Brain reserve and cognitive reserve in multiple sclerosis

What you've got and how you use it

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ABSTRACT

Objective: We first tested the brain reserve (BR) hypothesis in multiple sclerosis (MS) by examining whether larger maximal lifetime brain volume (MLBV; determined by genetics) protects against disease-related cognitive impairment, and then investigated whether cognitive reserve (CR) gained through life experience (intellectually enriching leisure activities) protects against cognitive decline independently of MLBV (BR).

Methods: Sixty-two patients with MS (41 relapsing-remitting MS, 21 secondary progressive MS) received MRIs to estimate BR (MLBV, estimated with intracranial volume [ICV]) and disease burden (T2 lesion load; atrophy of gray matter, white matter, thalamus, and hippocampus). Early-life cognitive leisure was measured as a source of CR. We assessed cognitive status with tasks of cognitive efficiency and memory. Hierarchical regressions were used to investigate whether higher BR (ICV) protects against cognitive impairment, and whether higher CR (leisure) independently protects against cognitive impairment over and above BR.

Results: Cognitive status was positively associated with ICV ($R^2 = 0.066$, $p = 0.017$). An ICV × disease burden interaction ($R^2 = 0.050$, $p = 0.030$) revealed that larger ICV attenuated the impact of disease burden on cognition. Controlling for BR, higher education ($R^2 = 0.047$, $p = 0.030$) and leisure ($R^2 = 0.090$, $p = 0.001$) predicted better cognition. A leisure × disease burden interaction ($R^2 = 0.037$, $p = 0.030$) showed that leisure independently attenuated the impact of disease burden on cognition. Follow-up analyses revealed that BR protected against cognitive inefficiency, not memory deficits, whereas CR was more protective against memory deficits than cognitive inefficiency.

Conclusion: We provide evidence of BR in MS, and show that CR independently protects against disease-related cognitive decline over and above BR. Lifestyle choices protect against cognitive impairment independently of genetic factors outside of one's control. *Neurology*® 2013;80:1–8

GLOSSARY

AD = Alzheimer disease; **BR** = brain reserve; **CR** = cognitive reserve; **GM** = gray matter; **ICV** = intracranial volume; **MLBV** = maximal lifetime brain volume; **MS** = multiple sclerosis; **WM** = white matter.

Many persons with multiple sclerosis (MS) have cognitive impairment, whereas others withstand considerable disease burden without cognitive decline.[1,2] A similar cognitive-pathologic dissociation in Alzheimer disease (AD)[3] prompted theories of "brain reserve"[4] and "cognitive reserve."[5] The brain reserve hypothesis posits that larger maximal lifetime brain volume (MLBV) (estimated with head size or intracranial volume [ICV]) protects against cognitive decline.[4] That is, cognitive impairment emerges when brain volume falls beneath a critical threshold; persons with larger MLBV withstand greater disease burden before reaching this threshold. Indeed, elders with larger MLBV have better cognition[6–10] and lower risk of dementia.[11,12] Herein, we investigate whether MLBV (brain reserve) protects patients with MS from cognitive impairment.

Brain reserve (MLBV) is determined almost entirely by genetics.[13,14] In contrast, the cognitive reserve hypothesis posits that enriching experiences (e.g., education, cognitive leisure) protect

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against dementia.[5] Indeed, educational attainment attenuates the effect of AD neuropathology on cognition.[15,16] We have extended the cognitive reserve hypothesis to MS,[17–20] showing that lifetime intellectual enrichment attenuates the effect of disease burden on cognition.[17,19] Importantly, brain reserve and cognitive reserve have been investigated separately, so it remains unclear whether enriching life experiences protect against cognitive decline independently of genetically determined MLBV. Given the moderate but robust correlation between brain reserve and cognitive reserve (brain size and intelligence[21]), it is unknown whether the protective effect of enriching experiences is explained through concomitantly higher brain reserve. Herein, we investigate whether early-life cognitive leisure (source of cognitive reserve) independently protects against cognitive impairment over and above MLBV (brain reserve) in patients with MS.

