Chapter 5

Cognitive Reserve and the Aging Brain

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Summary

- Cognitive reserve, which is often estimated with education and IQ, is the ability to make flexible and efficient use of available brain reserve during tasks. It has been found to be protective against the cognitive outcomes of brain injury.
- Cognitive reserve is reflected in neural reserve and neural compensation.
- Neural reserve allows healthy individuals more efficient processing (processing which requires less neural activity) as well as higher processing capacity (the ability to recruit more neural activity when task demands are high).
- Neural compensation is the activation of alternate brain regions to compensate for deficiencies in individuals with brain impairments.
- Young adults with high cognitive reserve display greater neural efficiency. This may be a result of better or more efficient use of strategies.
- Neural markers for cognitive reserve may differ between younger and older adults. This may be an indication of compensatory reorganization during aging.
- Activation patterns related to cognitive reserve are reversed between healthy older adults and individuals with Alzheimer's.
- Individuals with high cognitive reserve may present with pathology without functional deficits. Thus, accounting for cognitive reserve in addition to the underlying pathology may aid clinical judgment.

Introduction

The theory of reserve against brain insult arose to explain individuals who continue to function clinically despite brain pathology (Gertz et al., 1996; Davis et al., 1999; Gold et al., 2000; Jellinger, 2000; Riley et al., 2002). In an early example, the brains of 10 cognitively normal elderly women were found to have Alzheimer's plaques at autopsy (Katzman et al., 1988). These women's brains were heavier and contained more neurons, which were thought to provide "reserve," to help the women function despite their pathology. Indeed, later studies found that 25–67% of subjects characterized as cognitively normal throughout longitudinal assessments meet pathologic criteria for dementia at autopsy (Crystal et al., 1988; Morris et al., 1996; Price and Morris, 1999; Ince, 2001; Mortimer et al., 2003).

Two types of reserve contribute to maintaining functioning after brain insult: brain reserve and cognitive reserve. Standard proxies for brain reserve include brain size (Katzman, 1993) and/or neuronal count (Mortimer et al., 1981). For any level of pathology, more brain reserve is associated with better functional outcomes (Satz, 1993; Graves et al., 1996; Jenkins et al., 2000). The brain reserve model posits a threshold at which functional deficits

manifest and suggests that individuals with more brain reserve will accumulate more pathology before reaching that threshold. For example, in the case of Alzheimer's, the disease will advance longer and additional pathology will be acquired before deficits are seen in individuals who start with more neurons and/or a bigger brain.

The initial brain reserve model was entirely quantitative: a given brain injury affects each individual in the same manner, and brain injuries throughout the lifespan sum together. Evidence indicates that some brain deficits do sum across the lifespan. For example, the risk for Alzheimer's rises with each psychiatric episode (Kessing and Andersen, 2004) and/or concussion (Guskiewicz et al., 2005). A limitation of this model, however, is that brain reserve is thought to constitute the only meaningful difference between individuals, with the idea that accumulated damage either does or does not reach the threshold necessary for functional deficits.

Although the brain reserve model explains some observations, the generalization that more is better may be too simple. As one example, autism is associated with a brain that is bigger than normal, perhaps reflecting a failure of pruning mechanisms that eliminate unused or faulty neural connections, or a larger glia/neuron ratio (Redcay and Courchesne, 2005). Furthermore it has been

found that in healthy children, young adults, and elderly samples, more gray matter is associated with worse memory performance (Salat et al., 2002; Van Petten, 2004). This strongly suggests that those with the biggest brains are not always at the biggest advantage. Another limitation of brain reserve theory is that it does not explain the counterintuitive finding that, once Alzheimer's is diagnosed, higher IQ and more education are associated with faster deterioration and more rapid death (Stern et al., 1994; Stern et al., 1995; Teri et al., 1995; Stern et al., 1999; Scarmeas et al., 2006; Hall et al., 2007; Helzner et al., 2007).

