

Brain *BDNF* expression as a biomarker for cognitive reserve against Alzheimer disease progression

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Despite great scientific efforts to find treatments for Alzheimer disease (AD), only 5 medications are marketed, with limited beneficial effects on symptoms, on a limited proportion of patients, without modification of the disease course. The prevalence of AD doubles every 5 years, reaching the alarming rate of 50% in those aged 85 years and older. In the context of the demographic trends of modern society, where the elderly are the fastest growing segment of the population, identification of new therapeutic targets that may prevent, delay, or cure AD is critically needed.

Brain-derived neurotrophic factor (BDNF), encoded by the *BDNF* gene, is a member of the neurotrophin family of growth factors and exists both in the brain and periphery. BDNF's primary role in the brain is to support survival of postmitotic neurons, and growth and differentiation of new neurons and synapses. BDNF is expressed in areas that are vital for learning, memory, and executive function, i.e., hippocampus, cortex, and basal forebrain. It is also expressed in peripheral tissue, such as kidneys and prostate, and in blood and saliva.

In this issue of *Neurology*®, Buchman et al.¹ examined the expression of *BDNF* in the dorsolateral prefrontal cortex of 535 elderly participants who were followed annually for an average of 6 years for cognitive decline and dementia, and who died and underwent neuropathologic assessment. In this comprehensive clinicopathologic longitudinal study, high brain *BDNF* expression was associated with slower rate of cognitive decline during life. This relationship was strongest among those with high levels of AD neuropathology (analyzed in 4 ways: dichotomous AD diagnosed by National Institute on Aging consensus criteria, composite AD neuropathology, and individual amyloid or tangle burden). Similarly, the association of high *BDNF* with slower cognitive decline was strongest in participants with a clinical diagnosis of dementia, but less so in those with mild cognitive impairment; and in those with normal cognition, BDNF level was not associated with cognitive decline. Conversely, the association of AD pathology with cognitive decline was strongest in those with the lowest *BDNF* expression.

Postmortem studies are inherently cross-sectional, therefore temporal sequence and causality cannot be inferred (i.e., whether *BDNF* levels modify the effects of AD neuropathology on cognition, vice versa, or both). This limitation illustrates the critical importance of developing longitudinal studies using in vivo brain biomarkers, such as amyloid and tau imaging, and perhaps novel markers such as BDNF, to illuminate the temporal association and relevance of the neurobiological processes underlying cognitive decline and AD. Regardless of causal mechanisms, *BDNF* and AD neuropathology interact in their effect on the rate of cognitive decline in individuals with dementia. This may have substantive clinical implications, since slower rate of cognitive decline may postpone major AD-related negative outcomes, from patient and family suffering, to institutionalization and early death.

Of note, although high *BDNF* expression was associated with low extent of AD pathology (but not with macroscopic infarcts, Lewy body pathology, and hippocampal sclerosis), the contribution of *BDNF* to cognitive decline remained robust after accounting for AD neuropathology. This suggests that BDNF could affect cognition through enhancement of “brain reserve” mechanisms, such as neurogenesis,² synaptic plasticity,³ and dendritic density,⁴ which may counteract brain pathology as a compensatory mechanism. It should be noted, however, that in a combined model, point estimates for the variance in the rate of cognitive decline due to *BDNF* gene expression were more than an order of magnitude lower than that due to AD neuropathology, i.e., the contribution of neuropathology to cognitive decline was substantially stronger.

This is the first study to provide data on brain *BDNF* gene expression levels and cognitive outcomes in humans, and the multiple analyses performed revealed results that reinforced the conclusions presented. In individuals with moderate to high levels of AD pathology, *BDNF* gene expression levels similar to those of individuals with little or no AD pathology demonstrated a lower rate of cognitive decline. This specific finding promotes the idea that increasing *BDNF* gene expression might be a reasonable therapeutic strategy for

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AD in humans. Physical activity has been associated with slower rates of cognitive decline and lower risk of dementia,⁵ and with increased levels of peripheral serum or plasma BDNF,⁶ including patients with AD.⁷ However, we still lack systematic evidence that the benefits of physical activity on cognitive decline derive from increases in brain BDNF. Moreover, the relationship between peripheral serum or plasma BDNF and brain BDNF levels or gene expression is unclear, and these associations could not be examined in the current study. Social interactions⁸ and environmental enrichment² improve memory deficits in AD-like animal models through BDNF-dependent hippocampal neurogenesis. In humans, physical activity,⁵ social interactions,⁹ and environmental enrichment¹⁰ (typically measured as years of formal education) have all been associated with a lower risk of dementia and AD, suggesting brain *BDNF* upregulation as a candidate underlying mechanism, possibly through enhancement of cognitive reserve.

The study by Buchman et al. highlights brain BDNF as a potential substantial contributor to slowing cognitive decline in the elderly, especially in the setting of advancing AD neuropathology. *BDNF* gene expression or its gene products might thus serve as a biomarker for cognitive reserve against AD progression. Further study is needed to confirm these findings, to better elucidate the relationship between *BDNF* and systematic markers of cognitive reserve, and to clarify its potential therapeutic utility.

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DISCLOSURE

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