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COGNITIVE RESERVE IN AGING

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Abstract

Cognitive reserve explains why those with higher IQ, education, occupational attainment, or participation in leisure activities evidence less severe clinical or cognitive changes in the presence of age-related or Alzheimer's disease pathology. Specifically, the cognitive reserve hypothesis is that individual differences in how tasks are processed provide reserve against brain pathology. Cognitive reserve may allow for more flexible strategy usage, an ability thought to be captured by executive functions tasks. Additionally, cognitive reserve allows individuals greater neural efficiency, greater neural capacity, and the ability for compensation via the recruitment of additional brain regions. Taking cognitive reserve into account may allow for earlier detection and better characterization of age-related cognitive changes and Alzheimer's disease. Importantly, cognitive reserve is not fixed but continues to evolve across the lifespan. Thus, even late-stage interventions hold promise to boost cognitive reserve and thus reduce the prevalence of Alzheimer's disease and other age-related problems.

Keywords

aging; Alzheimer's disease; brain reserve; cognitive reserve; neural reserve; neural compensation

The idea of reserve against brain damage comes from the repeated observation [1–5] of individuals who manage to function clinically in the face of brain pathology. One particularly striking early example is a report including 10 cognitively healthy elderly women who were discovered to have Alzheimer's pathology in the form of plaques at autopsy [6]. These women had heavier brains and more neurons than both demented and other non-demented residents; these larger brains and extra neurons were hypothesized to provide "reserve" that helped them cope with the Alzheimer's-induced plaques. Subsequent studies reported that 25% to 67% of subjects characterized as nondemented throughout rigorous and repeated longitudinal assessments fulfilled pathological criteria for dementia at autopsy [7–11].

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There are two kinds of reserve that have been reported to make independent and interactive contributions to preserving functioning in the face of brain injury: brain reserve and cognitive reserve. Brain reserve refers to quantitative measures such as brain size [12] or neuronal count [13]. Those with more brain reserve tend to have better clinical outcomes for any given level of pathology [14, 15] although for a negative report and dissenting view see [16]. According to the brain reserve model, there is some threshold at which clinical deficits will become apparent and those individuals with more brain reserve require more pathology to reach that threshold. That is, in the case of Alzheimer's for example, the disease will progress longer and more pathology will accumulate before deficits will be seen in those that start out with a bigger brain and/or more neurons.

The brain reserve model is quantitative: a given brain injury will affect each individual the same way and brain injuries across the lifespan will sum together. There is some evidence that some injuries do accumulate across the lifespan such that Alzheimer's has been reported to be more likely with each psychiatric episode [17] and similarly that Alzheimer's is more likely in athletes that have sustained multiple concussions [18]. Yet, in this model individual differences are only observed in brain reserve, and damage either is or is not sufficient to reach the threshold needed to observe clinical symptoms.

While the brain reserve model does explain some observations, the assumption that more is better is likely overly simple. For example, it is well established that the condition of autism is associated with a childhood brain that is larger than normal, perhaps due to a failure of those pruning mechanisms that discard unused or maladaptive connections in the brain [19]. In the context of aging, there are preliminary reports that the orbital prefrontal cortex may actually grow larger with aging and that this increase may be associated with decreased (i.e., worse) working memory performance [20]. Thus, the assumption made by the brain reserve model that those with the biggest brain capacity are always at the biggest advantage may need to be tempered somewhat. A further limitation of this model is that it cannot explain why those with higher IQ and more education decline more quickly once Alzheimer's is diagnosed and progress to death sooner [21–27].

Cognitive reserve, by contrast, refers to how flexibly and efficiently one can make use of available brain reserve [28]. Standard proxies for cognitive reserve include education [29] and IQ [30] although this has expanded to include literacy [31, 32], occupational attainment [27, 33, 34], engagement in leisure activities [35–37], and the integrity of social networks [38, 39]. Some recent evidence suggests that personality variables may be important as well [40, 41]. At any rate, those individuals with higher cognitive reserve are thought to be able to accomplish more for any given level of pathology and brain reserve.

Indeed, Mortimer et al. [11] reported that while those with a lower brain capacity, operationalized by a smaller head circumference, have a greater risk of Alzheimer's; yet, those with a lower brain capacity but higher cognitive reserve, as operationalized by more years of education, did not have a greater risk of Alzheimer's. Thus, cognitive reserve allowed people to compensate for pathology by making better use of that brain reserve which was still available. In this study there was no one absolute threshold of brain capacity at which cognitive impairment was seen. Instead, the amount of brain reserve required to maintain performance varied between people as a function of their cognitive reserve.

