A life course approach to cognitive reserve: A model for cognitive aging and development?

A Life Course Approach to Cognitive Reserve: A Model for Cognitive Aging and Development?

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The concept of reserve in neuroscience maintains that there are aspects of brain structure and function that can buffer the effects of neuropathology such that the greater the reserve, the more severe the pathology must be to cause functional impairment. This article provides a concise overview of structural and functional approaches to reserve and shows how reserve may be conceived as the sum of its lifetime input. In this context, reserve therefore provides an empirical yet general model of cognitive aging and development.

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In 1992, Stern and colleagues[1] compared regional cerebral blood flow in three groups of patients with Alzheimer's disease (AD); these groups were matched for clinical disease severity but with different levels of education. They found that those patients with a high level of education had a more severe parietotemporal perfusion deficit than those with lower education and suggested that education, although not preventing the acquisition of AD, represents a "reserve" that somehow protects against its clinical expression. This made sense of long-reported findings that some individuals with neuropathological features of AD at autopsy had nevertheless remained cognitively spared[2]; these findings have been more recently corroborated.[3] A year later, Katzman, who himself had published such findings,[4] reviewed evidence for the protective effect of education against the prevalence, or at least the detection, of AD in the population,[5] and Satz formulated a threshold theory of "brain reserve capacity" for the expression of acquired neural injury.[6] Thus, the concept of reserve, although not itself new, gained currency in the neuroscience of aging, and a recent series of articles, a decade on, demonstrate the intellectual exchange and empirical research it has generated.[7–12] A concise overview of the concept is therefore timely. This article reviews the various approaches to reserve and shows how the concept can be developed from a life course perspective.

The Concept of Reserve in Neuroscience

In essence, the reserve concept maintains that there are aspects of brain structure and function that can buffer the effects of neuropathology such that the greater the reserve, the more severe the pathology must be to cause functional impairment. Structural, passive reserve, or "brain reserve capacity," focuses on the protective potential of anatomical features such as brain size, neural density, and synaptic connectivity.[5] Functional, active, or "cognitive" reserve emphasizes efficiency of neural networks and active compensation by alternative or more extensive networks after challenge.[7,12] However, both approaches imply a graded neural substrate that is capable, by degree, of protecting against the functional consequences of neuropathology.

These structural and functional approaches to reserve have parallels in general medicine. A structural analogy occurs in nephrology, for example, where small size at birth is hypothesized to be associated with small kidneys with fewer or smaller glomeruli, and thus a low-filtration surface area. Under these circumstances, diabetic patients, for example, may be more prone to renal failure when exposed to renal insult in later life.[13] Examples of active reserve may be seen in physiological compensation mechanisms, such as coronary artery enlargement in response to plaque, which delays func-

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tional stenosis until the lesion occupies at least 40% of the internal elastic lamina area.[14]

In the context of neuroscience, reserve has been investigated to some extent at the neural level, but typically its nature and efficacy have been inferred from proxies such as intelligence quotient and head size, and from the arguably more distal measures of education, occupation, and activity. This approach may apply to a range of neuropathology, but in practice, the emphasis has been on dementia, where function is impaired by definition. Thus, a large body of epidemiological evidence indicates that high ability,[15–18] larger head size,[4,19,20] high educational and occupational attainment,[5,7] and high levels of physical, social, and intellectual activity[21,22] are protective against dementia. In theory, this is because these factors protect against the functional consequences of neuropathology, thus delaying or preventing the detection of the disease, rather than protecting against disease acquisition itself. However, some of these reserve factors are indeed associated with the development of neuropathology, particularly lesions of vascular origin,[23,24] which, in turn, may be associated with AD.[25,26]

Does Reserve Protect Activities of Daily Living or Cognition?

But what does it mean to say that reserve protects against the functional consequences of neuropathology? In the context of dementia, function is often equated with activities of daily living (ADLs).[27] However, it would be unwise to place too much emphasis on ADLs as an index of underlying neuropathological severity because, in practice, the stage at which ADLs are likely to be classified as impaired will be at least partly determined by extrabiological factors such as availability and use of clinical services, level of social capital, social and cultural norms, and so forth. Furthermore, education, occupation, and lifestyle may interact with this social determination independently of their effects on the brain. A more tractable, empirical approach would be to equate function with measured cognitive performance, although acknowledging that it is just one of the phenomena that determine ADLs. In this way, the concept of reserve may become a viable model of cognitive aging.

The Measurement of Reserve

Some measures of reserve are thought to represent its neural substrate directly and are easy to conceptualize, although not necessarily to measure. Easiest to measure is head circumference, which is positively correlated with brain size[20] and cognitive function.[28] Direct volumetric measurements of brain size can be derived from imaging, where whole-brain volume is also correlated positively with cognitive function.[29] Obviously, the closer the cellular level is approached, such as neuronal count, synaptic density, or degree of dendritic arborization, the more difficult it becomes to measure these features in living humans. This distance between the concept of reserve and its biological substrate and its measurement is one of the more severe limitations of the theory.

