural brain magnetic resonance imaging (MRI), particularly measures of whole and regional brain atrophy (Amato et al., 2004; Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2009; Benedict, Bruce, et al., 2006; Christodoulou et al., 2003; Houtchens et al., 2007; Sanfilipo, Benedict, Weinstock-Guttman, & Bakshi, 2006; Tekok-Kilic et al., 2007). Most often, large individual variability can be observed with correlation coefficients falling in the vicinity of $r = 0.60$, thus accounting for roughly 1/3 of the variance in NP measures. This observation raises the question of why NP deficits are not consistently more severe in MS, and more strongly correlated with brain atrophy, in a disease that almost invariably affects the brain.

Cognitive reserve (CR) might explain some of this variation in the expression of MS neuropathology on NP testing. CR may be defined as individual differences in the baseline efficiency of cognitive processing, such that those with more efficient networks have greater capacity and are more flexible in coping with impairment (Stern, 2009). Common metrics of CR are achieved education level and irregular word reading ability (Alexander et al., 1997; Lynn & Mikk, 2007; McCarthy, Sellers, & Burns, 2003), and these CR proxies can be independent predictors of neuropsychological outcomes (Albert & Teresi, 1999). CR, therefore, represents

Correspondence and reprint requests to: Ralph H.B. Benedict, Department of Neurology, 100 High Street (D-6), Buffalo, New York 14203. E-mail: benedict@buffalo.edu

a potential mechanism for coping with brain damage (Jacobs et al., 1994; Stern, 2009; Stern, Gurland, Tatemichi, Tang, Wilder, & Mayeux, 1994). This model emphasizes behavioral adaptation or NP compensation, perhaps mediated by increased activation of either usual or alternate neural networks. CR could explain why a person with high intelligence or education, for example, can sustain more cerebral injury before showing a functional deficit. There is considerable evidence supporting this concept in the Alzheimer's disease (AD) literature (Roe, Xiong, Miller, & Morris, 2007; Stern, 2006). As noted by Sumowski and DeLuca (Sumowski, Chiaravalloti, Wylie, & Deluca, 2009), recent investigations in other neurological populations such as frontotemporal dementia (Borroni et al., 2009), stroke (Elkins, Longstreth, Manolio, Newman, Bhadelia, & Johnston, 2006), head trauma (Ropacki & Elias, 2003), Parkinson's disease (Glatt et al., 1996), and ischemic white matter disease (Dufouil, Alperovitch, & Tzourio, 2003), have also supported the CR hypothesis.

The course of MS differs markedly from AD in that cognitive impairment progresses much more slowly, with periods of stability in some patients and more rapid decline in others (Amato, Ponziani, Siracusa, & Sorbi, 2001; Kujala, Portin, & Ruutiainen, 1997; Sperling et al., 2001). Yet the CR hypothesis may be relevant in the presentation of neuropsychological compromise in MS. Indeed, in a recent functional MRI (fMRI) study (Sumowski, Wylie, Deluca, & Chiaravalloti, 2010), MS patients showed a positive correlation between higher estimated premorbid IQ and resting state activity, and a negative correlation with prefrontal recruitment which was presumably required to facilitate performance of the activation task (n-back). The authors concluded that patients with lower CR required more cerebral resources to perform the same cognitive task than patients with greater CR (Sumowski et al. 2010).

Sumowski and colleagues (2009) also investigated whether the adverse impact of brain atrophy on information processing speed and efficiency would be moderated by CR. In 38 patients, cognitive function was assessed using the Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT), which are widely accepted as reliable and sensitive in MS studies (Benedict, Cookfair, et al., 2006; Benedict et al., 2002; Rao et al., 1991). Sumowski et al. (2010) measured brain atrophy using the third ventricle width (TVW), which correlates strongly with cognitive impairment in MS (Benedict, Bruce, et al., 2006; Benedict, Weinstock-Guttman, Fishman, Sharma, Tjoa, & Bakshi, 2004; Houtchens et al., 2007; Tekok-Kilic et al., 2007). Hierarchical regression models showed that the expected relationship between brain atrophy and cognitive processing was moderated by estimated premorbid intelligence. The data revealed a significant atrophy × CR interaction in that the impact of atrophy on cognition was attenuated at higher levels of CR. In other words, among patients with more severe brain atrophy, those with greater CR showed better cognitive performance. The same was not true of patients with minimal atrophy.

