Cognitive impairment in multiple sclerosis

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Abstract
Cognitive impairment is common among persons with multiple sclerosis (MS), but some patients are able to withstand considerable disease burden (e.g. white matter lesions, cerebral atrophy) without cognitive impairment (cognitive inefficiency, memory decline). What protects these patients from cognitive impairment? We review the literature on cognitive reserve in MS, which shows that heritable (larger maximal lifetime brain growth) and environmental (greater intellectual enrichment) factors attenuate the negative effect of disease burden on cognitive status. That is, persons with larger maximal lifetime brain growth, greater vocabulary knowledge, and/or greater early life participation in cognitive leisure activities (e.g. reading, hobbies) are better able to cope with MS disease without cognitive impairment. We review evidence that benefits of intellectual enrichment on cognitive status may stem from more efficient patterns of brain function. We discuss clinical implications and highlight important unanswered questions for future research on reserve against cognitive impairment in MS.

Keywords
Multiple sclerosis, cognition, cognitive reserve, brain reserve, neuropsychology

Date received: 30 June 2013; accepted: 3 July 2013

Cognitive impairment in multiple sclerosis

Nearly two-thirds of persons with multiple sclerosis (MS) suffer cognitive impairment,¹ especially cognitive inefficiency and memory decline. Patients with cognitive inefficiency require more time to perform mental tasks, leading to difficulty multitasking and losing one’s train of thought. Patients with memory problems are often disorganized and forgetful, frequently misplacing objects and backtracking to perform missed steps. Cognitive inefficiency and memory decline during early and middle adulthood encumber successful attainment of normative goals, including gainful employment and household management.² Why do so many MS patients suffer these cognitive problems? MS is a chronic and progressive disease resulting in diffuse brain lesions as well as global and focal cerebral atrophy. As such, a more appropriate question may be: how do roughly a third of patients withstand MS disease without cognitive impairment?

Cognitive-pathologic dissociation

MS patients with more severe disease burden (lesion load and cerebral atrophy visualized with magnetic resonance imaging (MRI)) are at increased risk for cognitive impairment (see Filippi for review³), but correlations between disease burden and cognitive status are relatively modest, with disease burden accounting for about 30% and 15% of the variance in cognitive efficiency and memory, respectively.⁴,⁵ Our schematic of the typical relationship between cognitive status and MS disease burden shows a negative relationship between cognitive status and disease burden, with greater risk for cognitive impairment in persons with worse disease (Figure 1, red line = 1.5 standard deviations below normal); however, notable scatter around the regression line highlights variability in the cognitive expression of MS disease, with many MS patients withstanding considerable disease burden without cognitive impairment. This cognitive-pathologic dissociation is not unique to MS; rather, the disconnect between disease burden and cognitive status is observed across neurologic conditions, including Alzheimer’s disease (AD). The correlation between AD neuropathology (e.g. β-amyloid) and cognitive decline is relatively weak,⁶ and
many cognitive-intact elders meet neuropathological criteria for AD at autopsy. This cognitive-pathologic dissociation begs the question: How can some people better withstand neurologic disease without cognitive impairment/dementia?

Reserve against cognitive impairment

The theory of reserve posits that both heritable/genetic (maximal lifetime brain growth (MLBG)) and environmental (intellectual enrichment) factors contribute to reserve against disease-related cognitive decline. These sources of reserve are reviewed below, but a few key introductory points about reserve are necessary. First, persons with higher reserve withstand more severe neurologic disease burden (i.e. brain atrophy) before/without suffering cognitive impairment or dementia. That is, as illustrated in Figure 2, the theory of reserve posits an interaction between disease burden and reserve on cognitive status whereby the deleterious effect of disease burden on cognitive status is attenuated in persons with higher reserve (estimated with MLBG or intellectual enrichment, e.g. see Bennett et al. and Sumowski et al.). As such, the impact of disease burden on cognitive status is stronger among persons with lesser reserve. The theory of reserve does not posit that sources of reserve (e.g. MLBG) protect against neurologic disease progression itself. For instance, there is no correlation between lesion load and either MLBG or intellectual enrichment in MS patients.

