Review

Exploring the neural basis of cognitive reserve in aging

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The concept of reserve arose from the mismatch between the extent of brain changes or pathology and the clinical manifestations of these brain changes. The cognitive reserve hypothesis posits that individual differences in the flexibility and adaptability of brain networks underlying cognitive function may allow some people to cope better with brain changes than others. Although there is ample epidemiologic evidence for cognitive reserve, the neural substrate of reserve is still a topic of ongoing research. Here we review some representative studies from our group that exemplify possibilities for the neural substrate of reserve including neural reserve, neural compensation, and generalized cognitive reserve networks. We also present a schematic overview of our ongoing research in this area. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

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1. Introduction

The theory of reserve against brain insult arose to explain individuals who continue to function clinically despite brain pathology. In an early example, the brains of 10 cognitively normal elderly women were found to have Alzheimer’s plaques at autopsy [1]. These women’s brains were heavier and contained more neurons, which were thought to provide ‘reserve’ which helped the women to function despite their pathology. Later studies have found that 25% to 67% of subjects characterized as cognitively normal throughout longitudinal assessments meet pathological criteria for dementia at autopsy [2–6].

We have suggested that two types of reserve contribute to maintaining functioning in the presence of brain changes or insult: brain reserve and cognitive reserve [7,8]. In the original formulations of the brain reserve model, reserve derives from brain size or neuronal count. Larger brains can sustain more insult before clinical deficit emerges, because sufficient neural substrate remains to support normal function. Standard proxies for brain reserve include brain size [9] and/or neuronal count [10]. One posits a threshold at which functional deficits will manifest, and that individuals with more brain reserve can accumulate more pathology before reaching that threshold [11,12].

Cognitive reserve refers to the ability to make flexible and efficient use of available brain reserve when performing tasks [8]. Cognitive reserve has been most often estimated using education [13] and IQ [14], although other variables have also been used including literacy [15,16], occupational complexity [17–19], participation in leisure activities [20–22], as well as the cohesion of social networks [23,24]. Recently, personality variables have also been incorporated [25,26]. Those with higher cognitive reserve tend to have better clinical outcomes for any level of pathology and brain reserve.

Many aspects of cognitive reserve are potentially intercorrelated. For example, people with higher IQs obtain more education, which in turn increases IQ [27]. Richards et al. [17] examined how cognitive reserve variables collected at different points in the lifespan affected cognitive function at midlife. The authors found that life experiences at several points over the lifespan, including childhood IQ, educational attainment by early adulthood, and occupation in middle age, all contributed to cognitive performance at age 57. 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.

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 [28]. 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 in the form of neurogenesis in animals [29–31], upregulate BDNF, which fosters neural plasticity. Nonetheless, although in some ways interdependent, brain reserve and cognitive reserve make independent contributions to cognitive function.
and synergistic contributions to understanding individual differences in clinical resilience to brain pathology.

In this review, we discuss our laboratory’s research model of cognitive reserve as outlined in Fig. 1. We briefly outline this model here and then discuss its component features in detail along with supporting findings from our laboratory. Our model includes measures of age or Alzheimer’s disease (AD) related pathology, task-related neural activity, task, cognitive or neuropsychological performance (NP) or clinical outcome, and measured CR. The use of measures of age or AD related pathologies reflects the idea that these measures may partially remediate the effect of aging on cognition in clinical outcomes. Task related neural activities are derived measures from functional MRI studies and include regional or network measures of function. Task, NP or clinical outcomes are behavioral measures our model is attempting to explain. Cognitive reserve is derived either from behavioral and cognitive measures or, most recently, from networks of neural activity. The paths connecting these measures reflect the idea that age-related or pathological brain changes can result in changes in the other three nodes of the model. Changes in functional activity can result in changes performance. Cognitive reserve as operationalized by behavioral, cognitive or neural measures can help maintain performance by moderating the relationship between age or AD related pathology and performance or between neural activity and performance. Aspects of task-related neural activity such as efficiency or capacity may mediate the effect of CR on performance. It is important to point out that all arrows in Fig. 1 are directional. Although much of our work is essentially correlational our theory predicts these directions. The exception is the relationship between pathology and CR, which is bidirectional and discussed in detail later.