The findings from Sumowski and colleagues support the CR model and may explain some of the variance in NP outcomes not accounted for by MRI measured neuropathology. Their conclusions, however, were based on a small, cross-sectional sample, and our objective was to replicate this work using a longitudinal design emphasizing decline in cognitive function, and a larger sample size.

METHODS

Participants

We studied 91 patients with clinically definite MS (Polman et al., 2005) registered at the MS clinic within the Jacobs Neurological Institute (JNI) in Buffalo, NY. The patients entered the study for one of three reasons: participation in research (n = 52; 57%), routine monitoring of cognitive function (n = 10; 11%), or referral for evaluation of a specified management problem related to suspected cognitive impairment (n = 29; 32%). All provided informed consent for either participation in a prospective study, or the storage and analysis of their clinical data, in accordance with Institutional Review Board guidelines. Patients were excluded from the study if any of the following criteria were met: (a) past history of a medical or psychiatric disorder that could substantially influence cognitive function or have a lasting impact on brain integrity, including but not limited to craniocerebral trauma with greater than 5-min loss of consciousness, alcohol or drug dependence, and learning disability; (b) current major depression or alcohol/substance abuse; (c) neurological impairment that might interfere with cognitive testing; (d) an MS relapse or acute corticosteroid treatment within 6 weeks of testing. As in our previous work (Benedict, Cookfair, et al., 2006; Houtchens et al., 2007; Parmenter, Testa, Schretlen, Weinstock-Guttman, & Benedict, 2010; Parmenter, Zivadinov, et al., 2007), major depressive episode was assessed by means of a site-specific semi-structured interview based on the DSM-IV (APA, 2000), which mirrors the DSM-IV criteria while accounting for the influence MS may have on the neurovegetative symptoms of depression.

Baseline mean (±*SD*) age was 44.8 ± 8.8 years. The sample was 70% female and 92% Caucasian. Patients completed on average 14.3 ± 2.0 years of education. All patients were characterized according to their current disease course: relapsing-remitting (n = 71), secondary-progressive (n = 17), primary progressive (n = 3); thus 78% of the sample had relapsing-remitting course, which is consistent with population studies of MS (Jacobs et al., 1999). Mean disease duration was 11.0 ± 8.3 years. Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) within 6 months of testing was available in 82 patients, and the median was 2.5 (range, 0–7.5).

Tests and Procedures

Following Sumowski et al. (2010), we investigated information processing speed and efficiency using the SDMT

https://doi.org/10.1017/S1355617710000688 Published online by Cambridge University Press

and the PASAT. The SDMT (Rao, 1991a,b; Smith, 1982) was used as a measure of processing speed in the visual modality. Participants were presented a series of nine symbols, each paired with a single digit number in a key at the top of an 8.5 × 11-inch sheet of paper. The remainder of the page included a pseudo-randomized sequence of symbols for which the participant was instructed to express orally the digit associated with each corresponding symbol as quickly as possible. The dependent measure was the number of correct responses in 90 s. We used the 3.0 inter-stimulus interval version of the PASAT (Gronwall, 1977; Rao, 1991a,b) to measure of auditory processing speed and working memory. Participants were presented 60 single-digit numbers, at 3-s intervals, and asked to add each consecutive digit to the one immediately preceding it. The dependent measure was the number of correct responses across 60 trials. The 3-s version of the PASAT was selected because it is a gold standard measure of auditory processing speed in the MS literature and is included in the MS Function Composite (MSFC), a widely accepted measure of general neurological disability (Cutter et al., 1999; Rudick et al., 2001). For the present study we followed Sumowski and colleagues by calculating an information processing (IP) efficiency index, which is the mean *Z* score of the SDMT and PASAT based on previously published normative values (Benedict, Cookfair, et al., 2006). Each evaluation also included the North American Adult Reading Test (NAART) (Blair & Spreen, 1989; Friend & Grattan, 2000).

