Cognitive Reserve and Alzheimer Disease

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Abstract: Epidemiologic evidence suggests that individuals with higher IQ, education, occupational attainment, or participation in leisure activities have a reduced risk of developing Alzheimer disease (AD). The concept of cognitive reserve (CR) posits that individual differences in how tasks are processed provide differential reserve against brain pathology or age-related changes. This may take 2 forms. In neural reserve, preexisting brain networks that are more efficient or have greater capacity may be less susceptible to disruption. In neural compensation, alternate networks may compensate for pathology's disruption of preexisting networks. Imaging studies have begun to identify the neural substrate of CR. Because CR may modulate the clinical expression of AD pathology, it is an important consideration in studies of "preclinical" AD and treatment studies. There is also the possibility that directly enhancing CR may help forestall the diagnosis of AD.

Key Words: imaging, epidemiology, progression

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DEFINITIONS OF RESERVE

The idea of reserve against brain damage stems from the repeated observation that there does not seem to be a direct relationship between the degree of brain pathology or brain damage and the clinical manifestation of that damage. For example, Katzman et al[1] described 10 cases of cognitively normal elderly women who were discovered to have advanced Alzheimer disease (AD) pathology in their brains at death. They speculated that these women did not express the clinical features of AD because their brains were larger than average, providing them with "brain reserve."

Brain reserve[2] is an example of what might be called passive models of reserve, where reserve derives from brain size or neuronal count. The models are passive because reserve is defined in terms of the amount of brain damage that can be sustained before reaching a threshold for clinical expression. The threshold model,[3] one of the best articulated passive models, revolves around the construct of "brain reserve capacity" (BRC). Although BRC is a hypothetical construct, concrete examples of BRC might include brain size or synapse count. The model recognizes that there are individual differences in BRC. It also presupposes that there is a critical threshold of BRC. Once BRC is depleted past this threshold, specific clinical or functional deficits emerge.

In contrast, the cognitive reserve (CR) model suggests that the brain actively attempts to cope with brain damage by using preexisting cognitive processing approaches or by enlisting compensatory approaches.[4] Individuals with more CR would be more successful at coping with the same amount of brain damage. Thus, the same amount of brain damage or pathology will have different effects on different people, even if BRC (eg, brain size) is held constant. The concept of CR provides a ready explanation for why many studies have demonstrated that higher levels of intelligence and of educational and occupational attainment are good predictors of which individuals can sustain greater brain damage before demonstrating functional deficit. Rather than positing that these individuals' brains are grossly anatomically different than those with less reserve (eg, they have more synapses), the CR hypothesis posits that they process tasks in a manner that allows them to cope better with the brain damage.

I[5] have suggested that the neural implementation of CR might take 2 forms: neural reserve and neural compensation. Neural reserve refers to brain networks or cognitive paradigms that are less susceptible to disruption, perhaps because they are more efficient or have greater capacity. Using this type of CR is a normal process that is already in place in healthy individuals. Although healthy individuals may invoke these networks when coping with increased task demands, the networks could also help an individual cope with brain pathology. Neural compensation refers to the process by which individuals suffering from brain pathology use brain structures or networks (and thus cognitive strategies) not normally used by individuals with intact brains to compensate for brain damage. These concepts are particularly important when attempting to formulate and interpret functional imaging studies that investigate CR.

Some research findings might be more easily explained using an active CR reserve model than a passive model of reserve. For example, given no gross difference in brain size, passive models do not have a

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ready explanation for findings described below, which indicate that 1 patient can maintain more AD pathology than another but appear similar clinically. However, the brain reserve and CR concepts are not mutually exclusive, and it is likely that both are involved in providing reserve against brain damage.

MEASURES OF RESERVE

For advocates of the idea of brain reserve, anatomic measures such as brain volume, head circumference, synaptic count, or dendritic branching are effective measures of reserve. Mounting evidence suggests that many of these measures are malleable over the lifetime, and influenced by life experience. Therefore, brain reserve may represent a summation of many aspects of life experience that are also thought to summate into CR.