Rather, patients with higher reserve are better able to withstand disease burden without cognitive impairment. Also, the theory of reserve is not supported by simple positive correlations between a source of reserve and cognitive status. Although education (a proxy of intellectual enrichment) is correlated with memory in neurologic patients, this is also true for healthy persons. To support the reserve hypothesis, the source of reserve (e.g. intellectual enrichment) must be more correlated with cognitive status among neurologic patients than healthy persons (e.g. Sumowski et al.), or, ideally, must attenuate the relationship between disease burden and cognitive status (e.g. Sumowski et al.).

MLBG

It has been theorized that persons with larger MLBG are able to withstand more severe disease burden without cognitive impairment. MLBG is typically estimated with head size or intracranial volume (ICV, adjusted for sex). ICV is strongly correlated with MLBG in healthy persons ($r = 0.86$), and brain growth corresponds to increased ICV during development. The protective effect of larger MLBG, referred to as “brain reserve,” is explained through the following rationale by Satz: Cognitive impairment/dementia emerges when total brain volume falls below a critical (albeit unspecified) threshold. Persons with larger MLBG can lose more brain volume before reaching this critical threshold associated with cognitive impairment. Consequently, persons with larger MLBG can better withstand neurologic disease burden (and associated brain volume loss/atrophy) without suffering cognitive impairment/dementia.
Larger MLBG protects against incident dementia in the elderly,15 and larger MLBG attenuates the negative effect of brain atrophy on cognitive status in persons with AD.16 We have recently demonstrated the protective role of larger MLBG for the first time in MS.11 After controlling for demographics and disease burden, larger MLBG (estimated with ICV) was correlated with better cognitive efficiency in MS patients ($R^2\Delta = 0.100$, $p = 0.005$), and larger MLBG attenuated the negative effect of MS disease burden on cognitive efficiency (similar to Figure 2, with MLBG as the source of reserve). That is, the negative effect of MS disease burden on cognitive efficiency is reduced among patients with larger MLBG. This protective effect of larger MLBG was specific to cognitive efficiency, as MLBG was unrelated to memory ($R^2\Delta = 0.012$, $p = 0.335$). This specific benefit of MLBG on cognitive efficiency is consistent with stronger heritability of MLBG17 relative to hippocampal volume,18 and cognitive efficiency relative to memory.19

**Intellectually enriching lifestyles**

The majority of work on reserve in aging/AD and MS has assessed the contribution of intellectually enriching lifestyles to protection against cognitive decline. Intellectually enriching lifestyles are usually estimated with educational attainment or vocabulary. Tests of vocabulary estimate semantic knowledge acquired through enriching activities such as education, occupation, and reading. Indeed, longitudinal aging research shows that educational and occupational attainment contribute to vocabulary independently of childhood intelligence.20 As such, unlike MLBG, intellectual enrichment is largely the product of life experience. Higher intellectual enrichment reduces one’s risk for dementia,21 and moderates/attenuates the negative effect of AD neuropathology on cognitive status.19 We have used vocabulary knowledge to estimate intellectual enrichment in persons with MS, and have shown that higher intellectual enrichment protects MS patients from disease-related cognitive impairment.12,22,23 More specifically, higher intellectual enrichment attenuates the negative effect of MS disease burden on cognitive status (similar to Figure 2, with intellectual enrichment as the source of reserve).22,23 Other research has supported the reserve hypothesis in MS, with intellectual enrichment estimated with education,24 vocabulary,12,24–26 occupational attainment,27 cognitive leisure,11,28,29 or a combination of these sources.30