2. Epidemiology of cognitive reserve

In 1994, our group reported incident dementia data from a follow up study of 593 community-based, non-demented individuals aged 60 years or older [18]. The risk of dementia was increased in subjects with low education, where the relative risk (RR) of developing dementia over the follow-up period was 2.2 times higher in individuals with less than 8 years of education than in those with more education (95% confidence interval [CI], 1.33 to 3.06). Similarly, risk of incident dementia was increased in those with low lifetime occupational attainment (RR, 2.25; 95% CI, 1.32 to 3.84). Risk was greatest for subjects with both low education and low lifetime occupational attainment (RR, 2.87; 95% CI, 1.32 to 3.84). In a subsequent study, we assessed participation in a variety of leisure activities in a population sample of non-demented elderly in New York [20]. During follow-up, subjects who engaged in more of these activities had 38% less risk of developing dementia.

A review paper [32] found 22 papers published up to 2004 reporting cohort studies of the effects of education, occupation, premorbid IQ and mental activities in incident dementia. Ten out of 15 studies demonstrated a significant protective effect of education; 9 out of 12 a protective effect of occupational attainment; 2 out of 2 a protective effect of premorbid IQ; and 6 out of 6 a protective effect of engaging in leisure activities. Studies that did not find a protective effect had the lowest dementia rates. Integrating these studies, the authors reported that higher reserve was associated with significantly lowered risk for incident (i.e. newly developed) dementia. The summary odds ratio, 0.54 (95% CI, 0.49 to 0.59), indicates a decrease in risk of 46% in individuals with high reserve.

There is also evidence for cognitive reserve in studies of age-related cognitive decline. In an ethnically diverse cohort of non-demented elders in New York City, we found that increased literacy (presumably associated with quality and extent of education) was associated with slower decline in memory, executive function, and language skills [19]. Several other studies of normal aging reported 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. These studies provide evidence for arrow “a” in Fig. 1 which suggests that CR measures may moderate the influence of AD pathology on clinical outcome.

Our first imaging studies of CR were designed to test the hypothesis that at any given level of clinical AD severity, an individual with a higher level of CR should have greater AD pathology. In these studies, we used resting regional cerebral blood flow (rCBF) as a surrogate for AD pathology. This is based on observations that specific regional rCBF changes in AD are related to the underlying AD pathology and rCBF becomes lower as the pathology advances [41,42]. In AD patients matched for clinical severity (as assessed with measures of cognition and function), we found negative correlations between resting rCBF and years of education [13], such that higher education was associated with more depleted flow specifically in parietotemporal areas that are affected in AD. These findings imply that patients with higher education can tolerate more AD pathology than those with lower education and still appear clinically similar.

In a subsequent analysis of the same subjects we found a similar inverse relationship between rCBF and occupational attainment, even after controlling for educational attainment, suggesting that some aspects of occupational experiences imparted reserve over and above that obtained from education [43]. In a later O15 PET study, we replicated our initial observations and also extended the findings to leisure activities [21]: we found an inverse relationship between rCBF and increased engagement in leisure activities, even after controlling for educational and occupational attainment. These observations have been replicated several times by other groups as well [14,44] and provide support for arrow “b” in Fig. 1.

The implications of these imaging findings were confirmed in a prospective clinical study with subsequent neuropathological analysis. Education was found to modify the association between AD pathology assessed post mortem and levels of cognitive function proximate to death: for the same degree of brain pathology there was better cognitive function with each year of education [45]. The results of this study provide support for arrow “a” in Fig. 1 that CR moderates the relationship between pathological neural measures and cognitive/clinical measures.