METHODS

Subject enrollment. Subjects were 62 patients with definite MS[22] (30 women) without an exacerbation in the last 4 weeks, no current corticosteroid use, and no history of serious psychiatric illness, substance abuse, learning disability, or other neurologic condition. Mean age was 43.7 ± 11.1 years with 13.1 ± 3.4 years of education. Given that a) patients retrospectively reported cognitive leisure from their early 20s, and b) we wanted formal education completed before participation, all patients were at least 25 years old. Mean disease duration was 13.2 ± 6.9 years, with a mean Expanded Disability Status Scale score of 3.2 ± 2.1. MS phenotypes included relapsing-remitting (n = 41) and secondary progressive (n = 21). Current disease-modifying drug treatments included interferon β-1a (n = 26) or interferon β-1b (n = 4), glatiramer acetate (n = 19), azathioprine (n = 3), cyclophosphamide (n = 2), natalizumab (n = 2), mitoxantrone (n = 1), or no treatment (n = 5).

Standard protocol approvals, registrations, and patient consents. Approval was received from the local ethical standards committee on human experimentation, and written informed consent was obtained from all subjects participating in the study.

Cognitive functioning. Cognitive inefficiency and memory problems are the most prevalent cognitive deficits among patients with MS.[1] Cognitive efficiency was measured with the Symbol Digit Modalities Test (oral version) and the Paced Auditory Serial Addition Task (3-second version). Norm-referenced *z* scores were calculated for both tasks,[23] and the mean of these *z* scores comprised our *cognitive efficiency* composite. Memory was assessed with the Selective Reminding Test and Spatial Recall Test. Norm-referenced *z* scores were calculated for the Selective Reminding Test (Total Learning, Delayed Recall) and Spatial Recall Test (Total Learning, Delayed Recall),[23] and the mean of these *z* scores comprised our *memory* composite. A norm-referenced overall *cognitive status* score was derived as the mean of *cognitive efficiency* and *memory* composites. Analyses first investigated the impact of brain reserve and cognitive reserve on overall *cognitive status*, and then separately for *cognitive efficiency* and *memory*.

Lesion load and brain atrophy. Using a 3.0-tesla Philips Intera scanner (Philips Healthcare, Guildford, UK), the following brain sequences were acquired: a) dual-echo turbo spin echo (repetition time/echo time = 3,500/24–120 milliseconds; fractional anisotropy = 150°; field of view = 240 mm^2; matrix = 256 × 256; echo train length = 5; 44 contiguous, 3-mm-thick axial slices); and b) 3-dimensional T1-weighted fast field echo (repetition time = 25 milliseconds; echo time = 4.6 milliseconds; fractional anisotropy = 30°; field of view = 230 mm^2; matrix = 256 × 256; slice thickness = 1 mm, 220 contiguous axial slices; in-plane resolution = 0.89 × 0.89 mm^2). T2 lesion load was measured on dual-echo scans using a local thresholding segmentation technique (Jim 5.0, Xinapse System, www.xinapse.com). Brain atrophy was measured as normalized volumes of gray matter (GM) and white matter (WM) obtained using SIENAX (version 2.6, part of FSL 4.1), whereas normalized volumes of the thalamus and hippocampus were obtained using FIRST, then applying the same scaling factor calculated with SIENAX. To correct for the misclassification of WM lesions, all pixels classified as GM but lying neither in the cortical GM nor in the subcortical GM were reassigned to the WM before volume calculation. The scaling factor within SIENAX is derived from the transformation that matches the extracted brain and skull to standard-space brain and skull images (derived from the MNI152 standard image): values higher than one were obtained for heads with small ICV and values lower than one for ICVs larger than the MNI atlas. An advantage of this approach is that it does not require that CSF be robustly estimated, as it is difficult to distinguish between CSF and skull voxels in T images. Lesion load and brain atrophy were used as estimates of MS disease burden in subsequent analyses.