Although here cognitive reserve is discussed primarily in terms of better cognitive and functional outcomes in Alzheimer's disease and normal age-related decline it has also been shown to apply to cognitive outcomes in diverse conditions including but not limited to vascular injury [42, 43], Parkinson's disease [44], traumatic brain injury [45], HIV [46], and multiple sclerosis [47]. That cognitive reserve is protective against brain injury in terms of

cognitive and functional outcomes is established; yet it is unclear if cognitive reserve is similarly protective in terms of affective or psychiatric outcomes. One study suggested that higher cognitive reserve does not protect against the depressive symptoms that emerge early in the course of Alzheimer's [48]; yet, other studies of healthy individuals have shown that higher cognitive reserve is protective against psychiatric diseases including depression [49, 50].

Many of the cognitive reserve variables are intercorrelated. For example, a high IQ leads to more education, which in turn raises IQ [51]. Yet, while intercorrelated, the cognitive reserve variables appear to impart independent albeit synergistic effects that cumulate across the lifespan. Richards et al. [33] studied the lifetime antecedents of cognitive reserve in preventing normal age-related decline in midlife. The results of a path analysis revealed that childhood IQ, educational attainment, and occupation in middle age had statistically independent paths to cognitive decline. Of these antecedent variables, childhood IQ had the strongest path (0.33), educational attainment by early adulthood the next strongest path (0.22), and occupation in middle age the least strong path (0.10). The results of this study suggest that although early childhood factors are highly important for the development of cognitive reserve, yet, cognitive reserve is not fixed in childhood but continues to be affected by events and circumstances as they unfold across the lifespan.

One potential confound of cognitive reserve is that many of the variables used to measure it, such as years of education, are associated with socioeconomic status (SES). Yet, Karp et al. [52] reported that while both low education and low SES confer a greater risk for Alzheimer's disease, when both are in the model only education remains significant. Thus, SES did not mediate the relationship between education and clinical outcome. Further, Turrell et al. [53] reported that completing more years of education was associated with better cognitive functioning in middle age, and that this effect was independent of both childhood SES and current income. Hence, the advantage imparted from cognitive reserve cannot be reduced to SES.

Another potential confound is that those with higher education and IQ perform better on the tests used to measure cognitive decline and some of the tests used to diagnose Alzheimer's disease; this has been referred to as the ascertainment bias [54]. That is, although a person with high cognitive reserve might decline from a high level of performance due to Alzheimer's pathology or aging, this decline might be missed in testing because they may still perform at an average level. Yet, cognitive reserve has been shown to operate even when diagnosing dementia with an interview of daily functioning rather than using neuropsychological tests [55]. Further, cognitive reserve has been shown to provide benefit against cognitive decline even in longitudinal study designs which provide a clear baseline from which to compare performance for each subject [56].

Unlike brain reserve, cognitive reserve provides an explanation for the initially counterintuitive finding that those with higher IQ, more education, and/or more participation in leisure activities fare worse in that they decline more quickly and die sooner once Alzheimer's is diagnosed [21–27]. According to the cognitive reserve model, individuals with higher reserve have successfully compensated for pathology in the early stages of Alzheimer's pathology. By the time deficits are clinically observable in an individual with high cognitive reserve the pathology is in a more advanced stage and the patient is closer to death. This also means that for a given functional level, those with higher reserve have more pathology [57, 58].

While brain reserve and cognitive reserve are clearly distinct, there is some slight overlap between them. For example, there is a small but significant relationship between IQ and

brain volume [59]. Also, it has been demonstrated that enriching environments – a factor of cognitive reserve captured in humans by such variables as participation in leisure activities and occupational complexity – promote neurogenesis in the dentate gyrus of the hippocampus [60]. Finally, there is some evidence from animal studies that stimulating environments affect Alzheimer's pathology directly [61]. Nevertheless, while related, brain reserve and cognitive reserve likely make independent as well as interactive contributions to explaining individual differences in cognitive and functional resilience to brain insults.

In terms of the cognitive processes involved, cognitive reserve may operate by allowing for more flexible strategy usage, an ability thought to be captured by executive functions tasks. Indeed, using structural equation modeling across two samples of healthy older adults aged 53 to 97, cognitive reserve as operationalized by years of education, Wide Range Achievement Test (WRAT) score or for Spanish speakers the Word Accentuation Test (WAT) score, and picture vocabulary from the Peabody Picture Vocabulary Test third edition (PPVT-III), was found to highly overlap with the executive functions tasks of the letter-number (LN) sequencing subtest of the third version of the Wechsler Adult Inventory Scale (WAIS-III), the odd-man out task, and the difference score from the Color Trails Test [62]. In a third sample of healthy adults aged 20–81, cognitive reserve operationalized as above (education, WRAT, and picture vocabulary) was found to completely overlap with executive functions as operationalized by the same LN sequencing subtest but additionally the Wisconsin Card Sorting Task and the Matrix Reasoning Test. This strongly suggests that cognitive reserve may be related to fluid executive abilities.