People like to believe that accomplishments are the product of hard work and determination, but educational attainment is also impacted by factors outside our control (e.g. socioeconomic status, parental education). Indeed, there is a positive correlation between education and MLBG in MS patients ($r = 0.25$),11 indicating a heritable component of educational attainment that is outside of one’s control. Likewise, vocabulary knowledge is impacted by free choice to some degree (e.g. reading rather than watching television), but heritable factors related to intelligence surely impact overall semantic language capacity, hence a robust moderate correlation of 0.33 between intelligence and MLBG.31 As such, we have investigated whether personal choices to engage in early-life cognitive leisure contribute to reserve against cognitive decline independently of other sources of reserve,11,28 including MLBG, education, and vocabulary knowledge. We surveyed seven high frequency cognitive leisure activities (Table). Note that early-life cognitive leisure is unrelated to MLBG in MS patients ($r = 0.03$),11 indicating that choices to engage in cognitive leisure are independent of heritability. We have demonstrated that MS patients who engaged in more early-life cognitive leisure (a) exhibited better current cognitive status, even when controlling for vocabulary knowledge, and (b) were able to withstand more severe brain atrophy before/without suffering cognitive impairment.28 With our collaborators in Italy, we have recently shown that greater early life cognitive leisure protects MS patients from cognitive impairment independently of MLBG and education.11 This demonstrates for the first time that life experiences contribute to reserve against cognitive decline independently of fully heritable (MLBG) and partially heritable (intelligence, education) sources of reserve.

Most research on intellectual enrichment in MS has been cross-sectional, with a couple of exceptions. Benedict and colleagues demonstrated in a sample of 91 MS patients that higher intellectual enrichment (estimated with educational attainment and vocabulary) is associated with less decline in cognitive efficiency over an average of five years.24 Amato and colleagues30 did not observe a significant protective effect of intellectual enrichment against cognitive decline in a sample of 35 patients over an interval of 1.6 years. As illustrated in Figure 2, the reserve hypothesis states that higher intellectual enrichment protects against disease-related cognitive decline. If there is no disease-related cognitive decline to protect against (as when

<table>
<thead>
<tr>
<th>Cognitive leisure activities</th>
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<tbody>
<tr>
<td>Read books</td>
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<tr>
<td>Read magazines or newspapers</td>
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<tr>
<td>Produce art (e.g. painting, poetry, sculpture, songwriting, ballet)</td>
</tr>
<tr>
<td>Produce non-artistic writing (e.g. diary, newsletter, essay, blogs)</td>
</tr>
<tr>
<td>Play a musical instrument</td>
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<tr>
<td>Play structured games (e.g. cards, board games, crossword puzzles)</td>
</tr>
<tr>
<td>Participate in hobbies (e.g. gardening, model building, Web design)</td>
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the interval between baseline and follow-up is too short), then there is little room for enrichment to protect against decline. More longitudinal work is needed to investigate the protective effects of both MLBG and intellectual enrichment against cognitive decline over time, and intervals between baseline and follow-up should be long enough for cognitive decline to be observed.

**Neurophysiologic basis of reserve**

Stern and colleagues have posited that individual variability in the efficiency and/or plasticity of brain networks allows some individuals to better preserve cognitive function in the face of aging or neurologic disease.32 We have explored the neural basis of reserve in MS, identifying a pattern of cerebral activity associated with higher intellectual enrichment (estimated with vocabulary).33 MS patients performed the n-back working memory task during a functional MRI (fMRI) scan. Intellectual enrichment was unrelated to n-back performance when cognitive demands were low (0- and 1-back), as all patients performed well; however, patients with greater intellectual enrichment required less recruitment of the dorsolateral prefrontal cortex (DLPFC) to maintain performance, as well as lesser deactivation within the default network (DN). When cognitive demands increased (2-back), greater intellectual enrichment was then linked to faster reaction time and better accuracy. Lesser DLPFC recruitment by patients with greater intellectual enrichment is indicative of greater cerebral efficiency, as fewer cerebral resources were required to perform the cognitive task (n-back). This cerebral efficiency evident during lower cognitive load (0- and 1-back) may explain how patients with greater intellectual enrichment were better able to maintain cognitive performance during higher cognitive load (2-back). Greater DN activation among patients with greater intellectual enrichment likely represents maintenance of their resting state, as resting state activation is usually suppressed during recruitment of task-active cortical regions (i.e. DLPFC). This pattern of DN maintenance and lesser need for task-active cortical recruitment to produce adequate cognitive performance may represent the neural basis of reserve against cognitive decline, at least for MS patients. Note also that MS patients who showed greater expression of this pattern of brain activity (lower DLPFC, higher DN) were also better able to withstand brain atrophy without showing cognitive decline, thereby supporting this pattern as a potential neurophysiologic basis of reserve.