Whereas the structural approach to reserve refers to the "hardware," functional approaches place more emphasis on the "software,"[7] such as efficiency of neural network utilization and cognitive processing. Although more complex conceptually, the neural basis of active reserve is gradually being elucidated by functional imaging studies. For example, the level of general cognitive ability is related to changes in neural activity as subjects move from low cognitive task demand to a titrated level of demand.[30] An important aspect of this approach is that it applies equally to healthy individuals when coping with cognitive challenge and to individuals with brain damage.[12] A related idea is that of compensation,[7] where alternative or more extensive neural networks are activated when the brain is compromised, during normal[12] as well as abnormal[31] aging.

Other variables are suggested to represent reserve indirectly, particularly educational and occupational attainment, but also health and physical, social, and mental activity. All of these variables are associated with cognitive ability,[32–36] and it is clear that the central nervous system (CNS) is sensitive to their temporal effects. For example, in some studies, educational and occupational exposures enhance cognitive ability with respect to its level in childhood.[37,38] Taxi drivers show a topographic hippocampal reorganization, correlated with length of time in this employment, that favors visuospatial learning.[39] Although ability has genetic,[40,41] uterine,[42–45] and early postnatal[46–48] determinants, these studies bear out Rutter's[37] and Schaie's[49] observations that cognitive ability is capable of being augmented across the life course.

These studies are also supported by laboratory evidence of long-term neuroplasticity in mice. Attempts to explain the beneficial effects of physical or mental activity on cognitive function in humans have focused on factors such as increased blood flow or greater synaptic plasticity.[50] However, evidence suggests that neurogenesis may be an important mechanism, and that this can occur over an extended interval. Rats raised for 10 months in an enriched environment (a large cage equipped with rearrangeable plastic tubes, a running wheel, nesting material, and toys) showed a fivefold greater increase in hippocampal neurogenesis than control rats raised in standard cages.[51] They also showed reduced hippocampal lipofuscin, indicative of decreased age-associated degeneration. Furthermore, these changes were associated with improved learning, exploratory behavior, and locomotor activity. As Mc-

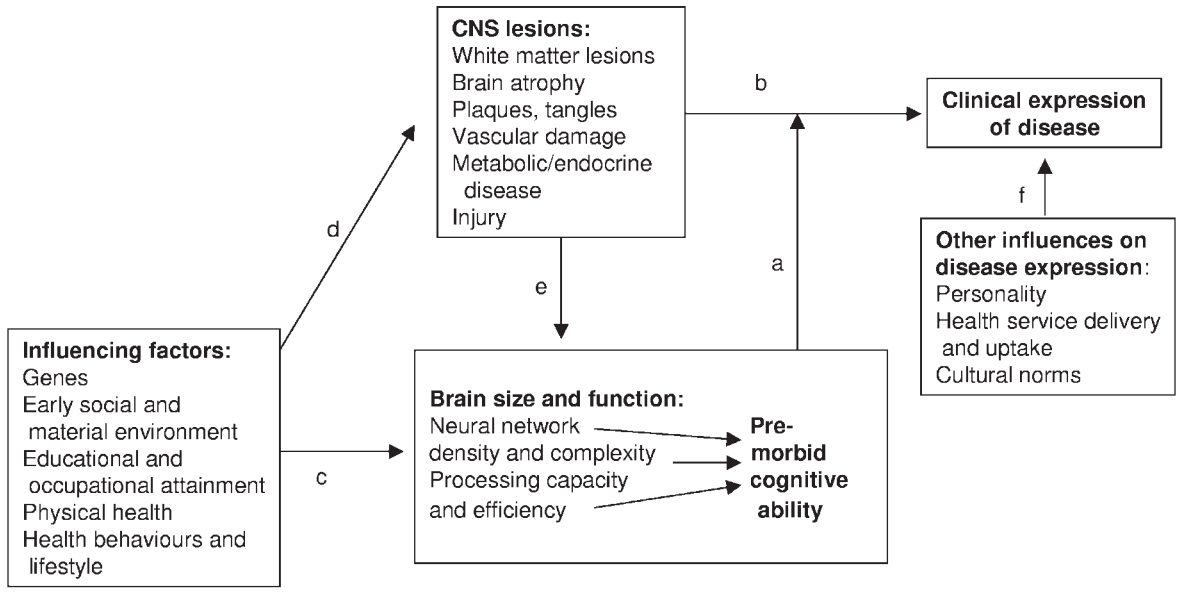
Khann[50] notes, "There has never been a satisfactory explanation of why more education in youth is associated with a later onset of AD many decades later. Possibly it is through some such regenerative mechanism."