Turning to neuroimaging data, cognitive reserve is theorized to manifest as neural reserve and neural compensation [63]. In the absence of pathology, neural reserve allows young healthy individuals with higher cognitive reserve to process tasks more efficiently, and with greater capacity. When tasks are of lower or moderate difficulty individuals with higher cognitive reserve may show lower neural activation, indicating higher neural efficiency. Conversely, when tasks are of high difficulty, individuals with higher cognitive reserve may show higher neural activation, indicating higher capacity. Addressing difficulty is thus of the utmost importance in interpreting activation differences between groups. Neural reserve also appears to operate in the cases of aging and Alzheimer's pathology as well as other forms of brain insult. Other key variables being equal, those with higher neural reserve should perform at either a better or equivalent level to those lower in neural reserve.

Neural compensation refers to the use of alternate brain regions not normally seen in healthy young adults in order to compensate for deficits in primary avenues for successful task performance [63]. By definition, then, neural compensation is not seen in healthy young adults but only in those with brain pathology. Addressing difficulty is essential in the context of neural compensation. For example, it may appear that a region activated in older adults is not activated in younger adults and that neural compensation is thus occurring. Yet, if the task were made more difficult this region might similarly be used by the young people. It may even be the case that the young people are using the area at the easier level of task difficulty, but due to the statistical threshold set for determining brain activation this area is not detected.

Another key aspect of neural compensation is that it is sometimes but not necessarily associated with better performance. Instead, neural compensation can in some instances be compared to a cane which allows individuals to continue walking but will not restore the ability to sprint. Indeed, more neural compensation has been associated with worse instead of better performance in terms of speed [64, 65]. Some have posited that slowing due to compensatory processing may be a consequence of traversing additional brain regions. An alternate possibility is that neural compensation shifts processing from a primary to a

secondary, less efficient network. Yet, neural compensation has also been associated with better performance in terms of successfully remembering more words [66]. In sum, neural compensation can be associated with performance that is either better or worse.

In this context it should be noted that the activation of additional brain areas in the face of pathology is not always compensation. Sometimes additional regions are activated in a dysfunctional manner due to negative processes such as dedifferentiation of neural tissue in responding to sensory inputs [67], as a failure to resolve competition among brain regions [68], or as a failure to inhibit the default network during task performance [69]. Thus, when additional regions are activated and performance is worse, such processes should be ruled out before concluding that neural compensation is taking place.

Imaging cognitive reserve in young healthy adults

Stern et al. [70] examined regions where event-related fMRI activation changed with load on a nonverbal serial recognition task in young adults. Half of the trials were of low difficulty and contained one shape to remember; the other half were of high difficulty with the number of shapes to remember adjusted for each subject so that accuracy was 75%. The authors performed univariate analyses looking for regions where the change in activation from the low to the high difficulty task correlated with cognitive reserve, here operationalized as National Adult Reading Test (NART) IQ score. During both the study phase (i.e., the time for encoding the shapes) and test phase (i.e., the time at which memory was probed), brain areas were noted where the brain's response to increasing difficulty varied as a function of measured cognitive reserve. These findings indicate that even in healthy young adults cognitive reserve can be associated with differential task-related activation. This is consistent with the concept of neural reserve. One might hypothesize that these differences in how the task is processed might provide advantages to the individuals with higher cognitive reserve when they are later confronted with age-related brain changes or Alzheimer's disease.

These same data were examined using multivariate analyses [71]. In this second article the question was whether a network of brain regions that ramped up with load would differ in expression between those high and low in cognitive reserve. First, a load-related network was identified in the study phase. Those higher in cognitive reserve activated this network less ($r^2 = 0.24$), reflecting higher neural efficiency. This network was forward applied to the test phase where it was also expressed less by those higher in cognitive reserve ($r^2 = 0.23$). Thus, using a more conservative method than in the first article, evidence for higher neural efficiency in those young adults higher in cognitive reserve was demonstrated.

Habeck et al. [72] investigated the same question using event-related fMRI and multivariate analyses on a delayed letter recognition task. Difficulty was parametrically manipulated in memory set sizes of 1, 3 and 6 letters. During the stimulus phase the load-related network did not correlate with cognitive reserve as operationalized by NART IQ. During the retention phase, or 7-second delay during which items had to be actively remembered, a load-related network was identified that correlated negatively with cognitive reserve ($r^2 = 0.15$). Again, then, evidence for neural efficiency was seen in young adults with higher cognitive reserve; here during a retention phase.