All participants were evaluated in an outpatient clinical setting housed within an urban hospital in Buffalo, NY. A trained technician or graduate student, under the supervision of a single board-certified neuropsychologist, administered all tests. Board certified neurologists reported the EDSS scores. A trained student, blinded to clinical data and presentation, entered data into an SPSS database accounting for all of the NP variables.

Analysis Plan

The primary cognitive outcomes were based on the work of Sumowski et al. (2009) and included the PASAT and SDMT, as well as an IP composite index, as noted above. The cognitive data were normalized in accordance with previously published norms (Benedict, Cookfair, et al., 2006). Baseline and follow-up data were compared using analysis of variance (ANOVA) and correlations were examined using the Pearson calculation. We accepted a p value of $< .05$ as significant. Linear regression analysis (forward stepwise with p to enter 0.10 and to exit 0.05) was pursued to determine significant predictors of follow-up cognitive test scores, first as measured by the IP index, and then SDMT alone as this test proved to be more sensitive to decline in cognitive capacity. Baseline score was entered and retained in Block 1. Then age, sex, disease course, and cognitive reserve measures were entered in Block 2 using a forward step procedure.

RESULTS

The mean test–retest interval was 1743.6 ± 440.6 days (or roughly 5 years), and there was no significant correlation between test–retest interval and CR measures (r values −0.01 for education and 0.14 for NAART). The correlation between education and NAART was $r = 0.62$ ($p < .001$).

For descriptive purposes the cognitive test data were compared with a demographically matched control sample from prior research (Benedict, Cookfair, et al., 2006). The mean IP efficiency Z score was −1.5 ± 1.5. The mean SDMT Z score was −1.9 ± 1.4, and the mean PASAT z score was −0.6 ± 1.2. These tests were correlated at $r = 0.59$ ($p < .001$). This degree of impairment observed is consistent with our prior research (Benedict, Bruce, et al., 2006; Benedict, Cookfair, et al., 2006; Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007; Strober, Englert, Munschauer, Weinstock-Guttman, Rao, & Benedict, 2009).

Table 1 shows the baseline and follow-up data for the disease characteristics and cognitive testing in the 91 MS patients. There was significant progression in EDSS from a median value of 2.5 to 3.5 over the 5-year course of the study. Likewise, there was significant worsening on the SDMT ($p < .003$) and a trend for worsening on the PASAT ($p = .189$). The SDMT had marginally superior test–retest reliability than PASAT ($r = 0.86$ *vs.* 0.75), and the IP index reliability was $r = 0.85$ (all p values $< .001$).

Cognitive reserve was estimated using years of completed education and the NAART. Correlations between these estimates and clinical measures are presented in Table 2. There

Table 1. Baseline and follow-up clinical data

	Baseline		Follow-up		*p*
Number (%) Progressive Course	20 (22.2%)		26 (28.6)		.07
EDSS	2.5	0.0 – 7.5	3.5	0.0 – 7.5	<.001
	Mean	*SD*	Mean	*SD*	
IP Index	−01.3	01.2	−01.6	01.6	.01
SDMT	46.5	12.4	43.5	16.0	.003
PASAT	40.7	12.7	39.1	15.6	.189

Note. Course and EDSS effects tested using Wilcoxon signed ranks test and cognitive test effects by paired-sample *t* test. All samples sizes are $n = 91$ except EDSS where the sample size was $n = 78$. EDSS = Expanded Disability Status Scale; SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test.

https://doi.org/10.1017/S1355617710000688 Published online by Cambridge University Press

Table 2. Correlation coefficients between cognitive reserve and clinical measures

	EDSS	Disease duration	IP index	SDMT	PASAT
NAART	0.05	−0.03	0.09	0.10	0.19
Education	−0.06	0.00	0.06	0.13	0.14

Note. No correlation reaches threshold for statistical significance at $p < .05$. EDSS = Expanded Disability Status Scale; IP = information processing; SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test; NAART = North American Adult Reading Test.

were no statistically significant correlations between cognitive reserve and baseline clinical measures.

