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Reviews and perspectives

Cognitive reserve☆

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ABSTRACT

The concept of reserve has been proposed to account for the disjunction between the degree of brain damage and its clinical outcome. This paper attempts to produce a coherent theoretical account the reserve in general and of cognitive reserve in particular. It reviews epidemiologic data supporting the concept of cognitive reserve, with a particular focus of its implications for aging and dementia. It then focuses on methodologic issues that are important when attempting to elucidate the neural underpinnings of cognitive reserve using imaging studies, and reviews some of our group's work in order to demonstrate these issues.

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The concept of reserve has been proposed to account for the disjunction between the degree of brain damage or pathology and its clinical manifestations. For example, a head injury of the same magnitude can result in different levels of cognitive impairment, and that impairment can vary in its rate of recovery. Similarly, several prospective studies of aging have reported that up to 25% of elders whose neuropsychological testing is unimpaired prior to death meet full pathologic criteria for Alzheimer's disease (Ince, 2001), suggesting that this degree of pathology does not invariably result in clinical dementia. As will be described in detail below, many studies indicate that a set of life experiences such as educational and occupational exposure and leisure activities are associated with reduced risk of developing dementia and with a slower rate of memory decline in normal aging. Cognitive reserve (CR) postulates that individual differences in the cognitive processes or neural networks underlying task performance allow some people to cope better than others with brain damage. This paper attempts to produce a coherent theoretical account of reserve in general and of cognitive reserve in particular. It then reviews some of my group's epidemiologic and imaging research that has lent support to the concept of cognitive reserve and helped elucidate its neural underpinnings. It should be stressed that this review is focused on my group's work, and is not a thorough review on the entire literature on the topic.

Because my work has focused on aging and dementia, I will discuss CRs relation to these brain changes. The concept of CR, however, is applicable to almost any situation where brain function is disrupted. Thus, for example, proxies for higher CR have also been reported to mediate incidence of dementia in HIV (Farinpour et al., 2003), as well as cognitive changes associated with schizophrenia, bipolar disorder and depression (Barnett, Salmond, Jones, & Sahakian, 2006), and traumatic brain injury (Kesler, Adams, Blasey, & Bigler, 2003).

1. Brain reserve and cognitive reserve

Reserve can be roughly classified into passive and active models. Brain reserve (Katzman, 1993) is an example of a passive model, where 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. This approach to reserve has been codified in the threshold model (Satz, 1993), which revolves around the construct of "brain reserve capacity". The model recognizes that there are individual differences in brain reserve capacity. It also presupposes that once brain reserve capacity is depleted past some fixed critical threshold specific clinical or functional deficits emerge. Thus, individual differences in brain reserve capacity lead to differences in the clinical expression of a particular degree of damage to the brain.

There are several reasons why threshold models can be termed *passive* models of reserve. First, this type of model assumes that there is some fixed cutoff or threshold below which functional impairment will occur for everyone. In the case of AD, this threshold might be depletion of synapses to the point where only a specific number remain. Second, threshold models are essentially quantitative models. They assume that a specific type of brain damage will have the same effect in each person, and that repeated instances of brain damage sum together. Individuals differ only in their overall brain capacity, and brain damage is either sufficient or insufficient to deplete brain reserve capacity to some critical level. Threshold models do not account for individual differences in how the brain processes cognitive or functional tasks in the face of the disruption caused by brain damage.

In contrast to passive models of reserve, active models such as CR suggest that the brain actively attempts to cope with brain damage by using pre-existing cognitive processes or by enlisting compensatory processes (Stern, 2002). Although two patients might have the same amount of brain reserve capacity, the patient with more CR may tolerate a larger lesion than the other patient before clinical impairment is apparent. Thus, an active model does not assume that there is some fixed cutoff or threshold at which functional impairment will occur. Rather it focuses on the processes that allows individuals to sustain brain damage and maintain function.

Table 1
Working definitions of key concepts.

Brain reserve: Individual differences in the brain itself allow some people to cope better than others with brain pathology. These differences can be quantitative, such as larger brain, more neurons, or synapses. In addition, life experience can influence brain anatomy via neurogenesis, angiogenesis, promoting resistance to apoptosis, and up-regulating compounds that promote neural plasticity.
Cognitive reserve: Individual differences in how people process tasks allow some to cope better than others with brain pathology.
Neural reserve: Inter-individual variability – perhaps in the form of differing efficiency, capacity, or flexibility – in the brain networks or cognitive paradigms that underlie task performance in the healthy brain. 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.
Neural compensation: Inter-individual variability in the ability to compensate for brain pathology's disruption of standard processing networks by using brain structures or networks not normally used by individuals with intact brains. This compensation may help maintain or improve performance.

As will be discussed below, I have suggested that the possible neural implementation of cognitive reserve be subdivided into two components, neural reserve and neural compensation. Neural reserve refers to inter-individual differences in cognitive processing that exist in the normal healthy brain. Neural compensation refers to alterations in cognitive processing that may take place in order to cope with brain pathology. Table 1 summarizes the working definitions for brain reserve, cognitive reserve and its subcomponents.

It has become clearer in recent years that the demarcation between brain reserve and cognitive reserve is not clear cut. First, from a strict point of view, the differences in cognitive processing envisioned by the cognitive reserve model must also have a physiologic basis, in that the brain must ultimately mediate all cognitive function. The difference is in terms of the level of analysis. Presumably, the physiologic variability subsumed by cognitive reserve is at the level of variability in synaptic organization, or in relative utilization of specific brain regions. Thus cognitive reserve implies anatomic variability at the level of brain networks, while brain reserve implies differences in the quantity of available neural substrate. Second, many of the factors associated with increased cognitive reserve, such as cognitively stimulating experiences, have a direct effect on the brain. The child developmental literature suggests that not only do individuals with higher IQ have larger brain volume (Willerman, Schultz, Rutledge, & Bigler, 1991) (Kesler et al., 2003), but that cognitively stimulating aspects of life experience may also be associated with increased brain volume. It is also now clear that stimulating environments and exercise promote neurogenesis in the dentate gyrus (Brown et al., 2003; van Praag, Shubert, Zhao, & Gage, 2005). Both exercise and cognitive stimulation regulate factors that increase neuronal plasticity (such as BDNF) and resistance to cell death. Finally, there is evidence to suggest that environmental enrichment might act directly to prevent or slow the accumulation of AD pathology (Lazarov et al., 2005). Thus, a more complete account of CR would have to integrate these complex interactions between genetics, the environmental influences on brain reserve and pathology, and the ability to actively compensate for the effects of pathology.