By contrast, cognitive reserve refers to the ability to make flexible and efficient use of available brain reserve when performing tasks (Stern, 2002). Cognitive reserve has been most often estimated using education (Stern et al., 1992) and IQ (Alexander et al., 1997), although other variables have also been used, including literacy (Manly et al., 2003; Manly et al., 2005), occupational complexity (Stern et al., 1994; Richards and Sacker, 2003; Staff et al., 2004), participation in leisure activities (Scarmeas et al., 2001; Wilson et al., 2002; Scarmeas et al., 2003a), and the cohesion of social networks (Fratiglioni et al., 2000; Bennett et al., 2006). Recently, personality variables have also been incorporated (Wilson et al., 2006; Wilson et al., 2007). Those with higher cognitive reserve tend to have better clinical outcomes for any level of pathology and brain reserve.

As one example, Mortimer et al. (2003) found that those with smaller brain reserve, operationalized with head circumference, were at increased risk of Alzheimer's. Yet this relationship was moderated by cognitive reserve such that those with smaller heads and more education were not at increased risk. This suggests that cognitive reserve allowed individuals to compensate for any pathology present in their smaller brains by making more optimal use of that brain reserve present. It further suggests that the threshold of brain reserve necessary to maintain functioning is not fixed, but instead varies among people such that those higher in cognitive reserve can maintain functioning at lower levels of brain reserve.

Although cognitive reserve is discussed most often in the context of Alzheimer's disease and normal aging, it has also been demonstrated to provide benefit in vascular injury (Dufouil et al., 2003; Elkins et al., 2006), Parkinson's disease (Glatt et al., 1996), traumatic brain injury (Kesler et al., 2003), HIV (Farinpour et al., 2003), and multiple sclerosis (Sumowski et al., 2009). While it has been established in these diverse conditions that cognitive reserve is protective against brain injury for cognitive outcomes, it remains to be determined whether cognitive reserve is similarly protective for affective or psychiatric outcomes. One report found that higher cognitive reserve is not protective against the depressive symptoms that arise with the early stages of Alzheimer's (Geerlings et al., 2000); however, other reports of healthy individuals have found

that higher cognitive reserve does protect against psychiatric diseases such as depression (Barnett et al., 2006; Koenen et al., 2009).

Many aspects of cognitive reserve are intercorrelated. For example, people with higher IQs obtain more education, which, in turn, increases IQ (Ceci, 1991). Yet, although they are intercorrelated, these aspects of cognitive reserve impart both independent and interactive effects that accrue over the lifespan. Richards and Sacker (2003) examined how cognitive reserve variables collected at different points in the lifespan affected cognitive function at midlife. The authors found that the earliest point, childhood IQ, had the strongest effect; a later point, educational attainment by early adulthood, less effect; and the latest point, occupation in middle age, the least strong effect. These results suggest that while early childhood factors are crucial for the buildup of cognitive reserve, cognitive reserve continues to be influenced by circumstances throughout the lifespan.

It has been pointed out that many of the variables used to measure cognitive reserve, such as education, are conflated with socioeconomic status (SES). However, Karp et al. (2004) found that while less education and lower SES are independently associated with higher risk for Alzheimer's disease, with both in the model simultaneously, only education is significant. Thus, the lower risk for Alzheimer's in those more highly educated is not mediated by SES. Furthermore, Turrell et al. (2002) found that a relationship between more years of education and better cognitive outcomes in middle age was independent of both childhood and current SES. Thus, the benefits arising from cognitive reserve are not reducible to SES.

Another potential limitation is that individuals with more education and higher IQ display superior performance on the tests used to measure cognitive decline and diagnose dementia; this has been called the ascertainment bias (Tuokko et al., 2003). In other words, although an individual high in cognitive reserve might slip from the previous high level of performance as a result of pathology or aging, this deterioration might go unnoticed in testing, because performance may still be average. Yet cognitive reserve still provides benefit even when dementia is diagnosed with measures of daily functioning instead of neuropsychological tests (Liao et al., 2005). Further, cognitive reserve has been demonstrated even in longitudinal studies with a clear baseline for each subject from which to assess performance (Scarmeas and Stern, 2004).