Linear regression models were calculated predicting follow-up cognitive capacity as measured by the IP index. Baseline score was entered and retained in Block 1. Then the demographic and cognitive reserve measures were entered in Block 2 using a forward step procedure. The results are presented in Table 3. In the second step, education entered the model increasing the R^2 by a small (0.02) but statistically significant amount ($p = .013$). When disease course and disease duration were included in Block 2, both NAART and course were retained, increasing the R^2 by 0.03 ($p = .049$).

Because patients showed greater decline on the SDMT, separate models were calculated for each cognitive measure separately. The PASAT model included no demographic and cognitive reserve measures after accounting for baseline performance. The SDMT models both included only education which raised the R^2 from 0.73 to 0.76 ($p = .001$).

The mean change in SDMT raw score was −3.0 ± 8.4. K-means cluster analysis was used to dichotomize subjects into high and low educational reserve groups, the resulting low group (10–14 years) corresponding to 2 years of college or less, the high group (15–20 years) corresponding to 3 years of college or more. A mixed factor general linear model (GLM) was performed to evaluate the effects of educational reserve on change in SDMT score over time and assess for interaction between time and educational reserve (high *vs.* low). This analysis revealed a significant interaction ($F(1,94) = 7.50$; $p = .007$) with low educational reserve subjects showing significant reduction in SDMT and the high sub-group showing little change. To illustrate the effect the data are presented in Figure 1, where high education patients show no significant change on SDMT (paired T test not significant, $p > .05$). In contrast, low reserve patients decline by roughly 4 points, from 47.6 ± 12.8 to 43.0 ± 16.8, significant at $p < .001$. ANOVA showed that the difference between the sub-groups on SDMT at baseline was not significant ($p > .05$).

DISCUSSION

The data described in this study support the CR hypothesis in MS patients and to some extent replicate or support the work of Sumowski et al. (2009) using different methods. In their cross-sectional study, Sumowski et al. (2010) found that the relationship between brain atrophy and IP efficiency was moderated by cognitive reserve. While patients with high and low reserve performed similarly on NP tests when atrophy was minimal, those with low reserve showed greater IP deficiency when brain atrophy was more severe. The present study used a longitudinal design to determine if CR moderates the degree of decline on neuropsychological testing over time. We used two measures of CR, a reading test of estimated premorbid IQ and years of education, which had differential effects on cognitive outcomes. Our primary finding was that CR measures moderated the degree of decline on NP tests assessing IP efficiency. Patients with low reserve were likely to show decline over time, especially on the SDMT, whereas those with high CR did not.

Brain reserve (BR) capacity is a hypothetical construct which proposes that the amount of cerebral injury that can be sustained before reaching a threshold of clinical expression is dependent upon an individual's baseline neural foundation (Satz et al., 1993). Individual differences in brain size, synapse count, or some other indicator of neural complexity may explain why neuropathology is more detrimental in one person than another with the same level of pathology. BR is a passive concept in that the clinical presentation is not dependent on a person's behavioral or psychological adjustment; a cerebral lesion of a particular size may cause clinical deficits in a person with relatively low BR, and not in another with higher BR (Stern, 2002; Tabert et al., 2002). BR and CR

Table 3. Results of linear regression models

	R^2 accounting for baseline	Variable entered in Step 2	Total R^2 final model	p value
IP Index	0.72	Education	0.74	0.013
IP index	0.71	Course NAART	0.76	0.049
SDMT	0.73	Education	0.76	0.001
PASAT	0.55	—	0.55	—

Note. IP = information processing; NAART = North American Adult Reading Test; SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test.

https://doi.org/10.1017/S1355617710000688 Published online by Cambridge University Press

