Evaluating Cognitive Reserve Through the Prism of Preclinical Alzheimer Disease

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KEYWORDS

• Cognitive reserve • Alzheimer disease • Mild cognitive impairment • Biomarkers • Amyloid • Tau • Atrophy

KEY POINTS

- Evidence indicates that higher levels of cognitive reserve (CR), as measured by proxy variables such as educational and occupational attainment, delay the onset of symptoms of mild cognitive impairment due to Alzheimer disease.
- Recent findings suggest that the protective effects of CR may be independent of amyloid pathologic features but interact with measures of neuronal injury to alter risk of cognitive impairment.
- It is unclear whether CR alters future risk of cognitive decline by directly affecting brain pathologic features.
- Prospective longitudinal biomarker studies are needed to investigate the mechanisms by which CR alters future risk of cognitive decline.

OVERVIEW: THE CONCEPT OF COGNITIVE RESERVE

The aging of the population, which is accompanied by an increasing prevalence of AD, makes it imperative to identify factors that reduce risk of onset of dementia. CR is increasingly being studied as a potential mechanism for reducing the risk of cognitive decline and dementia among older adults. The concept of CR grew out of observations that there can be a marked discrepancy between an individual's clinical symptomatology and estimates of the amount of neuropathologic features in the brain. For example, an early study by Stern and colleagues[1] (1992) that began investigating this issue reported that among individuals with probable AD and matched for clinical

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severity, those with more years of education had more advanced pathologic features, as indicated by less cerebral blood flow in AD-vulnerable regions.

It has been proposed that lifetime experiences that are associated with cognitive stimulation (eg, years of education, occupational attainment, and engagement in mentally stimulating leisure activities) modify the brain in a way that allows individuals to tolerate greater levels of neuropathologic features or injury before showing symptoms of functional decline.[2] Although the concept of CR has primarily been studied within the context of AD, it is hypothesized to apply to any brain disease or condition that results in brain damage, and an increasing number of studies support this proposal.[3–5] It has also been proposed that CR moderates the relationship between brain changes and age-related cognitive decline.[2,6]

This article first briefly summarizes the major lines of evidence in support of the concept of CR within the context of AD. It then provides a detailed review of longitudinal biomarker studies that have examined the relationship between measures of CR, AD pathologic features, and subsequent cognitive change or impairment among individuals who were cognitively normal when first evaluated. It focuses on studies of individuals with normal cognition at baseline because it is now recognized that AD pathologic features begin to develop when individuals are cognitively normal, a phase of the disease commonly referred to as preclinical AD.[7] As such, these types of studies provide insight into how and to what extent CR delays the onset of the symptomatic phase of the disease, which has major public health implications; it has been estimated that interventions that delay the onset of dementia by 5 years would reduce the prevalence of dementia by 50%.[8]

EVIDENCE IN SUPPORT OF COGNITIVE RESERVE

Supporting the concept of CR, many large prospective epidemiologic studies of initially nondemented individuals have shown that more years of education,[9] greater occupational breadth and complexity,[9,10] and greater lifetime engagement in cognitively stimulating activities[11] are associated with a reduced risk of dementia. The evidence regarding the relationship between measures of CR and rates of change in cognition is more mixed, with many recent studies reporting little or no association between CR and rates of cognitive decline, despite evidence that individuals with higher CR have a higher performance on cognitive tests.[12] It has been suggested that the differences in findings among these studies likely reflect methodological and cohort differences and, taken together, the evidence indicates that CR primarily influences baseline levels of cognitive performance.[12,13] Thus, epidemiologic studies strongly support the notion that higher levels of CR are associated with better cognitive performance, as well as a reduced risk of developing dementia later in life, whereas the impact of CR on the trajectory of cognitive decline is less clear. Epidemiologic research on CR, however, has generally been limited by a lack of measures of underlying AD pathologic features. As such, these types of studies cannot directly examine whether and how measures of CR affect the association between levels of neuropathologic features and cognitive performance.

Thus, studies that have incorporated biomarkers, which are considered an indirect reflection of underlying neuropathologic features, are of particular importance in clarifying the mechanisms by which CR may be protective. Most studies on CR with biomarker measures of AD pathologic features have been cross-sectional in nature. A common finding of cross-sectional studies is that, at similar levels of cognitive functioning, individuals with higher CR tend to have biomarker measures reflecting higher levels AD pathologic features in the brain. For example, atrophy measures based on