Variables descriptive of lifetime experience are the most commonly used proxies for CR. These include measures of socioeconomic status, such as income or occupational attainment. Educational attainment has also been a widely used proxy for reserve, probably because it is relatively easy to ascertain. Degree of literacy might be a better marker for CR than number of years of formal education because it is a more direct measure of educational attainment.[6,7] Finally, specific measured attributes have been used as indices of reserve, including IQ and measures of various cognitive functions.

Education might also be a marker for innate intelligence, which may in turn be genetically based or a function of exposures. Some studies suggest that an estimate of IQ, or premorbid IQ, might actually be a more powerful measure of reserve in some cases.[8,9] Still, education, or other life experiences, probably impart reserve over and above that obtained from innate intelligence. Studies have demonstrated separate or synergistic effects for higher educational and occupational attainment and leisure activities, suggesting that each of these life experiences contributes independently to reserve.[10–14] A prospective study showed that estimated IQ at age 53 was separately influenced by childhood cognition, educational attainment, and adult occupation.[15] These observations stress that CR is not fixed; at any point in one's lifetime it results from a combination of exposures.

The simplest explanation for how CR forestalls the clinical effects of AD pathology does not posit that experiences associated with more CR directly affect brain reserve or the development of AD pathology. Rather, CR allows some people to better cope with the pathology and remain clinically more intact for longer periods of time. This has been the working assumption underlying the design and interpretation of many of my studies. However, as mentioned above, many of the factors associated with CR may also have direct impact on the brain itself. There is a demonstrated relationship between IQ and brain volume.[16] Thus, the child development literature suggests that intracranial brain volume and aspects of lifetime exposure are predictive of differential susceptibility to the effects of traumatic brain injury.[17] Also, it is now clear that stimulating environments and exercise promote neurogenesis in the dentate of animals.[18,19] In addition, there is evidence to suggest that environmental enrichment might act directly to prevent or slow the accumulation of AD pathology.[20] Thus, a more complete accounting of CR would have to integrate these complex interactions between genetics, the environmental influences on brain reserve and pathology, and the ability to actively compensate for the effects of pathology.

EPIDEMIOLOGIC EVIDENCE FOR CR

A host of studies have examined the relation between CR proxy variables and incident dementia. Parallel studies have often examined the relation between these variables and cognitive decline in normal aging.

Several studies in India,[21] England,[22] and the United States[23–25] reported no association between education and incident dementia. However, lower incidence of dementia in subjects with higher education has been reported by at least 8 cohorts, in France,[26] Sweden,[27] Finland,[28] China,[29] and the United States.[10,13,30,31] Similar associations emerged in a pooled analysis of 4 European population-based prospective studies of individuals 65 years and older.[32]

There is also evidence for the role of education in age-related cognitive decline, with several studies of normal aging reporting slower cognitive and functional decline in individuals with higher educational attainment.[33–40] These studies suggest that the same education-related factors that delay the onset of dementia also allow individuals to cope more effectively with brain changes encountered in normal aging. In an ethnically diverse cohort of nondemented elders in New York City, increased literacy was also associated with slower decline in memory, executive function, and language skills.[7]

No or equivocal association between occupation and incident AD was found in several population-based longitudinal studies.[28,41,42] In 2 other prospective studies, occupational position did not predict incident dementia,[22] or its predictive value might have been mediated by educational status.[30] Nevertheless, several studies have noted a relationship between occupational attainment and incident dementia.[13,31,43–46] As mentioned above, occupational attainment was often noted to have independent effects or interact with educational attainment.

