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Cognitive Reserve: Implications for Assessment and Intervention

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Abstract

The concept of reserve is used to explain the observation that some individuals function better than others in the presence of brain pathology. This paper reviews the concept of reserve from its theoretical basis to the implication of reserve for clinical practice. A distinction between brain reserve, referring to individual differences in the anatomic substrate, and cognitive reserve, referring to differences in the flexibility or adaptivity of cognitive networks, is useful. Epidemiologic evidence indicates that a set of life exposures including higher educational and occupational attainment, and engaging in leisure activities is associated with a lower risk of incident dementia, suggesting that these life exposures may enhance cognitive reserve. This provides a basis for controlled clinical studies can test specific exposures that may enhance reserve. The concept of cognitive reserve also has important implications for clinical practice in terms of diagnosis and prognosis.

The concept of reserve is used to explain that observation that some individuals function better than others in the presence of brain pathology. In one study, the brains of 10 cognitively normal elderly women were found to have Alzheimer's plaques at autopsy [1]. It was observed that these women's brains were heavier in comparison to brains of normal elderly women in their data base. The authors suggested that this provided 'reserve' which helped the women to function despite their pathology. Later studies have suggested that specific life experiences are associated with reduced risk of developing Alzheimer's disease (AD), and it has been suggested that these life experiences may also impart reserve against the effects of developing AD pathology. These initial observations led to the concepts of brain and cognitive reserve. In this brief review, the theoretical basis for the concepts of brain and cognitive reserve are discussed. Epidemiologic evidence for the contribution of life exposures to reserve is reviewed. The use of studies to explore the neural substrates underlying cognitive reserve is described. Finally, studies intending to enhance reserve, and the implications of the concept of reserve for clinical practice are reviewed.

Brain and Cognitive Reserve

These two observations are examples of two types of reserve: brain reserve and cognitive reserve. 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. In one formulation of this concept[2], there is a threshold of remaining brain reserve at which functional deficits will emerge. Thus and individuals with more brain reserve can accumulate more pathology

before reaching that threshold. I suggested that this initial brain reserve model be termed a passive model in that it is entirely quantitative: a given brain injury affects each individual in the same manner and brain injuries throughout the lifespan sum together. [3]

In contrast, cognitive reserve refers to the ability to make flexible and efficient use of cognitive networks when performing tasks in the presence of brain pathology [3]. Thus two people with the same level of brain reserve can appear different because one can make better use of the remaining brain substrate than the other. For this reason, those with higher cognitive reserve tend to have better clinical outcomes for any level of pathology and brain reserve.

Although the initial conception of brain reserve was entirely quantitative, recent evidence suggests that this concept is more nuanced, in that the brain substrate can actually be altered by experience. For example, in animals stimulating environments foster the growth of new neurons in the form of neurogenesis [4-6], and upregulate brain derived neurotrophic factor (BDNF), which is associated with enhanced neural plasticity. In addition exercise and life experience can be associated with changes in brain volume. Still, both brain reserve and cognitive reserve can make independent contributions to understanding individual differences in clinical resilience to brain pathology.

This paper reviews cognitive reserve in the context of Alzheimer's disease and normal aging, but it has also been demonstrated to provide benefit in vascular injury [7-9], Parkinson's disease [10], traumatic brain injury [11], HIV [12], neuropsychiatric disorders [13], and multiple sclerosis [14].

Epidemiology of Cognitive Reserve

In 1994, my group reported incident dementia data from a follow up study of 593 community-based, non-demented individuals aged 60 years or older [15]. After 1 to 4 years of follow up, the risk of dementia was twice as high in subjects with low education (below 8 years) compared to those with higher education (relative risk (RR) = 2.2, 95% confidence interval [CI], 1.33 to 3.06). The risk of incident dementia was also higher in those with low lifetime occupational attainment (RR, 2.25; 95% CI, 1.32 to 3.84). We hypothesized that educational and occupational attainment reflect lifetime exposures that increase reserve against the expression of AD pathology. In a later study, we assessed participation in a variety of leisure activities [16]. During follow-up, subjects who engaged in more of these activities had 38% less risk of developing dementia.

Several studies have tested for a relationship between bilingualism and dementia. A retrospective chart review study of 184 patients from a memory clinic in Toronto reported that bilinguals were diagnosed with dementia an average of four years later than monolinguals [17]. Another retrospective study did not replicate this finding but noted a small protective effect of speaking three or more languages [18]. A study, in a small sample of Hispanics with probable AD reported an association between bilingualism and later age of dementia diagnosis only among those patients with low education (< 11 years) [19]. In all three of these studies, age of onset was not directly observed but was estimated from clinical history. In a study submitted for publication, our group examined the potential protective effect of bilingualism in a community-based study of initially non-demented Hispanic immigrants. The 1,238 elders were followed at 18-24 month intervals for up to 23 years. Spanish-English bilingualism was estimated via both self-report and an objective measure of English reading level. Bilingualism was associated with better memory and executive function at baseline. However bilingualism was not independently associated with rates of cognitive decline or dementia conversion.

