

# Premorbid cognitive leisure independently contributes to cognitive reserve in multiple sclerosis

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## ABSTRACT

**Objective:** Consistent with the cognitive reserve hypothesis, higher education and vocabulary help persons with Alzheimer disease (AD) and multiple sclerosis (MS) better withstand neuropathology before developing cognitive impairment. Also, premorbid cognitive leisure (e.g., reading, hobbies) is an independent source of cognitive reserve for elders with AD, but there is no research on the contribution of leisure activity to cognition in MS. We investigated whether premorbid cognitive leisure protects patients with MS from cognitive impairment.

**Methods:** Premorbid cognitive leisure was surveyed in 36 patients with MS. Neurologic disease severity was estimated with brain atrophy, measured as third ventricle width on high-resolution MRI. Cognitive status was measured with a composite score of processing speed and memory.

**Results:** Controlling for brain atrophy, premorbid cognitive leisure was positively associated with current cognitive status ( $r_p = 0.49, p < 0.01$ ), even when controlling for vocabulary ( $r_p = 0.39, p < 0.05$ ) and education ( $r_p = 0.47, p < 0.01$ ). Also, premorbid cognitive leisure was unrelated to brain atrophy ( $r = 0.03, p > 0.5$ ), but a positive partial correlation between leisure and atrophy emerged when controlling for cognitive status ( $r_p = 0.37, p < 0.05$ ), which remained when also controlling for vocabulary ( $r_p = 0.34, p < 0.05$ ) and education ( $r_p = 0.35, p < 0.05$ ).

**Conclusions:** Premorbid cognitive leisure contributes to cognitive status in patients with MS independently of vocabulary and education. Also, patients with MS who engaged in more cognitive leisure were able to withstand more severe brain atrophy at a given cognitive status. Premorbid cognitive leisure is supported as an independent source of cognitive reserve in patients with MS.

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## GLOSSARY

**AD** = Alzheimer disease; **MS** = multiple sclerosis; **TVW** = third ventricle width.

The cognitive reserve hypothesis posits that lifetime intellectual enrichment lessens the negative impact of neurologic disease on cognitive status.<sup>1,2</sup> That is, persons with higher intellectual enrichment are able to withstand more severe neuropathology before developing cognitive impairment or dementia. The cognitive reserve hypothesis has been well-supported in Alzheimer disease (AD),<sup>2</sup> and there is a growing literature on cognitive reserve in multiple sclerosis (MS).<sup>3-5</sup> Although intellectual enrichment is usually estimated with proxies such as educational attainment or vocabulary knowledge,<sup>1-5</sup> researchers have also shown that premorbid cognitive leisure activity (e.g., reading books, playing cards) independently protects elders from dementia.<sup>6-9</sup> The current research investigates whether premorbid cognitive leisure activity protects persons with MS from cognitive decline.

**METHODS Subject enrollment.** Subjects were 36 persons with MS<sup>10</sup> (31 women) with no 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  $45.1 \pm 7.1$  years (range 27–54). Disease duration was  $9.2 \pm 6.0$  years, with MS courses including

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relapsing-remitting (n = 28), secondary progressive (n = 6), and primary progressive (n = 2). Subjects retrospectively reported cognitive leisure activity in their early 20s before they developed MS. As such, only subjects who were diagnosed after age 25 years were enrolled. Educational attainment was  $16.0 \pm 2.3$  years, and vocabulary knowledge estimated with the Wechsler Abbreviated Scale of Intelligence was within normal limits (Vocabulary mean *T* score =  $52.9 \pm 7.7$ ).

**Standard protocol approvals, registrations, and patient consents.** Institutional review boards responsible for ethical standards at UMDNJ and the Kessler Foundation Research Center approved this study. Written informed consent was obtained from all subjects prior to participation.