In a German population survey, only poor quality living accommodations were associated with increased risk of incident dementia, whereas indicators of social isolation such as low frequency of social contacts within and outside the family circle, low standard of social support and living in single person household did not prove to be significant.[43] A study from France reported that traveling, doing odd jobs, and knitting were associated with lower risk of incident dementia.[47,48] Community activities and gardening were also protective for incident dementia in China.[44] A longitudinal study in

Sweden reported that having an extensive social network was protective for development of incident dementia.[49] The same group later reported that engagement in mental, social, and productive activities was associated with decreased risk for incident dementia.[50] Participation in a variety of leisure activities characterized as intellectual (eg, reading, playing games, going to classes) or social (eg, visiting friends or relatives etc.) was assessed in another population study of nondemented elderly in New York.[51] During follow-up, subjects with high leisure activity had 38% less risk of developing dementia. In another prospective study, frequency of participation in common cognitive activities (ie, reading a newspaper, magazine, books) was assessed at baseline for 801 elderly Catholic nuns, priests, and brothers without dementia.[52] During follow-up, 1-point increase in the cognitive activity score was associated with a 33% reduction in the risk for AD. Additionally, engagement in cognitive activities was also associated with slower rates of cognitive decline. Finally, in another prospective cohort from New York, participation in leisure activities, particularly reading, playing board games or musical instruments, and dancing, was associated with a reduced risk for incident dementia.[53] Increased participation in cognitive activities was also associated with reduced rates of memory decline in this study.

In contrast to the studies above, in which greater reserve was associated with better outcomes, a series of studies of patients with AD have suggested that those with higher reserve have poorer outcomes. In a prospective study of AD patients matched for clinical severity at baseline,[54] patients with greater education or occupational attainment died sooner than those with less attainment. Although at first these findings seem contra-intuitive, they are consistent with the CR hypothesis. The hypothesis predicts that at any level of assessed clinical severity, the underlying pathology of AD is more advanced in patients with CR than in those with CR. This would result in the clinical disease emerging when pathology is more advanced, as suggested by the incidence studies reviewed above. This disparity in degree of pathology would be present at more advanced clinical stages of the disease as well. At some point the greater degree of pathology in the high reserve patients would result in more rapid death. Although one study did not replicate this finding,[55] a follow-up study by the same group, using patients with more advanced dementia, did.[56] Higher measured CR has also been associated with more rapid cognitive decline in patients with AD.[57,58] Explanation of this finding is along similar lines. At some point, AD pathology must become too severe enough to support the processes that mediate CR. This point should arrive at an earlier stage of clinical severity in patients with higher CR because the underlying AD pathology is more severe.

IMAGING STUDIES OF CR

Several imaging studies of CR in AD used resting cerebral blood flow (CBF) as a surrogate for AD pathology.[59–61] In patients matched for clinical severity, these studies have found negative correlations between resting CBF and years of education, premorbid IQ, occupation and leisure.[9,14,62,63] The negative correlations are consistent with the CR hypothesis' prediction that at any given level of disease clinical severity a subject with a higher level of CR should have greater AD pathology (ie, lower CBF). These findings were confirmed in a prospective study with subsequent neuropathologic analysis. Education was found to modify the association between AD pathology and levels of cognitive function: for the same degree of brain pathology there was better cognitive function with each year of education.[64]

In contrast to the resting studies, cognitive activation studies can be used to elucidate the nature of CR. The general logic behind this approach is that to the extent that CR reflects differences in how tasks are processed, functional imaging studies should be able to capture these differences. One approach to this problem is to identify patterns of task-related activation that differ between AD patients and controls, and to determine whether they are compensatory. For example, Stern et al[65] tried to determine whether or not the pathology of AD alters the brain networks subserving performance on a memory task, while carefully controlling for task difficulty. $H_2^{15}O$ positron emission tomography was used to measure regional CBF in patients and healthy elders during the performance of a verbal recognition task. Task difficulty was matched across participants by adjusting the size of the list that each subject had to remember such that each subject's recognition accuracy was 75%. In the healthy elders, a network of brain areas involving left anterior cingulate, anterior insula, and left basal ganglia was activated during task performance. Higher study list size was associated with increased recruitment of this network, indicating that this network was associated with task performance and that subjects who could recruit the network to a greater degree could perform the task better. Only 3 AD patients expressed this network in a similar manner. This network used by the controls and a minority of AD patients may underlie neural reserve, in that it seems to be recruited to cope with the demands presented by the activation task, and differential recruitment of the network is directly related to the ability to perform the task. Individuals who are able to activate this network to a greater degree may have more reserve against brain damage. The remaining 11 AD patients recruited a different network during task performance, consisting of left posterior temporal cortex, calcarine cortex, posterior cingulate, and the vermis. Again, in these patients, higher study list size was associated with increased activation of this network. Stern et al hypothesized that this alternate network may be used by the AD patients to compensate for the effects of AD pathology. This is compatible with the concept of neural compensation, where patients use brain networks not used by unaffected individuals to perform a task.