In part, those high in cognitive reserve may achieve higher neural efficiency through using better strategies for performance. Indirect support for this idea comes from a study that controlled for strategy usage and did not find the usual neural efficiency differences with intelligence, suggesting that some of the neural efficiency differences seen in previous studies may have arisen due to differential strategy employment [73]. Other indirect support comes from a study that reported that higher activation was seen in a low-performing group

that post performance reported trying out a greater number of strategies. The high-performing group could quickly settle on an efficient strategy and showed less activation [74].

While the above studies converge in providing evidence for greater neural efficiency for those young individuals high in cognitive reserve compared to those young individuals low in cognitive reserve, they do not provide evidence for greater neural capacity as a function of cognitive reserve in young healthy adults. This is likely because difficulty ranged from low to moderate and it may be only at high levels of difficulty that neural capacity will come into play among young adults. There is a need to identify neural efficiency and neural capacity in the same task as a function of cognitive reserve in young people (our group has such a paper in revision [75]).

Imaging cognitive reserve in healthy young and older subjects

The relationship between high and low levels of cognitive reserve and the magnitude of neural activation in healthy elderly has not been established. There is a tantalizing suggestion that in the context of aging some of these patterns may sometimes be reversed. For example, Scarmeas et al. [76] studied PET activation in younger and older adults on a nonverbal serial recognition task; cognitive reserve was operationalized as a factor score derived from years of education, NART, and age-scaled vocabulary scores of the revised version of the Wechsler Adult Intelligence Scale (WAIS-R). There were two memory set sizes; the low demand set size was a single shape while the high demand set size was titrated to 75% accuracy for each subject. Univariate analyses were performed first to identify regions related to cognitive reserve in each group separately and then to identify regions which were differentially related to cognitive reserve between the two groups. The first set of analyses revealed that there were some regions related to cognitive reserve only in the young (positive activation of the right postcentral gyrus and right inferior temporal gyrus) and some regions related to cognitive reserve only in the old (positive activation of the right cuneus and posterior cingulate; deactivation of the right superior temporal gyrus, left insula, left inferior parietal lobule, cingulate gyrus, inferior frontal gyrus, and left parahippocampal gyrus). The second set of analyses revealed three patterns of differential brain activation between young and old subjects: some brain regions were positively related to higher cognitive reserve in the young and negatively related to higher cognitive reserve in the old (right inferior temporal gyrus, cingulate gyrus); another brain regions showed the opposite pattern in that it was negatively related to higher cognitive reserve in the young and positively related to higher cognitive reserve in the old (left cuneus); finally a last brain region was positively related to cognitive reserve in the young and positively although more weakly related to cognitive reserve in the old (right postcentral gyrus). The authors hypothesize that these differences in cognitive reserve expression between young and old reflect a compensatory reorganization that occurs with aging.

Stern et al. [77] reanalyzed the above data using multivariate analyses to examine regions where the magnitude of activation was differentially expressed with load and age. The authors were successful in finding a network of brain areas that was expressed differently between young and older subjects. This network included activation in right hippocampus, posterior insula, thalamus, and right and left operculum; and concurrent deactivation in right lingual gyrus, inferior parietal lobe and association cortex, left posterior cingulated and right and left calcarine cortex. The magnitude of network expression was positively related to cognitive reserve in young ($r = 0.45$), reflecting greater neural efficiency, and negatively related to cognitive reserve in older subjects ($r = -0.50$), reflecting greater neural capacity. In sum, the pattern of activation with cognitive reserve was reversed between young and older individuals. Again, the authors attribute this difference in cognitive reserve-related

activation between young and older subjects to functional reorganization of brain networks with aging; this reorganization is thought to reflect neural compensation.

Stern et al. [78] further investigated in both young and older adults whether cognitive reserve might be implemented in a similar way across different tasks. Specifically, they used event-related fMRI to search for a cognitive reserve-related network common to two tasks with differing cognitive demands: delayed letter and shape Sternberg tasks. Cognitive reserve was operationalized using the NART and the vocabulary subtest of the WAIS-R. Difficulty was parametrically manipulated in both tasks: for the letter task there were memory set sizes of 1, 3, and 6 letters while for the shape task there were memory set sizes of 1, 2, and 3 shapes. Overall, the shape task was much more difficult than the letter task. During the study phase, two networks were found. The first network was task-specific; it was used only during the letter task. The second network was expressed during both the letter and the shape tasks. In young subjects the magnitude of network activation during both the letter and the shape tasks was negatively related to cognitive reserve, reflecting greater neural efficiency in those higher in cognitive reserve. In older subjects, only expression of the network in the easier letter task was similarly negatively related to cognitive reserve. The results of this study suggest that there may be at least one “cognitive reserve network” that is generic and can be activated during the performance of many tasks. This might explain how cognitive reserve can provide protection against brain pathology for the performance of many different cognitive tasks and day-to-day functions.