Estimate of brain reserve: ICV. ICV is an estimate of MLBV, as brain growth corresponds to increased ICV during development,[24] and ICV is strongly correlated with brain size in healthy persons (e.g., $r = 0.86$[25]). ICV has been used as an estimate of brain reserve in previous research (e.g., references 6 and 9). The aforementioned scaling factor within SIENAX is a measurement of ICV; however, we reversed the direction of values such that larger values represent larger ICVs (for ease of presentation). Given that men have larger ICVs than women, as in our sample ($t[60] = 5.62$, $p < 0.001$), we adjusted ICV measurements for sex. The brain reserve hypothesis states that persons with higher brain reserve withstand more severe disease burden before experiencing cognitive decline, not that higher brain reserve slows disease progression. As expected, therefore, there was no relationship between ICV and disease duration ($r = -0.02$, $p = 0.88$) or T2 lesion load ($r = 0.08$, $p = 0.55$), nor was there a difference between disease phenotypes ($t[60] = 0.81$, $p = 0.41$).

Estimate of cognitive reserve: Cognitive leisure activity. As described previously,[20] patients were surveyed to quantify participation in 7 cognitive leisure activities during their early 20s (table 1). Frequency of participation in each activity was endorsed as 1) once or less per year, 2) several times per year, 3) several times per month, 4) several times per week, or 5) daily. Total frequency across items was our estimate of early-life cognitive leisure (mean = 18.8 ± 5.7). This score was interpolated for patients missing 1 (n = 3) or 2 (n = 4) items. There was no difference in leisure frequency between our sample and a larger independent matched pilot sample of 124 patients with MS aged 25 years or older (table 1), indicating that early-life cognitive leisure within our sample was representative of MS patients generally. We have previously shown no difference between item endorsement between patients with MS and healthy persons, indicating that cognitive leisure was unaffected by preclinical

Table 1 Means and SDs for the current sample and matched pilot sample on each of the 7 cognitive leisure activities, as well as the total cognitive leisure score[a]

Cognitive leisure activities	Pilot sample (n = 124),[b] mean ± SD	Sample (n = 62), mean ± SD	Difference, p values
Read books	3.1 ± 1.4	3.2 ± 1.5	0.80
Read magazines or newspapers	3.9 ± 1.2	3.8 ± 1.4	0.62
Produce art (e.g., painting, poetry, sculpture, song writing, ballet)	2.5 ± 1.3	2.2 ± 1.3	0.24
Produce nonartistic writing (e.g., diary, newsletter, essay, blog)	2.3 ± 1.3	2.3 ± 1.5	0.80
Play a musical instrument	2.1 ± 1.4	2.0 ± 1.5	0.54
Play structured games (e.g., cards, board games, crossword puzzles)	2.8 ± 1.2	2.7 ± 1.1	0.67
Participate in hobbies (e.g., gardening, model building, Web design)	2.5 ± 1.4	2.6 ± 1.3	0.59
Total cognitive leisure activity	19.0 ± 4.8	18.7 ± 5.6	0.71

[a] There were no differences between the current sample and the larger pilot sample on any items.
[b] The pilot sample did not differ in age (42.0 ± 10.3 years, $p = 0.29$), disease duration (13.2 ± 8.4 years, $p = 0.97$), education (13.6 ± 3.2 years, $p = 0.36$), or Expanded Disability Status Scale score (3.1 ± 1.9, $p = 0.70$). There was a marginally higher proportion of women (60.5%, $p = 0.076$) and patients with relapsing-remitting multiple sclerosis (78.2%, $p = 0.076$) within the pilot sample.

disease.[20] The cognitive reserve hypothesis states that lifetime enrichment helps patients better withstand disease without cognitive impairment, not that enriching lifestyles slow disease progression. As expected, therefore, there was no relationship between cognitive leisure and disease duration ($r = 0.14$, $p = 0.28$) or T2 lesion load ($r = -0.06$, $p = 0.67$), nor was there a difference between disease phenotypes (t[60] = 0.61, $p = 0.55$).