We have previously linked greater activity/maintenance within the DN during a low-load cognitive task to better memory in MS patients (see DN in Figure 3).34 For this review, we reanalyzed the data from that study to address an ancillary question of interest: Is DN activation not only related to memory, but also a neurophysiologic marker of reserve against cognitive decline? This is consistent with the notion that greater maintenance of DN activity is linked to lifetime intellectual enrichment.33 First, we show that DN activity is correlated with intellectual enrichment (r = 0.595, p = 0.001), and that memory is linked to both DN activity (r = 0.459, p = 0.014) and intellectual enrichment (r = 0.407, p = 0.031). Finally, we found that 78.7% of the association between memory and intellectual enrichment is explained by DN activation. These results suggest that the relationship between intellectual enrichment and memory may be mediated by DN activation, thereby supporting the role of DN activation in reserve against cognitive decline, which may also provide a target for treatment, and an outcome for interventions to build reserve.

**Clinical implications**

Clinical consideration of MLBG and intellectual enrichment may help identify patients at greatest risk for cognitive decline, and “at-risk” patients may then be targeted for early-intervention cognitive rehabilitation. It is conceivable that rehabilitation techniques designed to improve memory (e.g. see Sumowski35) may be most efficacious if patients at risk for memory problems learn and integrate these strategies into their daily routines before memory decline makes such learning and integration more challenging.

Patients with greater intellectual enrichment and larger MLBG are at less risk for cognitive impairment, but can these findings be translated into clinical recommendations aimed at building/bolstering reserve? Randomized controlled trials are needed to evaluate the efficacy of interventions to build reserve. That is, will a “prescription” of intellectual enrichment help avoid, delay, or attenuate...
cognitive impairment? Unlike intellectual enrichment, MS patients cannot increase their genetically-determined MLBG; however, patients may be able to preserve/maintain their existing “brain reserve” by living a “brain healthy” lifestyle, including physical activity, healthful diets, sleep, and adherence to prescribed disease-modifying therapies.

The theory of reserve helps us understand how MS disease burden (e.g. lesion load, cerebral atrophy) relates to cognitive status. Given that larger MLBG and intellectual enrichment attenuate the negative relationship between MRI estimates of disease burden and cognitive status, the correlation between cognitive status and MS disease burden is stronger in samples with lower MLBG and/or lower intellectual enrichment. Future clinical research aimed at identifying the best MRI predictors of cognitive status must consider the moderating effect of reserve on this relationship, especially when comparing results across study samples with differing levels of reserve (estimated with MLBG or intellectual enrichment).

Future research

We have reported a double dissociation whereby MLBG protects against cognitive inefficiency, but not memory problems, whereas intellectual enrichment protects more against memory problems than cognitive inefficiency. Future research is needed to further investigate (a) MLBG as a heritable/genetic source of reserve in MS, (b) the unique contribution of intellectual enrichment to protection against cognitive decline independently of MLBG, and (c) the aforementioned double dissociation between source of reserve and cognitive outcome.

Longitudinal studies of reserve are needed to indicate whether and how reserve protects against cognitive decline. Note that such longitudinal studies should be conducted over long enough time intervals to ensure that variability in cognitive decline is observed within the sample.

Samples in previous reserve research have consisted predominately of adult relapsing–remitting MS (RRMS) patients. Future research should investigate reserve in pediatric MS and adults with progressive disease subtypes. We have shown protective benefits of reserve in a small sample of secondary progressive MS (SPMS) patients without neuroimaging, but more research with SPMS patients is indicated. On a related point, it is unknown whether there is a point when disease burden becomes too severe for reserve to protect against decline, which has been shown in AD. Future research should investigate whether there is a point of disease burden after which reserve is diminished.

We have reviewed evidence for a neurophysiologic basis of reserve. This evidence comes from studies employing traditional fMRI during cognitive tasks (e.g. n-back). Future work to advance these findings should employ novel imaging methods such as functional connectivity, which will allow for inferences about the integrity of neural networks underlying cognition.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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