Fig. 1. Our conceptual research model of the neural basis of cognitive reserve. It includes measures of age or Alzheimer’s disease (AD) related pathologies as identified via imaging modalities; task related neural activity as identified via fMRI studies using appropriate tasks; task, neuropsychological performance (NP) or clinical outcome and measured CR or CR-specific network. The paths connecting these measures are labeled in the order they are discussed in the text and reflect our view that age or pathological changes result in changes in functional neural activity, path c; task/neuropsychological performance or clinical outcome, path g, and measures of cognitive reserve, path h. Changes in task-related activity result in changes performance, path d. Cognitive reserve directly affects performance path h; or its impact is mediated by alterations in neural activity, path e; or it modulates the impact of age or AD-related pathology on performance, path a; or it modulates the relationship between neural activity and performance, path f.
3. Neural mechanisms underlying CR

The epidemiologic and CBF at rest data provide evidence for the existence of CR. However, they cannot provide clues as to the neural mechanisms that may mediate the relationship between CR and performance. To pursue this question, we turned to cognitive activation studies using O15 PET and fMRI. We have suggested that the neural implementation of CR might take two forms: neural reserve and neural compensation [7,46]. Distinguishing between these two possible neural implementations of CR can be an important starting point for designing, analyzing and interpreting functional imaging studies in this area. We will first introduce these concepts and then give some applied examples of them using research studies from our group.

4. Neural reserve

The idea behind neural reserve is that there is inter-individual variability in the primary brain networks or cognitive paradigms that underlie the performance of any task. This variability could be in the form of differing efficiency or capacity of these networks, or in greater flexibility in the networks that can be invoked to perform a task. While healthy individuals may invoke these networks when coping with increased task demands, these networks could also help an individual cope with brain pathology. An individual whose networks are more efficient, have greater capacity, or are more flexible might be more capable of coping with the disruption imposed by brain pathology.

Efficiency refers to the change in neural activity occurring with a change in task demand. For an equal increase in task demand, someone with greater efficiency requires less of an increase in neural activity than does someone with less efficiency. In Fig. 2A, differences in efficiency are demonstrated as differences in the slope of the relationships between task demands and functional activity. Functional MRI support for differences in efficiency is obtainable by comparing groups of participants who perform a task with increasing task demands, such as the delayed item recognition task described below. As the task demands increase, the neural activity required to meet the demands also increases. Tests of the differences in slope between the two study groups would show larger slopes for the less efficient group. It is possible that CR alters this slope and evidence to support this idea would come from comparisons between groups of individuals with low and high CR. A greater slope of neural activity across task demands for low CR individuals as compared to high CR individuals would support the presence of CR operating via differential neural efficiency.

It is important to consider the idea that the mechanism by which CR operates should be present, and therefore possibly elucidated, in young adults. For example, greater educational attainment early in life might lead people to operate at relatively high cognitive levels throughout their productive years, and this may be a mechanism for increasing CR. Support comes from findings of a relationship between CR and occupational attainment [47] which again suggests that CR is developed across the lifespan. Our studies therefore include both young and old healthy adults.

In one study, 40 young and 18 old individuals were imaged while performing the letter Sternberg task, a working memory task that allows us to systematically increase task demand by increasing the number of letters to be recognized [48]. Using a multivariate approach to examine spatial patterns of task-related activation, we identified spatial patterns used while subjects encoded the letters which did not differ between the age groups. However, we found that as the task got harder, elders increased network expression to a greater degree than young subjects, but benefitted less from the use of the network in terms of performance. This is a demonstration of how age-related neural changes can limit the efficiency of a network, while the network itself remains unchanged. In the context of networks, the vertical axes in Fig. 2 refer to the degree an individual expresses, or utilizes, the network.

Fig. 2B elucidates the concept of capacity. As demand increases, there should be some point where network expression reaches a maximum. This maximum expression could be an index of network capacity. When conducting studies of this nature, task demands need to be great; however, the participants still need to successfully complete the task. This is important to ensure that error processes are not compared to successful neural task processing. When one is comparing age groups, the task demands for someone to reach their capacity limit may differ between the age groups. Young adults may require much greater task demands, higher memory load for instance, to reach their maximal neural capacity. Older adults however, may require lower task demands to reach their neural capacity. This raises the question of whether task demands should be the same between groups in order to study capacity differences. One approach we have taken is to use titrated task demands which equalize groups based on an individual’s perceived difficulty through differing task demands [46]. Another is the use of parametrically varied task demands.