Unlike brain reserve, cognitive reserve makes clear why those with higher IQ, more education, and/or more participation in leisure activities have poorer outcomes, in that they deteriorate more quickly and proceed to death soon after Alzheimer's is diagnosed (Stern et al., 1994; Stern et al., 1995; Teri et al., 1995; Stern et al., 1999; Scarmeas et al., 2006; Hall et al., 2007; Helzner et al., 2007). The cognitive reserve model posits that those with higher

reserve are able to compensate for pathology early on in the course of Alzheimer's disease. Not until the pathology is more advanced and the patient is nearer to death are deficits observable in an individual with high cognitive reserve. This also implies that, for any given functional level, those higher in reserve will have more pathology (Bennett et al., 2003; Bennett et al., 2005; Serra et al., 2011).

Although the initial conception of brain reserve was entirely quantitative, recent evidence suggests that this concept is more nuanced. First, brain and cognitive reserve share some overlap. For example, IQ and brain volume show a small but significant correlation (McDaniel, 2005). More importantly, stimulating environments—a component of cognitive reserve measured in humans by variables such as engagement in leisure activities and occupational attainment—foster the growth of new neurons (Churchill et al., 2002) and upregulate brain-derived neurotrophic factor (BDNF), which fosters neural plasticity. Furthermore, animal studies suggest that enriching environments may reduce Alzheimer's pathology directly (Costa et al., 2007). In humans, it has been demonstrated that higher IQ reflects higher metabolic efficiency in the brain, which may slow the development of neuropathology (Yeo et al., 2011). Nonetheless, although they are in some ways interdependent, brain reserve and cognitive reserve make independent yet synergistic contributions to understanding individual differences in clinical resilience to brain pathology.

In terms of cognitive performance, cognitive reserve may help by enabling more flexible strategy usage, a skill tapped by executive function tasks. In support of this, structural equation modeling performed in nondemented older adults aged 53–97 revealed that cognitive reserve—as measured using 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, 3rd edition (PPVT-III)—overlapped greatly with executive functioning measured using 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 (Siedlecki et al., 2009). In healthy adults aged 20–81, cognitive reserve measured as mentioned previously (education, WRAT, and picture vocabulary) was found to entirely overlap with executive functioning as measured using the same LN sequencing subtest and also the Wisconsin Card Sorting Task and the Matrix Reasoning Test. These results suggest that cognitive reserve could involve fluid executive abilities.

In terms of neuroimaging, cognitive reserve is thought to be reflected in neural reserve and neural compensation. Neural reserve provides young, healthy individuals the ability to process tasks with more efficiency and greater capacity. For tasks of low-to-moderate difficulty,

those higher in cognitive reserve may display less neural activation, because they are able to process the task with greater neural efficiency. Oppositely, when tasks involve high levels of difficulty, those higher in cognitive reserve may display more neural activation, because they have a greater neural capacity to use when performing the task. Attending to difficulty is thus vital for understanding the meaning of differences in neural activation between groups. Neural reserve operates similarly to mitigate the effects of aging and brain pathology. Those higher in neural reserve are expected to perform better than or equivalently to those with lower neural reserve.

Neural compensation is defined as the activation of alternate brain regions not often used by healthy young adults, to compensate for deficiencies in primary routes to effectual task performance. As defined, then, neural compensation occurs not in healthy young adults, but only in those with brain deficits. As for neural reserve, attending to difficulty is vital for accurately identifying neural compensation. For example, neural compensation may be suspected if a region is activated in older adults and not in younger adults. Yet in a more difficult version of the task, this region might also be activated by the young adults. Sometimes, it is even the case that young adults are using the brain area, but this is missed because of the statistical threshold chosen to define brain activation.