Whereas the criteria for neural compensation merely require that individuals with pathology use a

brain network that is not used by unaffected individuals, one may further ask whether use of this alternate network is associated with better performance. For example, in several studies, some elders showed additional activation in areas contralateral to those activated by younger subjects; the elders who showed this additional activation performed better than those who did not, indicating that it was compensatory.[66,67] Similarly, studies have shown that additional activation in AD patients compared with controls is compensatory.[68]

Other studies have taken a more direct approach to investigating brain networks associated with CR. One positron emission tomography study identified brain areas whose activation during performance of a nonverbal memory task correlated with an index of CR calculated from measures of education and literacy.[69] Such areas were identified in both healthy controls and patients with AD, suggesting that these areas may reflect the neural instantiation of CR. Interestingly, in some brain areas the directionality of the association between CR and cerebral activation differed in healthy controls and AD patients. For example, some brain areas showed increased activation as a function of increased CR in the elderly controls and decreased activation in the AD patients. Given the assumption that individuals with higher measured CR would activate in a more adaptive way, these findings suggest that there has been some compensation for the effects of AD pathology in the AD patients and that CR is mediated differently in the patients and controls. The changes in activation in the AD patients are consistent with our definition of neural compensation. Similar observations have been noted in comparisons of young and elderly subjects.[5]

In summary, the imaging evidence is beginning to provide support for the 2 hypothesized neural mechanisms underlying CR: neural reserve which emphasizes preexisting differences in neural efficiency or capacity, and neural compensation, which reflects individual differences in the ability to develop new, compensatory responses to the disabling effects of pathology.

IMPLICATIONS OF CR FOR DIAGNOSIS, EARLY DETECTION, AND TREATMENT OF AD

The evidence suggests that 2 individuals who appear the same clinically can have widely divergent levels of underlying AD pathology and that CR may account for some of this disparity. This observation has strong implications for our attempt to diagnose AD in its preclinical stages. For example, setting aside diagnostic errors, the clinical observation of mild cognitive impairment may be accompanied by very minimal pathology or more than enough to meet pathologic criteria for AD. A proportion of this variability may be explained by CR. Measuring CR therefore becomes an important component of the diagnostic process.

Most people recognize that clinical evaluation alone is an insufficient measure of a patient's true status, and there are active attempts to seek markers of underlying AD pathology. It remains to be seen whether the best index of pathology will be via biomarkers,[70] or by imaging AD pathology itself,[71] the effect of pathology on resting metabolism in entire brain,[72] or the effect of pathology on particularly vulnerable brain area.[73] However, even with the addition of an accurate index of AD pathology, clinical characterization is not complete. Also needed is a measure of an individual's CR, that is, the ability to cope with this pathology. Some idea of an individual's CR might be garnered from standard proxies for CR such as educational and occupational attainment. However, as functional imaging studies reveal greater insight into the neural networks that underlie CR, quantifying a patient's expression of such networks might allow us to directly assess CR in individual patients. The combination of clinical characterization, measures of underlying pathology and indices of CR would provide a more complete picture of a patient's status. Besides being important for early diagnosis, such an approach would help determine prognoses and progression over time. It would also be crucial for the assessment of the effect of any intervention, particularly one that purports to influence time of disease onset.

Finally, the fact that different life exposures including education, occupation and leisure, impart reserve against AD in epidemiologic studies raises the possibility that an individual's CR could be increased through some set of systematic exposures or interventions. This would result in a nonpharmacologic approach for reducing risk of developing AD.

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