

# Cognitive and brain reserve and the diagnosis and treatment of preclinical Alzheimer disease

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“Reserve” hypotheses in neurodegenerative disease are theoretical concepts that attempt to explain how some individuals are able to maintain normal cognition despite pathologic disease burden sufficient to cause cognitive decline or overt dementia in others.<sup>1</sup> This idea was born out of the seminal work of Katzman et al.<sup>2</sup> who described, at postmortem, a subset of older individuals with preserved cognition who harbored substantial levels of neocortical plaques. To explain this disconnect between pathologic burden and clinical state, 2 “reserve” terms have been proposed. Brain reserve refers to intrinsic differences in brain structure or neuronal capacity and is measured by assessment of brain volume and by postmortem assessment of synaptic density and neuronal number or size.<sup>1,3</sup> Cognitive reserve, on the other hand, refers to differences in how individuals utilize adaptive cognitive strategies and engage neural networks to maintain normal cognition in the face of pathologic burden.<sup>1</sup> Cognitive reserve is traditionally measured by surrogate markers, such as overall ability level, and lifestyle factors, such as education, occupation, and cognitive, social, and physical leisure activities.<sup>4</sup> With the advent of in vivo antemortem biomarkers of Alzheimer disease (AD) that allow us to quantify brain structure, function, and molecular composition, we now know that approximately 30% of elderly individuals with no clinical impairment have evidence for preclinical AD (pAD), indicated by abnormal A $\beta$  levels by imaging or CSF analysis.<sup>1,5</sup> As the field moves toward preclinical diagnosis and eventual treatment of individuals with pAD, it is critical that we understand the mediating factors of the relationships among cognition, function, and pathologic burden.<sup>6</sup> One potential mediating factor is the influence of cognitive and brain reserve.

In this issue of *Neurology*®, Ewers et al.<sup>7</sup> investigated the effect of education (a surrogate measure of cognitive reserve) on FDG-PET brain metabolism in 52 cognitively healthy older subjects with pAD, operationalized as those with abnormal CSF A $\beta$  levels in the absence of cognitive impairment.<sup>5,7</sup> Controlling for age, sex, and overall cognitive ability, subjects with normal CSF A $\beta$  (no AD) showed an expected positive

association between education and FDG-PET signal in temporal lobe structures, including the hippocampus, and ventral prefrontal cortices. Those with pAD (low CSF A $\beta$ ) showed an inverse or negative relationship between level of education and FDG-PET signal in the same anatomic regions. These results are consistent with previous findings<sup>1</sup> that suggest that individuals with higher education, a proxy of cognitive reserve, continue to maintain normal cognitive function despite hypometabolism in neuroanatomic areas common in AD. While the data presented failed to elucidate the compensatory biological mechanisms responsible for such processes, the findings suggest that evidence of FDG-PET hypometabolism, in the presence of normal cognitive performance, may be useful in the diagnosis of pAD. However, further research will be needed to determine whether other factors, such as white matter hyperintensities or other neural processes common in normal aging, may also have an influence on FDG metabolism in cognitively normal older adults.<sup>8</sup>

Also in this issue of *Neurology*, Wilson et al.<sup>9</sup> examined whether individuals with higher brain reserve differed in their capacity to tolerate neuropathologic lesions. Using data from the Rush Memory and Aging Project, including annual cognitive testing and postmortem pathologic examinations, investigators examined the relationship between neuronal density in discrete brainstem aminergic nuclei and rates of longitudinal cognitive change in 150 older subjects. The data demonstrate that neuronal integrity (i.e., higher neuronal density) in the locus ceruleus (LC) was associated with reduced cognitive decline independent of pathologic burden from other neurodegenerative lesions elsewhere in the brain, as well as tangles or Lewy bodies. The involvement of TDP-43 pathology or vascular insults was not included in the analysis but may play an important role in the vulnerability of this nucleus to neurodegenerative disease states and cognitive decline. Based on these findings, the authors suggest that the LC may represent a structural component of brain reserve that contributes to brain reserve capacity. This study is the

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first of its kind to examine brainstem nuclei and their distributed networks as a substrate for compensatory mechanisms of brain reserve and longitudinal cognitive change in cognitively intact subjects. These findings are intriguing because the LC norepinephrine neuromodulatory system interacts with multiple neural networks that subserve various cognitive processes including attention and memory consolidation and retrieval, and thereby is postulated to be the earliest site of anatomic involvement in the pathogenesis of AD.<sup>10</sup> As the authors suggest, increased understanding of the structural and functional components of neural reserve may lead to novel approaches to limiting cognitive decline, including the use of therapeutic agents such as  $\alpha$ -adrenergic agonists,  $\beta$ -adrenergic antagonists, and norepinephrine transport inhibitors that can directly modulate noradrenergic networks.

The articles by Ewers et al.<sup>7</sup> and Wilson et al.<sup>9</sup> in this issue of *Neurology* are relevant to defining and implementing the proposed criteria for pAD. Within the next few years, we will know whether treatment of pAD is effective in delaying or even preventing the devastating symptoms of AD. Taking into consideration the influences of cognitive and brain reserve will be important for understanding and interpreting the effects of current disease-modifying treatments for AD. While the current therapeutic pipeline is focused on agents that may prevent, slow, or stop disease processes, alternative approaches that augment cognitive and brain reserve may serve as complementary strategies that could further abrogate cognitive decline and dementia beyond the protection afforded by disease-modifying therapies alone.

#### AUTHOR CONTRIBUTIONS

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#### DISCLOSURE

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