Statistical analyses. ***Brain reserve.*** We performed a hierarchical regression to investigate the protective effect of brain reserve on overall cognitive status. After controlling for age, sex, and phenotype (block 1), estimates of disease burden (T2 lesion load, brain atrophy: normalized volumes of cerebral GM, cerebral WM, thalamus, and hippocampus) were entered in a stepwise fashion (block 2). ICV was entered within block 3 to test whether MLBV predicts cognitive status. (Stepwise entry of disease burden estimates within block 2 allowed us to assess the contribution of brain reserve over and above the estimate of disease burden most associated with cognitive status.) Finally, the interaction between ICV and disease burden (estimate retained within block 2) was evaluated in block 4. If brain reserve protects against cognitive decline, there should be an interaction between ICV and disease burden such that greater ICV moderates/attenuates the deleterious impact of disease burden on cognitive status. This hierarchical regression was repeated to predict cognitive efficiency and memory separately.

Cognitive reserve. We then investigated whether cognitive reserve independently protects against disease-related cognitive decline, even after controlling for brain reserve. A hierarchical regression was again performed to predict overall cognitive status. After controlling for the previous brain reserve analysis (block 1), education (block 2) and early-life cognitive leisure (block 3) were entered, followed by the interaction between disease burden and cognitive leisure (block 4). If cognitive reserve independently protects against disease-related cognitive decline, there will be an interaction whereby greater cognitive leisure moderates/attenuates the deleterious impact of disease burden on cognitive status. This hierarchical regression was repeated to predict cognitive efficiency and memory separately.

RESULTS

Brain reserve. The results for brain reserve analyses are presented in table 2.

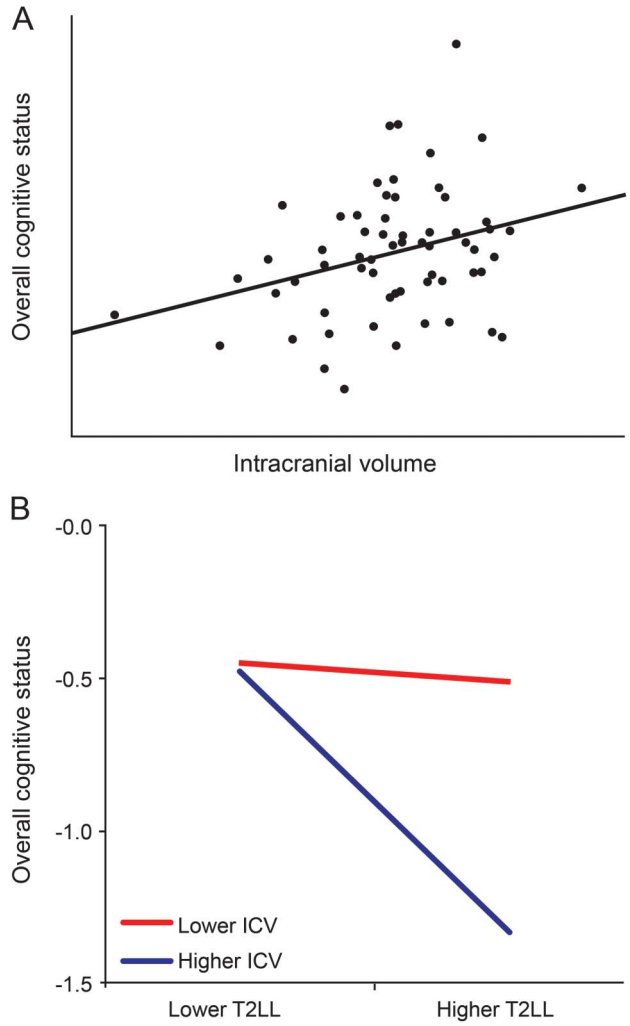
Overall cognitive status. After controlling for age, sex, and phenotype (block 1), T2 lesion load (the only estimate of disease burden retained) was negatively associated with cognitive status (block 2). There was a medium-sized positive relationship between ICV and cognitive status (block 3), such that patients with larger ICVs had better cognitive status (figure 1A).