In one study that explored capacity, we administered to young and old individuals a delayed recognition task where the items to be encoded were complex shapes [49]. This task is more challenging than the letter Sternberg because it uses novel shapes as stimuli rather than highly familiar letters. We found that load-related activation during the probe phase – i.e. when subjects determined whether a display shape was the same as the one they studied – was described in both the young and old subjects by a single neural network. Expression of this network was greater in the young than in the old subjects. Thus, in this case, the better performance by the younger subjects was accompanied by increased expression of the underlying brain network. This suggests a capacity difference, with the younger subjects able to activate the common network to a greater degree than the older subjects. The fact that the shape Sternberg task could elicit a difference in capacity while the letter Sternberg task did not should not be surprising as the shape task is much more demanding and, indeed, is more likely to stress the capacity of even young subjects. Although discussed independently, the possibility exists that changes in efficiency and capacity occur together, see Fig. 2C.
5. Neural compensation

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 in order to compensate for brain damage. This alternate network may not be engaged in performing a task until demands exceed some level or until the neural activity within a primary network reaches capacity, see Fig. 2D. In this situation, we can hypothesize that the alternate network is recruited to compensate for age-related neural changes. It is possible that those capable of recruiting a compensatory network to a greater degree can use it to cope better with neural changes. This idea is consistent with the HAROLD model put forward by Cabeza [50], where elder adults who recruited additional brain areas had better performance than those elder adults who did not recruit these brain regions. Typically, brain regions in the contralateral hemisphere from those typically recruited by younger subjects comprise the compensatory network in the HAROLD model. Others have also reported examples of compensatory reallocation without the proviso that this be limited to the contralateral hemisphere. Recruiting compensatory networks is not invariably associated with improved performance. In this alternate scenario, the primary neural network no longer adequately supports successful task performance, resulting in the recruitment of the compensatory resources [51–53]. Although the alternate network supports continued performance, it may not be as optimal as using the primary network and elders required to use this network perform more poorly. A simple analogy is the use of a cane, which allows an elder to walk, thus compensating for age-related changes, but not as well as an elder who does not require a cane. We provide an example of such a finding below.

In the study described above of 40 young and 18 old subjects on the letter Sternberg task [48], we found that load-related activation during the retention phase of the task was characterized by two spatial patterns. The first pattern was used by both young and old subjects, and consisted of areas often associated with working memory. In contrast, the second pattern was used only by the older subjects; mean expression of this pattern in the younger subjects did not differ significantly from zero. Interestingly, in the older subjects there was a negative correlation between activation of this additional network and overall task performance (as assessed by RT slope) – subjects who used the additional network more performed worse. No such relationship was observed in the younger subjects.

We considered two alternate explanations for this observation. One might argue that since the more older subjects use this second network the more poorly they perform, use of this network cannot be considered compensatory, and that its use is consistent with dedifferentiation [54–56]. An alternate view is that use of the second network is compensatory. As discussed above, according to this view the additional network is needed to maintain function as age-related neural changes impair the efficacy of the first, primary network. Thus, compensation in this case is associated with maintenance of function as opposed to improved function.

Testing this idea requires some measure of age-related neural change. The prediction is that individuals who express the second network are more likely to have age-related neural change that impairs performance of the primary network. In a follow-up analysis [57], we used gray matter brain atrophy as a measure of age-related change. Using voxel based morphometry we tested whether either global atrophy or atrophy specifically in the primary network was related to expression of the secondary network. Global atrophy was not associated with expression of the secondary functional network. However, regional gray matter density in the left pre-central gyrus – one key area within the primary functional network – was associated with increased secondary network utilization. This observation is consistent with the following scenario: as age-related neural changes affect the primary network used by young and old when performing this task, the older increasingly recruit an alternate network. Those that rely more on this alternate network can still perform the task, but do so more poorly. This result is consistent with neural compensation, in that age-related atrophy in the primary network induced the older participants to recruit additional neural resources (the second network) in order to maintain task performance, albeit at a lower level.