Neural compensation can sometimes be accompanied by worse performance, although this is not always the case. In some instances, neural compensation could act like a cane, which enables individuals to walk but will not return the ability to sprint. As this metaphor suggests, neural compensation is sometimes associated with slower performance (Zarahn et al., 2007; Steffener et al., 2009). Some think that this happens because, with neural compensation, processing travels across more brain regions, each of which may take some additional amount of time. An alternate idea is that, with neural compensation, processing shifts from a primary network to a slower secondary network. It should be remembered that neural compensation has been found to correlate with better performance in terms of accurately remembering more words (Stern et al., 2000). To sum, neural compensation can accompany performance that is either enhanced or degraded.

A further consideration is that when additional brain areas are activated in the presence of pathology, this does not always indicate compensation. The activation of additional regions can be malfunctioning when it arises from detrimental processes such as dedifferentiation (blurring) of sensory maps (Park et al., 2004), deficits in handling competition between brain regions (Logan et al., 2002), or a deficit in the ability to inhibit the default network (Lustig et al., 2003). Thus when performance is worse, it is necessary to rule out these detrimental processes before labeling the activation of neural compensation.

An implicit assumption is that neural compensation differs from task to task (that is, it is an emergent property of the task at hand). Yet, as cognitive reserve protects functioning on a wide variety of tasks, it is possible that one generic cognitive reserve network subserves one general cognitive function. Some evidence in support of this idea (Stern et al., 2008) is reviewed in the next section. If this is true, activation of this network would likely indicate a positive, helpful form of neural compensation.

Neural markers of cognitive reserve in young, healthy adults

Stern et al. (2003) conducted an event-related fMRI analysis of young adults performing a nonverbal serial recognition task, looking for regions whose activation changed with difficulty. Low-difficulty trials involved one shape to remember, while the number of shapes to remember for high-difficulty trials was customized for each subject to achieve 75% accuracy. Univariate analyses were performed to find regions where the change in activation with difficulty was associated with cognitive reserve, here measured using the National Adult Reading Test (NART) IQ score. Such regions were found for both study and test task phases. These results indicate that cognitive reserve is linked to differential task-related activation (neural reserve) even in healthy young adults. These differences in task-related processing may provide benefits to those higher in cognitive reserve when they become challenged by age-related brain changes or pathology.

The previous data were re-examined using multivariate analyses (Habeck et al., 2003). For this study, first a network of regions was sought that changed activation with difficulty. Next, it was investigated whether this network showed differential expression as a function of cognitive reserve. First, a difficulty-related network was found in the study phase. As hypothesized, individuals higher in cognitive reserve expressed this network less ($r^2 = 0.24$), demonstrating higher neural efficiency. Then forward application of this network to the test phase similarly found that those higher in cognitive reserve had lower network activation ($r^2 = 0.23$). Thus, even with this more conservative method, young adults higher in cognitive reserve displayed evidence for greater neural efficiency.

Habeck et al. (2005) explored the same question on another task: delayed letter recognition. In this task, memory set sizes of one, three, and six letters constituted the manipulation of difficulty. At the study phase, the difficulty-related network was not associated with cognitive reserve as measured by NART IQ. At the retention phase, or 7-second delay over which items had to be actively held in mind, a difficulty-related network was found that was expressed less by those higher in cognitive reserve ($r^2 = 0.15$). In a second task, then, neural efficiency

was again detected in young adults higher in cognitive reserve, here during retention.

To some extent, individuals higher in cognitive reserve may have higher neural efficiency as a result of employing better performance strategies. This idea is supported by a study that failed to find the usual neural efficiency advantage with intelligence after controlling for strategy usage (Toffanin et al., 2007). Further support comes from a study that found that more activation was associated with trying out more strategies. The idea is that those with higher intelligence are able to decide on a good strategy more quickly and, as a result, show less activation (Jaeggi et al., 2007).