**Brain atrophy.** Brain atrophy was estimated with third ventricle width (TVW), which has been identified as the best neuro-anatomic predictor of cognitive status in patients with MS.<sup>11</sup> Consistent with established procedures,<sup>3,5,11</sup> TVW was defined as the distance in millimeters between the left and right boundaries of the third ventricle as imaged in the axial plane of high-resolution 3-dimensional images of the brain acquired from magnetization-prepared rapid gradient echo scans performed in a 3.0 T Siemens Allegra scanner. Detailed procedures are provided elsewhere,<sup>3</sup> with high interrater and intrarater reliabilities ( $r > 0.96$ ). Mean TVW was  $5.0 \pm 2.1$  mm.

**Cognitive leisure activity.** Subjects completed a questionnaire to quantify participation in cognitive leisure activities during their early 20s before they developed MS. We focused on premorbid cognitive leisure activity to ensure that our estimate of leisure activity was independent of neurologic disease progression, which is consistent with investigations in AD.<sup>6-9</sup> As the first investigation of cognitive leisure in MS, we limited our survey to a single premorbid age range (early 20s) to best control for age-related differences in lifestyle that may impact leisure activity (e.g., interpersonal differences in parenting responsibilities during early 30s). Seven items were chosen based on similar studies examining cognitive leisure in aging/AD (table).<sup>6-9</sup> Consistent with previous methods,<sup>9</sup> frequency of participation was endorsed as 1) once/less per year, 2) several times per year, 3) several times per month, 4) several times per week, or 5) daily. Pilot testing of this questionnaire was conducted with 52 healthy persons (mean age  $41.4 \pm 11.1$  years) who were asked to retrospectively report on leisure activity in their early 20s. Responses by persons with MS in the current sample matched those of pilot healthy subjects

(table), which is consistent with our aim of estimating cognitive leisure activity before the onset of MS. The leisure questionnaire showed very good test-retest reliability after 2 weeks in a subset of 16 pilot subjects ( $r = 0.95$ ,  $p < 0.001$ ).

Although many patients with MS have memory impairment, such memory problems are characterized by deficits in new learning/anterograde memory rather than dysfunctional remote autobiographical memory.<sup>12</sup> In fact, research using the Autobiographical Memory Interview found little to no difference in autobiographical memory accuracy between patients with MS and healthy persons.<sup>13</sup> Moreover, the consistency between autobiographical memory and collateral reports was essentially perfect for both patients with MS and healthy persons.<sup>13</sup> Given this, there is no reason to doubt the accuracy of autobiographical reports by patients with MS regarding their early-life cognitive leisure activity.

**Cognitive status.** Slowed processing speed and learning/memory problems are the most prevalent cognitive deficits among persons with MS.<sup>12</sup> We assessed processing speed with the Symbol Digit Modalities Test, and learning/memory with the total learning score of the open-trial Selective Reminding Test.<sup>4</sup> Performance on tasks was converted to sample-based *z* scores, which were then averaged into a single cognitive status score.

**Statistical analyses.** To investigate the association between premorbid cognitive leisure and current cognitive status, we performed a partial correlation between these variables controlling for brain atrophy. We repeated this correlation controlling for vocabulary knowledge and education to determine whether cognitive leisure makes an independent contribution to cognitive status in patients with MS.