Table 2 Results for the hierarchical regression analyses investigating the protective effect of brain reserve (ICV) on overall cognitive status, cognitive efficiency, and memory

	Overall cognitive status		Cognitive efficiency		Memory	
	ΔR^2	p Value	ΔR^2	p Value	ΔR^2	p Value
Age, sex, phenotype	0.236	0.001	0.203	0.004	0.180	0.009
T2LL	0.089	0.008	0.040	0.090	0.119	0.003
ICV	0.066	0.017	0.100	0.005	0.012	0.335
T2LL × ICV	0.050	0.030	0.087	0.005	0.005	0.528

Abbreviations: ICV = intracranial volume; T2LL = T2 lesion load.

Figure 1 Brain reserve protects against disease-related cognitive decline



Graphical depiction of (A) the positive correlation between intracranial volume (ICV) (brain reserve) and overall cognitive status, and (B) the interaction between ICV and T2 lesion load (T2LL) whereby larger ICV moderates the negative impact of T2LL on cognitive status.

The interaction between ICV and disease burden (T2 lesion load) was also significant (block 4), such that greater ICV moderated/attenuated the negative impact of disease burden (T2 lesion load) on cognitive status (figure 1B).

Cognitive efficiency and memory. There was a large positive relationship between ICV and cognitive efficiency (block 3), such that patients with larger ICVs showed better cognitive efficiency. There was also an interaction whereby greater ICV moderated/attenuated the negative impact of T2 lesion load on cognitive efficiency. In contrast, there was no relationship between ICV and memory (block 3), nor was the interaction significant (block 4). Brain reserve protected against disease-related cognitive inefficiency, not memory problems.

Cognitive reserve. The results of cognitive reserve analyses are presented in table 3.

Overall cognitive status. After accounting for the brain reserve analysis (block 1: age, sex, phenotype, T2 lesion load, ICV, ICV × T2 lesion load), there was a positive relationship between cognitive status and education (block 2). There was also a large independent positive relationship between cognitive leisure and cognitive status (block 3), such that patients who engaged in more early-life cognitive leisure had better cognitive status (figure 2A). The interaction between T2 lesion load and cognitive leisure was significant (block 4), with greater cognitive leisure moderating/attenuating the negative impact of T2 lesion load on cognitive status (figure 2B).