Gray et al. (2003) examined healthy young adults performing a three-back working memory task. In this study, event-related activation differed as a function of fluid intelligence, as measured with the Raven's Advanced Progressive Matrices, for trials at various levels of difficulty, here manipulated through high-interference as opposed to low-interference items. Although this was not explicitly a study of cognitive reserve, fluid intelligence would be expected to be a good proxy for cognitive reserve (Siedlecki et al., 2009). The authors found that activation on the most difficult trials was greater for those higher in fluid intelligence. Higher fluid intelligence was also associated with improved accuracy for lure trials. Interestingly, the increase in activation from nonlure to lure trials mediated the intelligence-accuracy relationship on lure trials by 99%. These results provide support for the idea that those higher in cognitive reserve have greater neural capacity to use, which provides an advantage when tasks are highly difficult.

One limitation of these studies is that the tasks used did not have the range of difficulty needed to see neural efficiency and neural capacity operating in the same individuals. There is thus an outstanding research need to find neural efficiency and neural capacity operating with higher cognitive reserve in the same task in young people. Our group has one such report (Stern et al., 2012).

Neural markers of cognitive reserve in healthy young and older adults

In older as compared to younger adults, the neural activation associated with cognitive reserve is sometimes the same but can be altered as well. Scarmeas et al. (2003b) examined PET activation in healthy younger and older adults on a nonverbal serial recognition task; cognitive reserve was measured by a factor score extracted from years of education, NART, and age-scaled vocabulary scores from the revised version of the Wechsler Adult Intelligence Scale (WAIS-R). The low-difficulty condition was a single shape, while the high-difficulty condition was adjusted to each subject so that they achieved 75%

accuracy. Univariate analyses were used to find regions associated with cognitive reserve for each group separately and next to find regions differentially associated with cognitive reserve between the young and the old. The first analyses found some regions associated with cognitive reserve only for the young and other regions associated with cognitive reserve only for the old. The second analyses found three types of differential expression between the two groups: some regions were positively expressed with higher cognitive reserve in the young and negatively expressed with higher cognitive reserve in the old; some regions showed the opposite pattern; and some regions were positively expressed with cognitive reserve in the young and positively, albeit more faintly expressed with cognitive reserve for the old. The authors posit that these differences between young and old in cognitive reserve expression indicate that compensatory reorganization happens with aging.

Stern et al. (2005) re-examined the data with multivariate analyses to find regions that were differentially activated with difficulty and age. The authors found a network of brain regions that were activated differently between young and older individuals. Expression of this network was positively associated with cognitive reserve in the young ($r = 0.45$), indicating higher neural efficiency, and negatively associated with cognitive reserve in older individuals ($r = -0.50$), indicating higher neural capacity. To sum, young and older individuals expressed the cognitive reserve pattern in opposite ways. The authors posit that this difference reflects helpful reorganization of brain networks in aging, or neural compensation.

Stern et al. (2008) next examined in young and older adults whether cognitive reserve might operate similarly in different tasks. Event-related fMRI was used to probe for a cognitive-reserve-related network shared by two different tasks: delayed letter and shape Sternberg. Cognitive reserve was measured with the NART and the vocabulary subtest of the WAIS-R. The letter task contained difficulty levels of one, three, and six letters, while the shape task contained difficulty levels of one, two, and three shapes. On the whole, the shape task was considerably more challenging than the letter task. Two networks were found for the study phase. While the first network was used only during the letter task, the second network was used during both the letter and shape tasks. For young subjects, network activation in both tasks was negatively associated with cognitive reserve, indicating higher neural efficiency in those with greater cognitive reserve. For older subjects, network expression was negatively associated with cognitive reserve only for the less challenging letter task. These results suggest a generic "cognitive reserve network" that can be utilized for performing many tasks. This is concordant with the observation that cognitive reserve provides benefits against brain pathology for many different tasks and real-world functions.