Our investigations into efficiency, capacity and compensation map onto our research model as follows. Age related differences in neural efficiency and capacity provide support for arrow “c” in Fig. 1. The finding that age-related structural changes affect neural activity provides further support for this relationship. The impact that such age-related neural activity changes have on performance supports the idea that neural activity relates to performance, arrow “d” in Fig. 1.

5.1. Efficiency, capacity, compensation and CR

Efficiency, capacity and compensation within the context of neural reserve and neural compensation are potential mechanisms underlying CR. However, identification of age-group or inter-individual differences in neural reserve and/or neural compensation alone does not provide evidence for the presence of CR. These differences in measures of efficiency, capacity or compensation need to be directly related to measures of CR in order to establish them as potential mechanisms of CR. To explore these issues we have used tests of mediation and moderation. Mediation tests whether there is an indirect relationship between CR and a behavioral measure via a measure of neural activity, i.e. whether CR is related to a neural measure while that neural measure is related to the behavioral measure. Such a finding implies that the neural measure mediates the relationship between CR and behavior. In order to further support such a conclusion based on finding an indirect relationship, alternate statistical models must be tested to demonstrate that they do not better fit the data [58]. Alternate models are created by reversing and switching the arrows in the theoretical model of CR. Although the alternate models in some cases may not be physiologically plausible, e.g. neural activity causing increased age, if they prove to be a better fit to the data than the theoretical model it implies that a better understanding of one’s data is needed. A recent review by Salthouse has an in-depth treatment of these concepts [59]. The overall purpose of such alternates tests is to increase confidence that the theoretical model provides the best explanation of the data.

Mediation tests for CR operating by increasing efficiency would be evident if A) CR was related to neural measures of efficiency, such as measures of slope of neural activity for increasing task demands, B) the neural measure of efficiency was related to a behavioral measure and C) the indirect effect was significant. In practice, this is a negative relationship between CR and the neural slope measure such that as CR increases the slope decreases. As the slope measure decreases, with increasing CR, the behavioral measure will improve.

The choice of behavior measure makes a number of important implications which are reviewed here. It is also important to point out that variance in the behavioral measures should ideally vary as a measurable function of the neural activity. If the behavioral measure is accuracy, then the neural measure should also vary as a function of accuracy. This would not be the case if the modeling of the neural data only uses correct trials. The alternative of using neural data from all trials to relate to a measure of accuracy also has its own problems. If the neural activity during error trials differs from that during correct trials, then by collapsing across both response types the two different patterns of neural activity would be blended together. This simply decreases the ability to reliably detect the neural activity.

The choice of response time as a behavioral measure has its own special conditions. Response time may be calculated from only correctly answered trials, and the neural data can be similarly modeled. When taking a univariate data analysis approach, one is testing for differences in the amplitude of neural measure as a function of task demands or age-group. This makes the assumption that the duration of time required to perform a task is related to the amplitude of the neural
activity. The assumptions with this concept have been previously discussed in depth [60,61]. Essentially, it is important to disambiguate changes in neural duration from changes in neural amplitude, both of which can result in similar changes when using hemodynamically linked neural measures such as BOLD fMRI.

In a follow-up analysis [62], we more formally evaluated the role of cognitive reserve in the findings described above. The results of this study are outlined in Fig. 3 using the concepts laid out in Figs. 1 and 2.

Using path analysis, we evaluated the relationship between proxies for CR (i.e. IQ measures) and the variables considered above: gray matter density and the primary network, expression of the primary and secondary network, and task performance. This analysis found that cognitive reserve influenced two aspects of our findings. First, we found that individuals with higher cognitive reserve could tolerate more atrophy in the primary network and still preserve that network’s performance without having to resort to using the secondary network. One possible explanation of this finding is that individuals with higher cognitive reserve had a more efficient primary network to begin with; this is represented by arrow “e” in Fig. 1. The second finding was that cognitive reserve moderated the relationship between expression of the secondary network and task performance; this is arrow “f” in Fig. 1. That is, even though greater expression of the secondary network was associated with poor cognitive performance, individuals with higher cognitive reserve performed the task better at any level of expression of the secondary network. This second finding is of interest because it cannot be explained simply by invoking differential expression of the networks involved in performing the task. Rather, even when using the secondary network, individuals with higher cognitive reserve somehow had resources that allowed them to maintain better performance. This suggests that they are using some cognitive resources that are separate from those involved with task performance. This finding raises the possibility that cognitive reserve might be mediated in part by neural networks that are not related to the demands of any specific task. Rather, there may be one or more generalized neural networks that help mediate cognitive reserve.