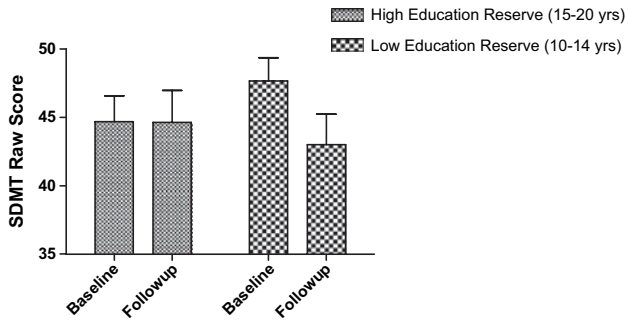

Fig. 1. Baseline and follow-up Symbol Digit Modalities Test (SDMT) performance in high (education > 14 years, $n = 38$) and low (< or = 14 years, $n = 53$) cognitive reserve subgroups. Paired t tests show no significant change in the high reserve group. Low reserve patients decline from 47.6 ± 12.8 to 43.0 ± 16.8, significant at $p < .001$.

are interrelated constructs. High baseline cognitive ability likely has a biological substrate such as high dendritic density. Patients with greater BR are, therefore, better equipped to compensate for brain injury mediated by increased activation of either usual or alternate neural networks. The study by Sumowski et al. (2010) shows that BR or CR either help patients with brain atrophy function normally, and our data show that such patients are less likely to evidence decline on cognitive tests over time.

It is now widely agreed that MS is both a neurodegenerative and inflammatory demyelinating disease (Trapp & Nave, 2008). Gray matter atrophy and cortical lesions are correlated with cognitive performance, and these lesions contain fewer inflammatory cells but many activated microglia (Bo, Vedeler, Nyland, Trapp, & Mork, 2003a,b). Similar microglial activation patterns, leading to oxidative stress and excitotoxicity, have been found in MS and Alzheimer's disease (Dal Bianco, Bradl, Frischer, Kutzelnigg, Jellinger, & Lassmann, 2008). A slow loss of dendritic density as demonstrated by gray matter atrophy, due to ongoing neurodegenerative processes, is the more likely explanation of cognitive impairment in MS patients (Zivadinov et al., 2001). MS also affects the brain in younger individuals and sometimes may affect children before full cognitive development is achieved. Recent data from our group show that patients with an early onset MS (before age of 18) have slower decline in neurological disability and better brain tissue preservation as measured per MRI, than their adult counterparts (Yeh et al., 2009). Marked differences in clinical MRI and NP outcomes can also be seen across disease course in adult MS patients (Benedict, Bruce, et al., 2006), and recent work suggests that compensatory fMRI changes are more apparent in patients with higher baseline CR (Sumowski et al. 2010). Future longitudinal studies using both repeat MRI and cognitive evaluations, in patients with and without pediatric onset or with progressive *versus* nonprogressive course, will hopefully shed more light on the many factors that facilitate the effects of BR and CR in MS.

Our study is limited by the lack of MRI data which would have permitted a more direct replication of the work by Sumowski et al. (2010) Our study was retrospective, and the education sub-groups described in Figure 1 were not entirely matched on processing speed measures at the baseline cognitive assessment. In addition, the lack of correlation between the IP and CR measures in this sample at baseline is of some concern, adding to the importance of replication. Our study did not include a normal control group which would have enabled us to determine the extent to which our measure of decline in cognition was confounded by practice effects. The strength of our study is that it presents a longitudinal analysis supporting the importance of CR in preserving cognitive function.

In summary, we have noted the report of Sumowski et al. (2009) showing that BR or CR help MS patients with brain atrophy function normally on cognitive processing tasks. Our longitudinal data support this hypothesis in that MS patients with higher CR are less likely to evidence decline in IP over time. This is a novel area of research in MS that requires replication. Future prospective studies using MRI measures as well as parallel disease onset age groups are under way.

ACKNOWLEDGMENTS

We report that the information in this manuscript and the manuscript itself has never been published either electronically or in print. There are no financial or other relationships that could be interpreted as a conflict of interest affecting this manuscript. There were no sources of financial support for this project.