Steffener et al. (2009) examined event-related fMRI activation between young and older subjects performing a delayed letter recognition task. Memory set sizes of one, three, and six letters comprised three levels of difficulty; networks were found that changed expression with increasing difficulty during retention. While young adults utilized a single network, older adults utilized this network along with an additional network. The authors demonstrated that greater pathology in the primary network, operationalized here as more atrophy in the precentral gyrus, was associated with greater utilization of the secondary network in the elders. Because the young subjects did not use the secondary network, it can be presumed to reflect neural compensation in the older subjects. Importantly, older individuals with more cognitive reserve were able to tolerate greater pathology before having to employ the secondary network.

Neural markers of cognitive reserve in healthy elderly and Alzheimer's patients

Scarmeas et al. (2004) examined PET activation in healthy older and Alzheimer's patients performing a nonverbal serial recognition task. The low-difficulty condition involved a single shape, while the high-difficulty condition was adjusted so that each subject achieved 75% accuracy; cognitive reserve was measured using a factor score extracted from years of education, NART IQ, and the vocabulary subtest of the WAIS-R. Activation patterns differed between healthy older and Alzheimer's patients. In some regions, Alzheimer's patients with higher cognitive reserve displayed greater activation, while healthy older individuals with higher cognitive reserve displayed less activation, while in other regions, the relationships were reversed. These region-specific differences were posited to reflect compensatory reorganization of brain networks in Alzheimer's patients.

Solé-Padullés et al. (2009) compared cognitive-reserve-related fMRI activation on a recognition task between healthy old, mild cognitive impairment patients and Alzheimer's patients. Stimuli were images of landscapes and people engaging in outdoor activities; cognitive reserve was measured with a composite score of the vocabulary subtest of the WAIS-III, an education-occupation scale, and a scale of participation in leisure activities. Univariate analyses were performed after adjusting for the differential performance between the groups. In healthy older individuals, more cognitive reserve was associated with less activation, indicating higher neural efficiency. Conversely, in mild cognitive impairment and Alzheimer's disease, those with more cognitive reserve displayed greater activation, thought to indicate greater neural capacity. Taken together with the previous study, reverse cognitive-reserve-related brain activation is seen between healthy and diseased older individuals.

Implications of cognitive reserve for diagnosis and prevention

Individuals with greater cognitive reserve create a diagnostic challenge, as pathology may be present without functional consequences. Furthermore, for patients with dementia at any stage of clinical severity, individuals with greater cognitive reserve will have more advanced pathology. Neuroimaging biomarkers are currently being developed to assist in early detection of Alzheimer's pathology, even prior to clinical consequences. Complicating this endeavor, individuals with greater cognitive reserve can tolerate more decreases in cortical thickness (Querbes et al., 2009), levels of amyloid peptides in cerebrospinal fluid (Shaw et al., 2009) and plasma (Yaffe et al., 2011), and more regional atrophy (Hua et al., 2008) before clinical consequences emerge. For these reasons, the predictive accuracy of biomarkers is improved when adding cognitive reserve variables to the model (Roe et al., 2011). More generally, clinical status can best be understood when both underlying pathology and cognitive reserve are taken into account.

With the future growth of the aging US population, the number of dementia cases will triple by 2050 if interventions are not applied (Hebert et al., 2003). Katzman (1993) reasoned that as higher education staves off Alzheimer's for 5 years, it may considerably lessen its prevalence. Thus, cognitive reserve interventions may constitute a chief nonpharmacologic approach for preventing this disease (Stern, 2006). Although Alzheimer's has a large genetic component (Gatz et al., 2006), behavioral and environmental factors still exert considerable influence over its expression and timing of onset. Even in early-life onset Alzheimer's, which has a stronger genetic component than does late-life onset Alzheimer's, cognitive reserve has recently been demonstrated to play a protective role (Fairjones et al., 2011). Future studies might elucidate optimal strategies for augmenting cognitive reserve in order to delay or prevent Alzheimer's disease and other age-related afflictions.

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