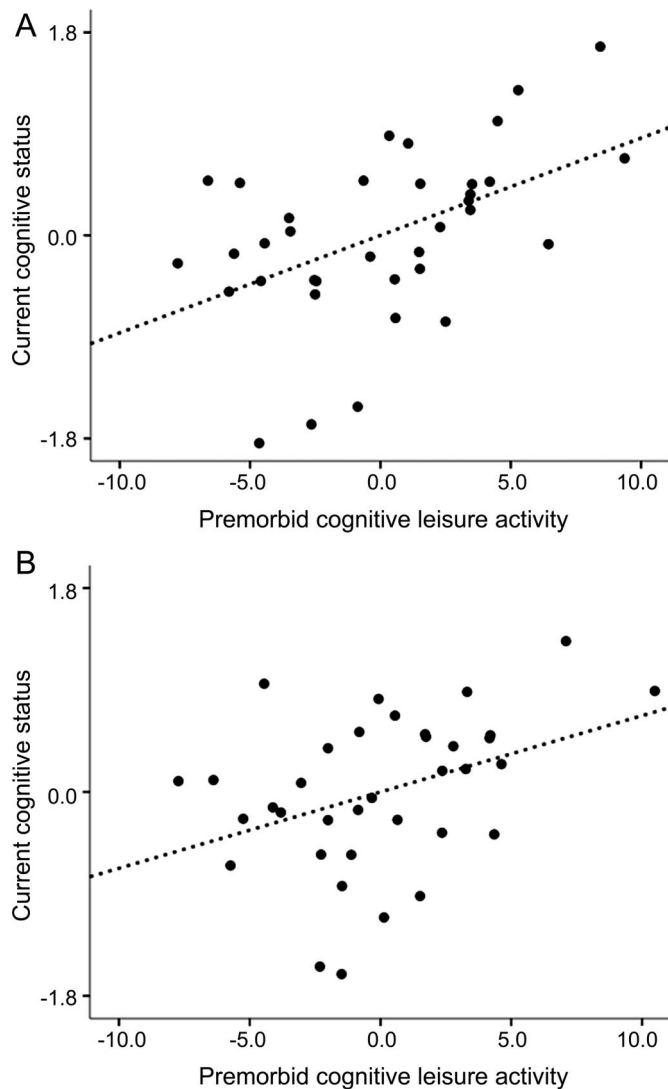
The cognitive reserve hypothesis posits that persons with greater intellectual enrichment are able to withstand more severe neuropathology before developing cognitive impairment.<sup>12</sup> As such, at a given cognitive status (e.g., dementia), persons with greater intellectual enrichment possess more severe neuropathology than persons with lesser enrichment, because more severe neuropathology is required for persons with higher enrichment to have comparable cognitive decline. To demonstrate this statistically, previous research on cognitive reserve in aging and dementia has shown no direct relationship between intellectual enrichment and neuropathology, but a positive partial correlation between intellectual enrichment and neuropathology when controlling for current cognitive status.<sup>1,2,7,14,15</sup> Consistent with this statistical approach, we first calculated the correlation between premorbid cognitive leisure activity and brain atrophy in patients with MS, followed by a partial correlation between cognitive leisure activity and brain atrophy controlling for current cognitive status. Similar to previous research, we expect no relationship between cognitive leisure and atrophy; however, a partial correlation should emerge when controlling for cognitive status. This procedure was repeated controlling for vocabulary knowledge and education.

**RESULTS** There was a positive partial correlation between premorbid cognitive leisure and current cognitive status controlling for brain atrophy ( $r_p = 0.49$ ,  $p < 0.01$ ). That is, patients with MS with higher premorbid cognitive leisure activity exhibit greater cognitive functioning. This correlation remained when also controlling for vocabulary knowl-

Table	Cognitive leisure activities		
Cognitive leisure activities	Pilot sample, n = 52, mean ± SD	MS sample, n = 32, mean ± SD	p Value
Reading books	3.2 ± 1.4	3.6 ± 1.5	0.16
Reading magazines or newspapers	3.8 ± 1.1	3.8 ± 1.4	0.87
Producing art (e.g., painting, poetry, sculpture, song writing, ballet)	1.8 ± 1.1	1.7 ± 1.1	0.68
Producing nonartistic writing (e.g., diary, newsletter, essay, blogs)	2.0 ± 1.2	1.8 ± 1.0	0.52
Playing a musical instrument	1.5 ± 0.9	1.4 ± 0.8	0.81
Playing structured games (e.g., cards, board games, crossword puzzles)	2.9 ± 1.0	2.8 ± 1.2	0.83
Participating in hobbies (e.g., gardening, model building, Web design)	2.3 ± 1.2	2.4 ± 1.2	0.59
Total cognitive leisure activity	17.3 ± 4.0	17.6 ± 4.3	0.79

Abbreviation: MS = multiple sclerosis.