REFERENCES

Albert, S.M., & Teresi, J.A. (1999). Reading ability, education, and cognitive status assessment among older adults in Harlem, New York City. *American Journal of Public Health*, *89*, 95–97.

Alexander, G.E., Furey, M.L., Grady, C.L., Pietrini, P., Brady, D.R., Mentis, M.J., et al. (1997). Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: Implications for the cognitive reserve hypothesis. *American Journal of Psychiatry*, *154*, 165–172.

Amato, M.P., Bartolozzi, M.L., Zipoli, V., Portaccio, E., Mortilla, M., Guidi, L., et al. (2004). Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. *Neurology*, *63*, 89–93.

Amato, M.P., Ponziani, G., Siracusa, G., & Sorbi, S. (2001). Cognitive dysfunction in early-onset multiple sclerosis: A reappraisal after 10 years. *Archives of Neurology*, *58*, 1602–1606.

APA. (2000). *Diagnostic and statistical manual of mental disorders, fourth edition, text revision*. Washington DC: American Psychiatric Association.

Benedict, R.H.B., Bruce, J.M., Dwyer, M.G., Abdelrahman, N., Hussein, S., Weinstock-Guttman, B., et al. (2006). Neocortical atrophy, third ventricular width, and cognitive dysfunciton in multiple sclerosis. *Archives of Neurology*, *63*, 1301–1306.

Benedict, R.H.B., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., et al. (2006). Validity of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *12*, 549–558.

Benedict, R.H.B., Fischer, J.S., Archibald, C.J., Arnett, P.A., Beatty, W.W., Bobholz, J., et al. (2002). Minimal Neuropsychological

Assessment of MS Patients: A Consensus Approach. *Clinical Neuropsychologist*, *16*, 381–397.

Benedict, R.H.B., Ramasamy, D., Munschauer, F., Weinstock-Guttman, B., & Zivadinov, R. (2009). Memory impairment in multiple sclerosis: Correlation with deep grey matter and mesial temporal atrophy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *80*, 201–206.

Benedict, R.H.B., Weinstock-Guttman, B., Fishman, I., Sharma, J., Tjoa, C.W., & Bakshi, R. (2004). Prediction of neuropsychological impairment in multiple sclerosis: Comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Archives of Neurology*, *61*, 226–230.

Blair, J.R., & Spreen, O. (1989). Predicting premorbid IQ: A revision of the National Adult Reading Test. *Clinical Neuropsychologist*, *3*, 129–136.

Bo, L., Vedeler, C.A., Nyland, H., Trapp, B.D., & Mork, S.J. (2003a). Intracortical multiple sclerosis lesions are not associated with increased lymphocyte infiltration. *Multiple Sclerosis*, *9*, 323–331.

Bo, L., Vedeler, C.A., Nyland, H.I., Trapp, B.D., & Mork, S.J. (2003b). Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *Journal of Neuropathology and Experimental Neurology*, *62*, 723–732.

Bobholz, J.A., & Rao, S.M. (2003). Cognitive dysfunction in multiple sclerosis: A review of recent developments. *Current Opinion in Neurology*, *16*, 283–288.

Borroni, B., Premi, E., Agosti, C., Alberici, A., Garibotto, V., Bellelli, G., et al. (2009). Revisiting brain reserve hypothesis in frontotemporal dementia: Evidence from a brain perfusion study. *Dementia and Geriatric Cognitive Disorders*, *28*, 130–135.

Chiaravalloti, N.D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurology*, *7*, 1139–1151.

Christodoulou, C., Krupp, L.B., Liang, Z., Huang, W., Melville, P., Roque, C., et al. (2003). Cognitive performance and MR markers of cerebral injury in cognitively impaired MS patients. *Neurology*, *60*, 1793–1798.

Cutter, G.R., Baier, M.L., Rudick, R.A., Cookfair, D.L., Fischer, J.S., Petkau, J., et al. (1999). Development of a multiple sclerosis funcitonal composite as a clinical trial outcome measure. *Brain*, *122*, 871–882.