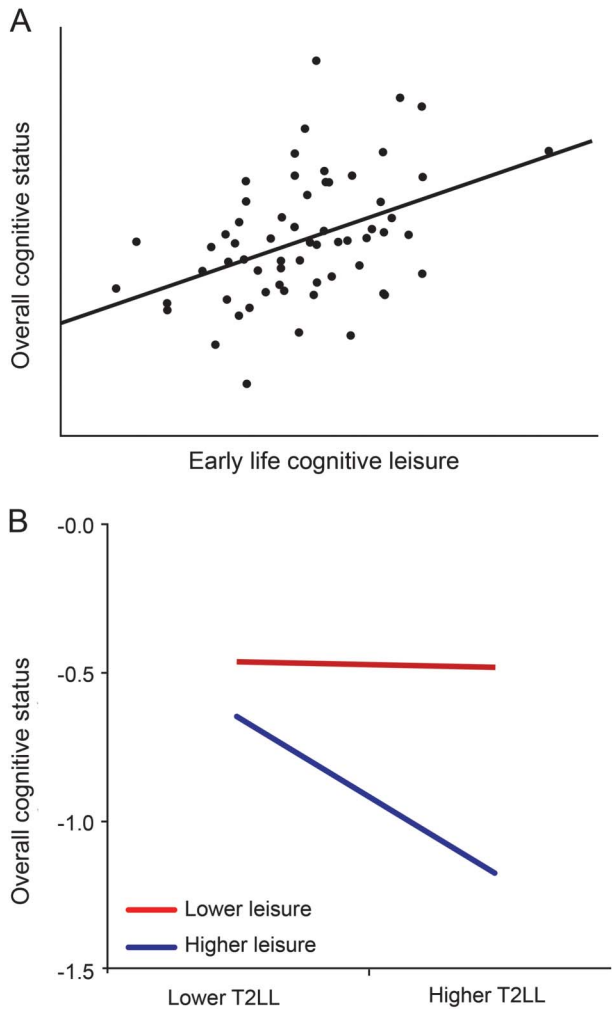
Cognitive efficiency and memory. Cognitive efficiency was unrelated to education (block 2) but positively related to cognitive leisure (block 3). The interaction between T2 lesion load and cognitive leisure on cognitive efficiency was small and nonsignificant (block 4). Memory was strongly and positively related to both education (block 2) and cognitive leisure (block 3), and there was a significant small- to medium-sized interaction between T2 lesion load and cognitive leisure (block 4) such that greater cognitive leisure moderated/attenuated the negative impact of T2 lesion load on memory. In summary, cognitive leisure independently contributed to both cognitive efficiency and memory over and above brain reserve, but the interaction between cognitive leisure and disease burden was only significant for memory. The cognitive

Table 3 Results for the hierarchical regression analyses investigating the independent protective effect of cognitive reserve (leisure) on overall cognitive status, cognitive efficiency, and memory

	Overall cognitive status		Cognitive efficiency		Memory	
	ΔR^2	*p* Value	ΔR^2	*p* Value	ΔR^2	*p* Value
BR analysis	0.441	<0.001	0.368	<0.001	0.315	0.001
Education	0.047	0.030	0.012	0.278	0.086	0.007
Leisure	0.090	0.001	0.061	0.014	0.083	0.005
T2LL × leisure	0.037	0.030	0.021	0.136	0.040	0.042

Abbreviations: BR = brain reserve; T2LL = T2 lesion load.

Figure 2 **Cognitive reserve independently protects against disease-related cognitive decline over and above brain reserve**



Graphical depiction of (A) the positive correlation between early-life cognitive leisure (cognitive reserve) and overall cognitive status, and (B) the interaction between early-life cognitive leisure and T2 lesion load whereby greater engagement in cognitive leisure moderates the negative impact of T2 lesion load on cognitive status. These results demonstrate the independent protection afforded by cognitive reserve over and above brain reserve (intracranial volume).

reserve hypothesis was upheld for memory, but less so for cognitive efficiency.

Supplemental analyses. We entered brain reserve into regression models before cognitive reserve, as MLBV is established before education and leisure. Given a correlation between education and ICV ($r = 0.25$, $p = 0.05$), we examined whether the relationship between brain reserve (ICV) and cognitive efficiency is explained by the relationship between education and ICV. We reran the brain reserve regression predicting cognitive efficacy, now controlling for education in block 1 (before ICV). The main effect of ICV ($\Delta R^2 = 0.064$, $p = 0.022$) and the ICV × T2 lesion load interaction ($\Delta R^2 = 0.075$, $p = 0.009$) remained, indicating that brain reserve provides independent protection from cognitive inefficiency over and above education. Although there was no link between ICV and leisure ($r = 0.03$, $p = 0.84$), to be thorough we reran the regression analysis controlling for education and leisure (block 1). There were relatively no changes to the effect of ICV ($\Delta R^2 = 0.067$, $p = 0.014$) or the ICV × T2 lesion load interaction ($\Delta R^2 = 0.067$, $p = 0.010$). Similar to education, premorbid intelligence is a common proxy of cognitive reserve, and correlated with maximal lifetime brain size.[21] Verbal intelligence (an estimate of premorbid intelligence) was only available for a subsample of patients (n = 36), but was strongly correlated with education ($r = 0.62$, $p < 0.001$), indicating that they measure similar constructs. Note that verbal intelligence was only weakly related to cognitive leisure ($r = 0.16$, $p = 0.350$), so the protective effects of cognitive leisure reported herein are not explained by higher intelligence.