**Figure** Relationship between premorbid cognitive leisure activity and current cognitive status



(A) Controlling for brain atrophy, patients with multiple sclerosis (MS) who participated in more premorbid cognitive leisure activity demonstrated better current cognitive status ( $r_p = 0.49, p < 0.01$ ). (B) This positive relationship between premorbid cognitive leisure and current cognitive status remained when also controlling for vocabulary knowledge and educational attainment ( $r_p = 0.38, p < 0.05$ ). That is, premorbid cognitive leisure was identified as an independent contributor to cognitive reserve in patients with MS.

edge ( $r_p = 0.39, p < 0.05$ ), education ( $r_p = 0.47, p < 0.01$ ), or vocabulary and education ( $r_p = 0.38, p < 0.05$ ), indicating that premorbid cognitive leisure activity makes an independent contribution to cognitive reserve in persons with MS (figure).

There was no relationship between premorbid cognitive leisure and brain atrophy ( $r = 0.03, p > 0.5$ ); however, a positive partial correlation emerged with controlling for cognitive status ( $r_p = 0.37, p < 0.05$ ). That is, persons with greater premorbid cognitive leisure were able to withstand more severe MS neuropathology before showing cognitive impairment. Importantly, the protective effect of premorbid cognitive leisure remained when controlling for

vocabulary knowledge ( $r_p = 0.34, p < 0.05$ ), education ( $r_p = 0.35, p < 0.05$ ), or vocabulary and education ( $r_p = 0.34, p = 0.05$ ).

**DISCUSSION** Intellectual enrichment (estimated with education or vocabulary knowledge) lessens the negative impact of neurologic disease on cognition in persons with AD<sup>1,2</sup> and MS.<sup>3,4</sup> Research with elders has also shown that premorbid cognitive leisure protects against dementia.<sup>6-9</sup> The current research demonstrates the independent contribution of premorbid cognitive leisure to cognitive status in persons with MS, with greater leisure activity linked to lesser cognitive dysfunction. Moreover, patients with MS who engaged in more premorbid cognitive leisure were able to withstand more severe brain atrophy before showing cognitive decline. To our knowledge, this research may be the first to document the protective impact of premorbid cognitive leisure activity in a neurologic sample other than aging/dementia.

The independent contribution of leisure activity to cognition in patients with MS supports the emerging notion that lifestyle choices can have a direct impact on the brain. Stern and colleagues<sup>2,16</sup> posit that intellectual enrichment is related to the elaboration of synaptic networks, which results in greater cerebral efficiency. Indeed, environmental enrichment has been linked to neural plasticity and synaptogenesis in animals,<sup>17</sup> and the popular “London taxi driver” study (among others) provided neuroanatomic support for the cognitive reserve hypothesis in humans, as the amount of time spent as a taxi driver was positively correlated with posterior hippocampal volumes (brain regions associated with spatial memory).<sup>18</sup> Finally, a recent fMRI study linked cognitive reserve to cerebral efficiency in patients with MS, as patients with higher vocabulary knowledge showed greater maintenance of the brain’s default network (resting state) and lesser recruitment of prefrontal cortex to perform cognitive tasks.<sup>5</sup> That is, patients with MS with higher cognitive reserve required fewer cerebral resources to perform cognitive tasks, likely explaining the protective impact of reserve on cognition in patients with MS.<sup>3,4</sup>

Limitations of the current study include the modest sample size and single estimates of brain atrophy and cognitive status. Future research should investigate the impact of cognitive leisure across distinct cognitive domains. Occupational complexity has been supported as an independent source of cognitive reserve among elders,<sup>15</sup> but occupational variables were not investigated in the current study. Future research should consider whether the degree and duration of cognitively stimulating occupations afford independent protection from cognitive de-

cline, even if such careers are ended prematurely due to MS disease.

The current findings highlight the importance of premorbid cognitive leisure activity to current cognitive status. Future research is needed to investigate whether cognitive leisure activity initiated after a diagnosis of MS can bolster cognitive reserve against impairment. That is, would a regimen of cognitively stimulating activity “prescribed” at the time of MS diagnosis protect persons with MS from future cognitive impairment? Although this question is yet to be answered directly, there appears to be adequate evidence in the cognitive reserve literature to encourage all persons to maintain a cognitively stimulating lifestyle.

### AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. J.F. Sumowski.

### DISCLOSURE

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