Steffener et al. [65] compared event-related fMRI activation during a delayed letter recognition task between older and younger subjects. Difficulty was parametrically manipulated between memory set sizes of 1, 3, and 6 letters; networks where the magnitude of activation changed with increasing memory set size during the retention phase of the task were identified. It was found that younger subjects used a single network while older subjects used this network and a second network as well. The authors showed that greater pathology of the primary network, seen here as lower regional grey matter volume in the pre-central gyrus, led to greater recruitment of the secondary network in the elders. As this second network was not seen in the healthy young subjects, it can be presumed to reflect the elders’ neural compensation. Interestingly, elders with higher cognitive reserve could tolerate more pathology in the primary network before they needed to recruit the secondary network.

Imaging cognitive reserve in healthy elderly and Alzheimer’s patients

Scarmeas et al. [79] compared PET activation between healthy elderly subjects and Alzheimer’s disease subjects on a nonverbal serial recognition memory task. In the low demand condition, the memory set consisted of a single shape while the high demand condition was titrated to 75% accuracy for each subject; cognitive reserve was operationalized using a factor score derived from years of education, NARTIQ, and the vocabulary subtest of the WAIS-R. Patterns of activation were reversed between healthy elderly and Alzheimer’s disease subjects. In some areas Alzheimer’s disease subjects with higher cognitive reserve had a greater magnitude of activation while healthy elderly with higher cognitive reserve had a lesser magnitude of activation. In other areas the reverse pattern was seen where Alzheimer’s disease subjects with higher cognitive reserve had less activation while healthy elderly with higher cognitive reserve had more activation. These differences were hypothesized to occur in the Alzheimer’s patients as a result of compensatory reorganization of neural networks; this reorganization is theorized to compensate for the pathological changes taking place.

Solé-Padullés et al. [80] also examined how cognitive reserve affected fMRI activation in healthy old, mild cognitive impairment patients, and Alzheimer's disease patients on a recognition memory task. Stimuli were emotionally neutral pictures of landscapes and people performing outdoor activities; cognitive reserve was operationalized as a composite score of the vocabulary subtest of the WAIS-III, an education-occupation scale, and a scale reflecting participation in leisure activities. Univariate analyses of fMRI data were performed; these were adjusted for the differential performance between the two groups. Among healthy older individuals, those with higher cognitive reserve showed a lesser magnitude of activation in task-related networks. This was hypothesized to reflect greater neural efficiency. By contrast, in mild cognitive impairment and Alzheimer's disease those with higher cognitive reserve showed a greater magnitude of activation of task-related networks. This was hypothesized to reflect greater neural capacity. Thus, opposite brain activation patterns were observed between healthy and diseased groups as a function of cognitive reserve.

Diagnosis and Prevention

Those with higher cognitive reserve present a diagnostic challenge in conditions such as Alzheimer's disease as pathological changes may be present with no observable clinical effect. Similarly, at any level of clinical severity of patients with Alzheimer's, those with higher cognitive reserve will have more severe underlying pathology. Neuroimaging biomarkers are being developed to aid in early detection of Alzheimer's pathologic changes, even prior to their clinical expression. There is now evidence that individuals with higher cognitive reserve require greater decreases in cortical thickness [81], higher levels of amyloid peptides in cerebrospinal fluid [82], and greater regional atrophy [83] before clinical symptoms emerge. When describing clinical severity of Alzheimer's, it may be more meaningful to examine a combination of pathologic severity (perhaps measured with these biomarkers) and cognitive reserve as opposed to a summary mental status score.

With the aging of the US population, the prevalence of dementia will triple by 2050 if interventions are not found [84]. Katzman [12] estimated that secondary education delays Alzheimer's for 5 years and thus may substantially reduce its prevalence. Hence, cognitive reserve interventions may be a key nonpharmacological approach to preventing this disease [85]. While Alzheimer's has been shown to have a strong genetic component, even with late-life onset [86], even so, lifestyle and environmental factors play a strong role in shaping its expression and timing of onset. More studies are needed to identify the optimal way to intervene to boost cognitive reserve and prevent Alzheimer's disease.

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