5.2. Identifying a generic cognitive reserve network

We investigated the possibility of a general, non-task-specific cognitive reserve network in another study [63]. Our strategy was to see if we could find a single network that showed increased load-related activation as a function of CR across two tasks with differing cognitive processing demands. Young and elder subjects were scanned with fMRI while performing either the letter or the shape Sternberg task. Load-dependent fMRI signal corresponding to each trial component (i.e., stimulus presentation, retention delay, and probe) and task (letter or shape) were regressed onto putative CR variables. We then used a multivariate analytic approach to summarize the imaging data — CR relationships. We wished to determine if there were patterns of CR-related brain activity whose latent predictors had similar contributions from both the letter and shape tasks. Such a pattern, expressed across two tasks with divergent processing demands, would be a likely candidate for a generic neural substrate underlying CR. We identified a pattern like this in the young group: a spatial pattern expressed during the stimulus presentation phase manifested similar relationships between CR and load-related activation across both the letter and shape WM tasks. Thus, in the young subjects we identified a common CR network that was expressed across both tasks. Elders expressed the network in a manner similar to the younger subjects when performing the letter task, but not the shape task. The inference that we wish to draw is that this network might represent the neural instantiation of CR, or alternatively that the ability to invoke this network might underlie the benefits that CR imparts when performing any task. Of course, further follow-up and refining of this approach to identify generic cognitive reserve networks is needed. However, it would certainly be useful to identify a neural pattern of activation that is associated with generic cognitive reserve.

5.3. A model for study the neural representation of CR

We can now update the research model presented in Fig. 1 by incorporating the reviewed studies (Fig. 4). To further pursue our research goals using this model we are casting a wide net in characterizing age and AD-related pathological changes, including measures of brain volume, cortical thickness, white matter tract integrity, white matter hyperintensities, cerebral blood flow, resting or default networks, and amyloid. It is important to establish a relationship between these measures and age-related cognitive change because the concept of cognitive reserve specifically addresses the mechanisms used to cope with these brain changes, arrow “g” in Fig. 1. Next, we posit that the effects of age- or AD-related pathologic changes on task performance may be mediated by changes in the underlying neural activity responsible for performing these tasks, this is the path through arrows “c” and “d” in Fig. 1. There are four possibilities of how CR could operate in this model. Line “a” represents how increased cognitive reserve modulates, or decreases, the effect that age or AD-related pathology has on performance or clinical outcome. Line “e” demonstrates how cognitive reserve is mediated by efficiency and capacity of task related activation. For example, we described a situation where network efficiency is maintained in the face of volume loss, thus maintaining function. Line “f” indicates a situation where cognitive reserve serves as a moderator. For example, we described a situation where, among individuals using a less advantageous, compensatory network, individuals with higher measured reserve still maintain better performance. Line “h” indicates that CR could also operate directly to improve task performance or clinical outcomes in a manner that is completely independent of task-related activation. This situation is demonstrated by our finding of a generalized cognitive reserve network that is unrelated to task-related activation. In our current studies, we generate measures for all nodes of this figure and ultimately test the complex hypothesized mediation and moderation effects using path analysis.
6. Conclusion

Epidemiologic and imaging evidence support the concept of cognitive reserve. However, the neural implementation of cognitive reserve is still the subject of ongoing research. This paper reviews some of our efforts to pursue this question. Beyond simply understanding how cognitive reserve is reserved. However, the neural implementation of cognitive reserve is still the subject of ongoing research. This paper reviews some of our efforts to pursue this question. Beyond simply understanding how cognitive reserve is implemented, the identification of the neural implementation of reserve may help pinpoint foci for intervention. In addition, if the generative cognitive reserve network could be identified, this would be extremely useful for patient diagnosis and assessment of cognitive intervention.

References