A Life Course Model of Cognitive Reserve

The Figure shows a proposed life course model of cognitive reserve. At the center is premorbid cognitive ability, which modifies (path a) the clinical expression (path b) of disease that is influenced by CNS lesions. The major proximal input into premorbid cognitive ability comes from brain size and function, based on structural neural network complexity (Satz), and functional processing capacity and efficiency (Stern). Influencing brain size and function are a range of more distal factors (path c), beginning with genes.[52–55] These influencing factors then range through the early social and material environment,[56,57] through the major inputs of education, occupation, and the socioeconomic environment, to physical health, health behaviors, and degree of engaged lifestyle activity. Thus, although much of the neuropathology highlighted in the CNS lesions box is associated with later life, the model is capable of application to earlier phases of the life course. For example, it might apply to protection against the cognitive effects of head injury at any age.

It is important to emphasize that influencing factors not only determine cognitive ability at any given age, but also are capable of augmenting ability (or protecting it from decline) over time. That is, taking prior ability into account, the signature of the accrual of reserve is the identification of something that adds variance to later cognitive function. For example, education and occupation are positively associated with mature ability, even after taking childhood ability into account[38]; physical exercise is associated with slower cognitive decline in midlife after taking adolescent ability into account, as well as educational and occupational attainment and cardiorespiratory function.[58] Occupation contributes significant variance in fluid reasoning in old age after childhood ability and white matter lesions are taken into account.[59] As these latter authors suggest, "Reserve should account for significant variance in the cognitive outcomes in old age after adjusting for variance contributed by childhood mental ability and burden. In other words, possessing some reserve means that one's cognitive score is greater than would be predicted from the person's childhood ability and the amount of overt, accumulated burden" (p. 1192).[59]

Note that there are paths connecting the "influencing factors" to "brain structures" (see Fig, path c) *and* to "CNS lesions" (path d). For example, poor education



a. Cognitive reserve is represented by peak pre-morbid cognitive ability.
b. Cognitive reserve modifies the clinical expression of CNS lesions.
c. Cognitive reserve is influenced by many factors across the life course.
d. These same factors influence the accumulation of CNS lesions.
e. CNS lesions in turn damage brain size and function.
f. There are also factors other than CNS lesions that affect disease (especially dementia) expression.

Fig. CNS = central nervous system.

may not only inhibit optimal brain development, but also may lead to increased risk for cerebrovascular damage, via cardiovascular disease and diabetes,[60] exacerbated by negative health behaviors such as sedentary lifestyle, poor diet, and smoking.[23,61,62] As noted earlier, from the perspective of dementia, brain reserve and neuropathology are regarded as fully independent entities; there is no suggestion that education protects against the *acquisition* of AD neuropathology, rather only against its clinical expression. If, however, the model is broadened to address a range of CNS pathologies, particularly cerebrovascular disease, but also injury and toxic or metabolic disruption, it is clear that this independence is not sustainable.

This, however, raises a difficulty for the concept of cognitive reserve. Note that CNS lesions by definition damage brain size and function, as represented by path e in the Figure. If brain size and function are the major proximal determinants of peak premorbid cognitive ability, then the model is capable of working in a negative circular manner. That is, negative influences on brain size and function, such as low educational and occupational attainment, are also risk factors for the development of CNS lesions, which, in turn, can deplete cognitive reserve and reduce protection against their clinical expression. However, only certain cognitive domains, particularly "fluid" skills requiring effortful information processing, are likely to be vulnerable to the effects of CNS damage. Verbal or "crystallized" ability, in contrast, is not only resistant to age-associated decline, but is capable of being augmented across the adult life course,[38,63] and it is to some extent robust to the effects of frank neuropathology,[64] although it does eventually decline with increasing severity of dementia.[65,66] Whether preserved crystallized ability in the face of impaired fluid ability is sufficient to protect against the clinical expression of neuropathology is a matter for further debate.

Conclusions: A Dynamic Approach to Cognitive Aging and Development

The concept of reserve has proved to be heuristic in neuroscience as a potential mechanism to explain why diseases of the CNS that affect cognition are less likely to be detected, and less likely to impair daily function, in some individuals than in others. However, because disease detection and perceived functional capacity are partly determined by factors that are independent of the individual, the most important focus for reserve theory arguably should be cognitive function itself. This is not a new idea. Indeed, Stern[12] has argued that an active approach to reserve is equally viable for normal cognitive function as it is for explaining the clinical manifestations of disease. Our suggestion is to extend this further by allowing the reserve model to apply across the life course, to cognitive development in childhood, as well as to adulthood and later life, recognizing that cognitive ability is modifiable at all stages of the life course.

Above all, we hope that this approach shines light into reserve as an empirical construct, that is, nothing more, as such, than the sum of its parts. Thus, the potential obscurity of reserve as a semantic black box is eased, allowing empirical work to concentrate on the difficult task of untangling its neural substrate and the determinants of this substrate.

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