A review paper [20] found 22 studies of the protective effects of education, occupation, premorbid IQ and mental activities on incident dementia. The great majority demonstrated significant protective effects. Overall, the authors reported that these life exposures were associated with significantly lowered risk for incident dementia (odds ratio, 0.54, 95% CI, 0.49 to 0.59).

Epidemiologic evidence for cognitive reserve can also be noted in studies of age-related cognitive decline. Several studies have found that higher educational attainment or literacy were associated with slower cognitive or functional decline [21] [22-29].

Neuroimaging Studies of Cognitive Reserve

The first imaging study of CR was 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. Resting regional cerebral blood flow (rCBF) served as a surrogate for AD pathology, because specific rCBF changes in AD are related to the underlying AD pathology and rCBF becomes lower as the pathology advances [30,31]. When AD patients were matched for clinical severity based on measures of cognition and function, there was a negative correlation between resting rCBF in the parietotemporal area affected in AD and years of education [32]: higher education was associated with more depleted flow. This suggests that patients with higher education were tolerating more AD pathology than those with lower education even though they were clinically similar. Many years later, this observation was confirmed in a prospective clinical study where deceased subjects' brains were subjected to post mortem neuropathological evaluation. 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 [33].

Neural Mechanisms Underlying CR

I have suggested that the neural implementation of CR might take two forms: neural reserve and neural compensation [34,35]. Neural reserve refers to the inter-individual variability in the brain networks or cognitive paradigms that underlie the performance of any task in healthy individuals. 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. An individual with greater neural reserve might be more capable of coping with the disruption imposed by brain pathology.

Neural compensation refers to the use of brain structures or networks not normally used by individuals with intact brains in order to compensate for brain damage. In some cases the greater use of the alternate network may be associated with better performance in the face of brain pathology. This type of compensation might represent the recruitment of alternate solution strategies to cope better with brain pathology. It is also possible that the use of compensatory networks may result in poorer performance. This could occur if brain pathology impacted on the the typical network underlying performance. This could result in the recruitment of an alternate network that supports performance, but in a suboptimal way. A simple analogy is the use of a cane, which allows an elder to walk but not as well as if he did not need it. There are several reviews of my group's efforts to explore these ideas using imaging studies [35,36]

Implications of Cognitive Reserve for Remediation and Prevention

The epidemiologic evidence suggests that many exposures over the life course are associated with increased reserve against age-related or disease related pathology. Further,

the evidence suggests that experiences at all stages of life, even in late life, can impart such reserve. These findings support the possibility that it may be possible to intervene even later in life in order to impart reserve, slow age-related cognitive decline, and prolong healthy aging. These observations are in line with the increasing realization of the plasticity of the aging brain and the fact that cognitive intervention might be useful in aging and dementia. The key difference between the general perspective towards cognitive intervention and my point of view is that my goal would be to increase reserve, rather than enhance any particular cognitive function.

The most successful remediation approach to date has been aerobic exercise. Many controlled studies in elderly individuals have demonstrated that, in individuals with below median respiratory capacity, aerobic exercise that increases this respiratory capacity also results in increases in cognitive performance [37]. The results of cognitive intervention studies have been more mixed. One of the largest such studies was the ACTIVE study, in which a large number of elders were trained using protocols aimed at improving one of three cognitive domains: speeded attention, memory, and reasoning ability [38]. Each of these training protocols yielded improved performance within their domain that persisted over a long period of time. However, there was no evidence that training in one domain generalized to performance in any of the other two domains. In addition, there is no convincing evidence that training resulted in any improvement in activities of daily living.

More promising have been studies that have immersed subjects in complex gameplay. For example, Basak et al. [39] had elders play a complex role-playing game “Rise of Nations” for 23.5 hours, and demonstrated that gameplay was associated with improved performance on a wide range of cognitive tasks. Our group has been working with another complex game, “Space Fortress,” that was designed by human operations psychologists as a test bed for training approaches to teach young adults complex tasks [40]. In this game, the player must control a spaceship and circle around a space fortress. The fortress shoots missiles at the player ship, and the player must avoid these missiles and in turn attempt to shoot at and destroy the fortress. Several other features of the game occur at the same time including the appearance of friend or foe mines that the player must attempt to destroy and the appearance of markers that are signals that the player can make a specific response to get bonus points. Each individual game lasts 3 min. and participants typically play 12 games in a single session. In research with young adults, one particular training approach produced excellent improvement in gameplay, but, more importantly, also showed transfer of training to other tasks. In this approach, which is called emphasis change training, players are instructed to focus on all of the features of the game, but to give specific emphasis to one particular feature, either ship control or mine handling, during each individual game. By shifting emphasis from game to game, participants cannot fall into a fixed strategy. They must develop the ability to deal with the entire task as a whole – skills that might be termed attentional allocation or executive control. Younger people who learn to play the game using this training approach were more able to incorporate new demands while playing the game [41]. In addition, they showed more successful performance on real-world tasks such as flight simulator or flight training performance [42,43]. In a preliminary study with older adults, we explored the capacity of the elders to learn to play the game, and the possibility that gameplay might improve cognitive performance [44]. 90 subjects were divided into three groups: a non-gameplay condition, gameplay without emphasis change training, and gameplay with emphasis change training. The two gameplay groups played the game three times a week for 12 weeks. Interestingly, although the game itself was very challenging for the elders, there were few dropouts and performance improved over time. Analysis of various features of gameplay indicated that elders and the pure gameplay condition were not as focused on the key goals of the game as the emphasis change group; they were more likely to respond to signals for bonus points as opposed to attempting to destroy the space