Dal Bianco, A., Bradl, M., Frischer, J., Kutzelnigg, A., Jellinger, K., & Lassmann, H. (2008). Multiple sclerosis and Alzheimer's disease. *Annals of Neurology*, *63*, 174–183.

Dufouil, C., Alperovitch, A., & Tzourio, C. (2003). Influence of education on the relationship between white matter lesions and cognition. *Neurology*, *60*, 831–836.

Elkins, J.S., Longstreth, W.T., Jr., Manolio, T.A., Newman, A.B., Bhadelia, R.A., & Johnston, S.C. (2006). Education and the cognitive decline associated with MRI-defined brain infarct. *Neurology*, *67*, 435–440.

Friend, K.B., & Grattan, L. (2000). Use of the North American Adult Reading Test to estimate premorbid intellectual function in patients with multiple sclerosis. *Journal of Clinical & Experimental Neuropsychology*, *20*, 846–851.

Glatt, S.L., Hubble, J.P., Lyons, K., Paolo, A., Troster, A.I., Hassanein, R.E., et al. (1996). Risk factors for dementia in Parkinson's disease: Effect of education. *Neuroepidemiology*, *15*, 20–25.

Gronwall, D.M.A. (1977). Paced auditory serial addition task: A measure of recovery from concussion. *Perceptual and Motor Skills*, *44*, 367–373.

Houtchens, M.K., Benedict, R.H.B., Killiany, R., Sharma, J., Jaisani, Z., Singh, B., et al. (2007). Thalamic atrophy and cognition in multiple sclerosis. *Neurology*, *69*, 113–123.

Jacobs, D., Sano, M., Marder, K., Bell, K., Bylsma, F., Lafleche, G., et al. (1994). Age at onset of Alzheimer's disease: Relation to pattern of cognitive dysfunction and rate of decline. *Neurology*, *44*, 1215–1220.

Jacobs, L.D., Wende, K.E., Brownscheidle, C.M., Apatoff, B., Coyle, P.K., Goodman, A., et al. (1999). A profile of multiple sclerosis: The New York State Multiple Sclerosis Consortium. *Multiple Sclerosis*, *5*, 369–376.

Kujala, P., Portin, R., & Ruutiainen, J. (1997). The progress of cognitive decline in multiple sclerosis. *Brain*, *120*, 289–297.

Kurtzke, J.F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Annals of Neurology*, *13*, 227–231.

Lynn, R., & Mikk, J. (2007). National differences in intelligence and educational attainment. *Intelligence*, *35*, 115–121.

McCarthy, F.M., Sellers, A.H., & Burns, W.J. (2003). Prediction of IQ in the Mayo older adult normative sample using multiple methods. *Journal of Clinical Psychology*, *59*, 457–463.

Parmenter, B.A., Testa, S.M., Schretlen, D.J., Weinstock-Guttman, B., & Benedict, R.H.B. (2010). The utility of regression-based norms in interpreting the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *16*, 6–16.

Parmenter, B.A., Weinstock-Guttman, B., Garg, N., Munschauer, F., & Benedict, R.H.B. (2007). Screening for cognitive impairment in MS using the Symbol Digit Modalities Test. *Multiple Sclerosis*, *13*, 52–57.

Parmenter, B.A., Zivadinov, R., Kerenyi, L., Gavett, R., Weinstock-Guttman, B., Dwyer, M., et al. (2007). Validity of the Wisconsin Card Sorting and Delis-Kaplan Executive Function System (DKEFS) Sorting Tests in Multiple Sclerosis. *Journal of Clinical & Experimental Neuropsychology*, *29*, 215–223.

Polman, C.H., Reingold, S.C., Edan, G., Filippi, M., Hartung, H.P., Kappos, L., et al. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". [Review]. *Annals of Neurology*, *58*, 840–846.

Rao, S.M. (1991a). *A manual for the brief, repeatable battery of neuropsychological tests in multiple sclerosis*. New York, NY: National Multiple Sclerosis Society.