Consistent with the MS population, half of our sample was diagnosed with MS before age 30. As such, for some patients, cognitive leisure was performed after disease onset. We investigated whether the protective effect of cognitive leisure differed based on age of diagnosis. A cognitive leisure × disease burden (T2 lesion load) × age at diagnosis interaction term (controlling for 2-way interactions) was not significant for models predicting overall cognitive status ($\Delta R^2 = 0.011$, $p = 0.217$), cognitive efficiency ($\Delta R^2 = 0.008$, $p = 0.361$), or memory ($\Delta R^2 = 0.010$, $p = 0.300$). That is, the protective effect of cognitive leisure did not differ based on age of diagnosis.

DISCUSSION Larger MLBV moderated/attenuated the negative impact of disease burden on cognitive status, thereby supporting the brain reserve hypothesis in MS. Given the moderate but robust correlation between estimates of cognitive reserve and brain reserve,[21] the protective effect of higher cognitive reserve in previous research may be partially or fully explained by concomitantly higher brain reserve. Our results demonstrate that early-life intellectual enrichment (cognitive reserve) protects patients from disease-related cognitive impairment independently of MLBV (brain reserve), thereby supporting the independent role of enriching experiences in protecting against cognitive decline.

Brain reserve protected against cognitive inefficiency, not memory decline. This may seem inconsistent with the aging/AD literature linking larger head size or ICV to better cognition in elders[6–10] and lower risk of dementia[11,12]; however, closer examination of these aging/AD studies confirms that larger head size or ICV predicts cognitive efficiency, not memory.[6,8,9] Furthermore, longitudinal studies link age-related brain atrophy to declines in cognitive efficiency, not memory.[26,27] Other aging/AD studies link larger ICV or head size to better Mini-Mental State Examination

scores,[7,10] but the Mini-Mental State Examination makes minimal memory demands. Finally, some studies show that larger head size protects against dementia,[11,12] but other studies do not.[28,29] Although memory impairment is the hallmark of dementia, all elders with dementia also have a decline in nonmemory cognition. It is conceivable that higher brain reserve protects against nonmemory cognitive decline associated with conversion from amnestic mild cognitive impairment to dementia. Indeed, cognitive inefficiency is among the best predictors of conversion from mild cognitive impairment to dementia.[30] In summary, the aging/AD literature appears to be largely consistent with our finding that brain reserve is protective against declines in cognitive efficiency, not memory.

The specific link between brain reserve and cognitive efficiency is consistent with the strong heritability of both MLBV[13,14] and cognitive efficiency (much more than memory).[31,32] Strong heritability may contraindicate rehabilitation efforts to bolster brain reserve and cognitive efficiency. However, rather than building brain reserve, persons may be able to preserve their remaining brain reserve (and protect cognitive efficiency) through effective disease-modifying therapies (which may slow brain volume loss) and by maintaining a "brain healthy" lifestyle (e.g., aerobic exercise). Indeed, cardiorespiratory fitness is positively correlated with brain volume and cognitive efficiency in healthy persons[33] and patients with MS.[34] In contrast to brain reserve, cognitive reserve is developed through enriching life experiences. The stronger protective impact of life experience on memory relative to cognitive efficiency in the current study is consistent with lower heritability of memory relative to cognitive efficiency,[31,32] which is further aligned with lower heritability of hippocampal volume (estimated genetic variance = 0.40) relative to ICV (0.81).[35] That is, 60% of the variance in hippocampal volume seems to be attributable to environmental factors (relative to 19% for ICV). Indeed, enriching cognitive experiences may have a positive impact on hippocampal volume in humans.[36,37]