fortress. In contrast, the elders in the emphasis change condition were more likely to focus on features central to the game, in particular they were eventually more successful at destroying the space fortress than elders and the other group. Our primary cognitive measures were five tasks that involve executive control. On one of these tasks, a test of working memory, the emphasis change group showed greater improvement from pre- to post-testing than the other two groups[45]. We consider this a promising finding, and are currently conducting a study which combines space fortress game play with aerobic exercise. By combining a cognitive intervention with aerobic exercise we are hoping for a synergistic effect. The aerobic exercise may in effect boost brain reserve, for example by improving plasticity via upregulation of BDNF. The cognitive intervention, in turn, may help increase cognitive reserve by increasing the efficiency of the cognitive networks underlying executive control. This cognitive efficiency would be facilitated by the improved level of brain reserve.

More generally, the epidemiologic data clearly suggest that aspects of life experience can impart reserve against age- or disease-related pathology. However, the exact “recipe” for helping to create this reserve is still unknown. The most meaningful endpoints for such an intervention would be slowed rate of cognitive decline in aging or reduced risk of developing Alzheimer's disease. Studies using these endpoints will be very expensive and will have to be conducted over long periods of time. Most likely, these studies should use multiple intervention strategies including exercise, cognitive stimulation and social stimulation.

Cognitive Reserve In Clinical Practice

It can be very helpful to consider CR when evaluating patients. By definition, individuals with high reserve can tolerate more age-related brain changes or disease pathology than individuals with low levels of reserve. More challenging tests with higher ceilings may better detect changes in individuals with very high levels of CR. Tests that are directly tailored to tap performance changes related to underlying pathology should have greater sensitivity in high reserve individuals. However, clinicians must be aware that even the most sensitive measures can fail to detect cognitive change when pathology is present.

Biomarkers that detect brain changes, for example PET scans sensitive to amyloid plaque, can detect pathological changes even when there is no impairment on neuropsychological testing. Thus, neuroimaging can be an aid in clinical evaluation. Theoretically, the optimal characterization of any clinical syndrome would be a combination of the measured pathology and measured reserve. For example, in AD we can now measure some aspects of disease pathology including plaques and tangles, and CR can be characterized by proxy such as educational or occupational attainment, and IQ. However, integration of this concept into day-to-day practice is premature because the prognostic implications of the current pathologic measures are not fully established. Still, the availability of these biomarkers provides a fruitful avenue for research into cognitive reserve.

CR should also be recognized as a factor that will influence rate of cognitive decline following diagnosis of AD. The rate of decline is more rapid in AD patients with high reserve than those with low reserve[46,47]. We believe that this is because once an individual with high CR reaches the point where pathology begins to affect performance, the level of pathology is quite advanced. We theorize that at that point the remaining reserve is quickly overcome by advancing pathology, resulting in rapid decline. This observation has strong implications for the design of clinical drug trials in AD because they typically compare rate of decline in a treated and placebo group. A mismatch in CR across the two

groups could lead to differential rates of decline that have nothing to do with the medication under study.

Epidemiologic evidence clearly links a set of lifetime exposures to lower rates of dementia. This might encourage clinicians to recommend engaging in specific activities in order to prevent or delay dementia. However, intervention studies are needed to firmly establish causal links between life experiences, individual characteristics, and CR, and such studies are underway. Therefore, while recommending that patients engage in certain activities such as mental enrichment and physical fitness is likely not to be harmful and may in fact have numerous positive effects, clinicians should be careful not to present these activities as established treatments or fully proven preventative strategies against dementia.

The differentiation between brain and cognitive reserve is important theoretically, but also can serve as a guide for future research into clinical interventions that enhance reserve. It will be important to understand how life activities such as exercise or cognitive stimulation influence the brain the substrate itself, and differentiate this from how cognitive reserve is enhanced. The potential synergy referred to above of attempting to enhance both brain and cognitive reserve simultaneously also has great promise.

Conclusion

The concept of CR is very useful for explaining the disjunction between the degree of brain pathology and the clinical manifestations of that pathology. Epidemiologic observations support the idea that sets of lifetime exposures and individual characteristics are associated with greater reserve against the clinical expression of brain changes or pathology. Functional imaging studies have great promise for helping us to understand the neural basis of CR. Such studies may suggest optimal targets for intervening to increase CR. CR has practical implications for the clinical evaluation of patients. Finally, controlled studies may suggest interventions that can enhance CR in order to maintain successful aging and slow the onset of dementia. While CR was discussed in the context of aging and dementia in this review, the same concepts are applicable to any other condition associated with brain pathology. Finally, the concept of CR provides a frame for generating powerful and empirically testable research ideas.

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