Rao, S.M. (1991b). *Neuropsychological screening battery for multiple sclerosis*. New York, NY: National Multiple Sclerosis Society.

Rao, S.M., Leo, G.J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*, *41*, 685–691.

Roe, C.M., Xiong, C., Miller, J.P., & Morris, J.C. (2007). Education and Alzheimer disease without dementia: Support for the cognitive reserve hypothesis. *Neurology*, *68*, 223–228.

Ropacki, M.T., & Elias, J.W. (2003). Preliminary examination of cognitive reserve theory in closed head injury. *Archives of Clinical Neuropsychology*, *18*, 643–654.

Rudick, R.A., Cutter, G., Baier, M., Fisher, E., Dougherty, D., Weinstock-Guttman, B., et al. (2001). Use of the multiple sclerosis functional composite to predict disability in relapsing MS. *Neurology*, *56*, 1324–1330.

Sanfilipo, M.P., Benedict, R.H.B., Weinstock-Guttman, B., & Bakshi, R. (2006). Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology*, *66*, 685–692.

Satz, P., Morgenstern, H., Miller, E.N., Selnes, O.A., McArthur, J.C., Cohen, B.A., et al. (1993). Low education as a possible risk factor for cognitive abnormalities in HIV-1: Findings from the multicenter AIDS Cohort Study (MACS). *Journal of Acquired Immune Deficiency Syndromes*, *6*, 503–511.

Smith, A. (1982). *Symbol digit modalities test: Manual*. Los Angeles: Western Psychological Services.

Sperling, R.A., Guttmann, C.R., Hohol, M.J., Warfield, S.K., Jakab, M., Parente, M., et al. (2001). Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: A longitudinal study. *Archives of Neurology*, *58*, 115–121.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*, 448–460.

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Disease and Associated Disorders*, *20*(Suppl. 2), S69–S74.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*, 2015–2028.

Stern, Y., Gurland, B., Tatemichi, T.K., Tang, M.X., Wilder, D., & Mayeux, R. (1994). Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA*, *271*, 1004–1010.

Strober, L., Englert, J., Munschauer, F., Weinstock-Guttman, B., Rao, S., & Benedict, R.H.B. (2009). Sensitivity of conventional memory tests in multiple sclerosis: Comparing the Rao Brief Repeatable Neuropsychological Battery and the Minimal Assessment of Cognitive Function in MS. *Multiple Sclerosis*, *15*, 1077–1084.

Sumowski, J.F., Chiaravalloti, N., Wylie, G., & Deluca, J. (2009). Cognitive reserve moderates the negative effect of brain atrophy on cognitive effi ciency in multiple sclerosis. *Journal of the International Neuropsychological Society*, *15*, 606–612.

Sumowski, J.F., Wylie, G.R., Deluca, J., & Chiaravalloti, N. (2010). Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: Functional magnetic resonance imaging evidence for cognitive reserve. *Brain*, *133*(Pt 2), 362–374.

Tabert, M.H., Albert, S.M., Borukhova-Milov, L., Camacho, Y., Pelton, G., Liu, X., et al. (2002). Functional deficits in patients with mild cognitive impairment: Prediction of AD. *Neurology*, *58*, 758–764.

Tekok-Kilic, A., Benedict, R.H.B., Weinstock-Guttman, B., Dwyer, M., Carone, D., Srinivasaraghavan, B., et al. (2007). Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis. *Neuroimage*, *36*, 1294–1300.

Trapp, B.D., & Nave, K.A. (2008). Multiple sclerosis: An immune or neurodegenerative disorder? *Annual Review of Neuroscience*, *31*, 247–269.

Yeh, E.A., Weinstock-Guttman, B., Ramanathan, M., Ramasamy, D.P., Willis, L., Cox, J.L., et al. (2009). Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis. *Brain*, *132*(Pt 12), 3392–3400.

Zivadinov, R., Sepcic, J., Nasuelli, D., De Masi, R., Bragadin, L.M., Tommasi, M.A., et al. (2001). A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *Journal of Neurology, Neurosurgery, & Psychiatry*, *70*, 773–780.