Cognitive reserve may protect against cognitive decline through superior/optimal neurocognitive processing.[5] Consistent with this notion, functional MRI research has revealed differences in cerebral processing among patients with MS who have greater lifetime intellectual enrichment, including greater activation (or lesser deactivation) within the brain's default network.[18] The default network consists largely of limbic structures, including the hippocampus,[38] and has been implicated in memory.[39] We have subsequently demonstrated that default network activity during functional MRI predicts performance on neuropsychological tasks of memory (but not cognitive efficiency) on a separate day.[40] These links among cognitive reserve, default network activity, and memory are consistent with our current finding that cognitive reserve is specifically protective against memory decline; however, future research should more directly investigate whether differences in default network activity mediate the relationship between intellectual enrichment and memory. Although the current study provides less support for the role of intellectual enrichment in protection against cognitive inefficiency, there was a positive correlation between cognitive leisure and cognitive efficiency. We have previously shown that higher cognitive reserve protects against cognitive inefficiency in MS,[17] although we did not control for brain reserve in that study. Taken together, the protective impact of cognitive reserve appears to be more pronounced for memory than for cognitive efficiency, at least for patients with MS.

Given that larger MLBV (estimated with ICV) protects against disease-related cognitive inefficiency in MS, clinical consideration of patient ICV may improve identification of patients at risk for cognitive impairment, and efforts to maintain cardiorespiratory fitness may help preserve brain reserve and cognitive efficiency. As discussed, the specific link between brain reserve and cognitive efficiency (not memory) in this study is consistent with results from aging studies, and should be further explored in aging, AD, and other neurologic populations. The current study also demonstrates that a cognitively enriching lifestyle (a source of cognitive reserve) independently protects against cognitive impairment (especially memory decline) over and above brain reserve. This is critical, because estimates of cognitive reserve and brain reserve are correlated, and the protective effects of higher cognitive reserve in previous research may have been at least partially attributable to concomitantly higher brain reserve. Our finding that early-life cognitive leisure protects against memory decline more than cognitive inefficiency is consistent with lower heritability of memory and hippocampal volume relative to cognitive efficiency and ICV. Cognitive rehabilitation efforts targeting memory in MS stand to be most beneficial as the hippocampus is more affected by experience than other brain regions. Future prospective and/or experimental studies should investigate whether intellectual enrichment is associated with larger/increased hippocampal volume (or lesser/reduced hippocampal atrophy) in patients with MS. Finally, the positive link between intellectual enrichment and cognition in the current and previous studies is observational, and cognitive leisure activity is almost always sampled from a period before disease onset. Longitudinal research is needed to investigate whether cognitive leisure moderates decline within MS patients as disease progresses, and randomized controlled trials of intellectual

enrichment are required to establish a causal link between enrichment and protection from disease-related cognitive decline in patients already diagnosed with MS. Such evidence is needed to support a prescription of intellectual enrichment as a therapeutic intervention to minimize or prevent disease-related cognitive decline.

AUTHOR CONTRIBUTIONS

James F. Sumowski, PhD, drafted the manuscript for content, contributed to the study concept and design and analysis/interpretation of the data, and performed statistical analyses. Maria A. Rocca, MD, assisted in drafting the manuscript for content and analysis/interpretation of data, as well as acquisition of data and study supervision/coordination. Victoria M. Leavitt, PhD, assisted in drafting the manuscript for content and contributed to the interpretation of the data. Gianna Riccitelli, PhD, assisted in the analysis of data and acquisition of data. Giancarlo Comi, MD, assisted with interpretation of the data. John DeLuca, PhD, assisted in drafting the manuscript for content. Massimo Filippi, MD, assisted in drafting the manuscript for content and interpretation of data, as well as acquisition of data, study supervision, and obtaining funding.

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