Reserve, Brain Changes, and Decline

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Reserve is a heuristic concept used to explain the apparent discrepancy between pathologic changes in the brain normally associated with aging and disease, and the manifestation of those changes in terms of clinical presentation and cognitive decline. It has been used to explain this discrepancy in a range of situations such as multiple sclerosis, dementia, and individual differences in cognitive aging. It is not the intention of this article to document an anthology of research concerned directly or indirectly with reserve, but to provide an overview of the concepts and applications being used to explore reserve and proposed connections between empiric proxies of reserve, hypothesized biological mechanisms, and the protection from aging and disease that reserve imparts.

A BRIEF HISTORY OF RESERVE

Interest in reserve has steadily increased since the early 1990s, with a Web of Science search identifying 138 publications using the term (or similar) in 2010 and more than 1200 publications since 1990. One of most frequently cited publications that refers to reserve is by Katzman and colleagues in 1988, who noted that those individuals with high levels of Alzheimer’s disease (AD) pathology post mortem, who otherwise remained nondemented in life, had almost double the number of large pyramidal neurons throughout their neocortex in comparison with those who expressed clinical symptoms. This publication goes on to suggest that those nondemented in life might have started with a larger brain and more neurons and thus might be said to possess greater reserve against incipient AD, but did not become clinically demented because of this greater reserve.

Although this is a modern articulation, the concept of brain reserve is not new. In the 1960s work done in and around Newcastle upon Tyne in the United Kingdom noted “it would appear that a certain amount of the change estimated by plaque counts may be accommodated within the reserve capacity of the cerebrum without causing manifest intellectual impairment,” and that “although the association between dementia and brain degeneration is impressive the extent of the degeneration varies considerably; moreover, occasionally, the brains of individuals who have never become demented have been found to show quite marked changes.” Moreover, “the condition of the brain seems therefore to be only one of several factors determining the threshold at which dementia appears.” Collectively these publications make two clear points: (1) the brain has a buffer or reserve capacity to withstand a degree of change brought about by aging and disease, and (2) the size of that capacity is different between individuals.

Although less scientifically vigorous, publications from the early twentieth century discuss the concept of reserve in mediating behavior in the face of pathologic change. Pickworth in the 1930s comments that “no clinical abnormality is noticed unless the damage is quantitatively so great as to exceed the reserve.” Indeed, Fleming in the 1920s goes as far as to suggest how reserve is acquired. “...The great storehouse for personal memories, the residue of individual experience. These reserves are drawn on to cooperate in deciding, on the basis of personal as well as racial experience, what act is appropriate to the situation.” These early publications are by no means the only two to articulate the concept of reserve in the early twentieth century.
With the increased availability of modern imaging techniques, the discrepancy between brain changes characteristic of disease and aging and an individual’s clinical presentation or cognitive performance has been reemphasized. The advent of specific β-amyloid (Aβ) ligands for positron emission tomography (PET), such as Pittsburgh compound B (PIB), has brought about great optimism for a new era in AD imaging diagnosis. However, not all patients with positive PIB PET have or develop AD. This fact may be attributable to the lack of specificity of the ligand and/or the exact role of Aβ in the development of AD, but it is also consistent with the notion that individual differences in reserve allow some people to maintain function in the face of disease-like pathologic burden. Similarly, a study using 18F-fluorodeoxyglucose (FDG) PET indicated that some individuals (those with more years of schooling) were able to maintain function in the face of similar metabolic deficits. Stern and colleagues found that AD patients with more education had larger regional cerebral blood flow (rCBF) deficits, measured using single-photon emission computed tomography (SPECT), suggesting that more education enabled an individual to cope with greater levels of pathologic change. Reed and colleagues showed that schooling attenuates the cognitive effect of brain atrophy measured using magnetic resonance (MR) imaging.

RESERVE MODELS

It is unclear how reserve enables an individual to withstand the effects of age and disease-related pathologic change. Stern has suggested conceptual models for reserve and postulates different mechanisms for the implementation of reserve; the first he refers to as “brain reserve,” suggesting that individuals have different amounts of brain reserve and that, for a given amount of pathologic burden, those with more reserve will be less affected. This brain reserve could, therefore, be said to passively protect an individual against the effect aging and disease. Structural proxies of passive brain reserve suggested in the literature are indices such as brain or head volume, head circumference, synaptic count, or dendritic branching. An active mechanism through which function is maintained has also been proposed, which has been described as cognitive reserve. An individual with this type of reserve uses brain networks or cognitive paradigms that are less susceptible to disruption and could be said to have “neural reserve.” The second mechanism is described as neural compensation. Here, in the face of pathology, the brain recruits structures and/or networks not normally used by individuals with intact brains, to compensate for pathologic burden. The literature has consistently identified proxies of active or cognitive reserve, such as premorbid cognitive ability, education, physical activity, intellectual engagement, and occupational attainment. These insightful models have structured reserve research and have provided a vocabulary with which to discuss the phenomenon.

These models may not be as discrete as they first appear and are not mutually exclusive. When examining brain reserve proxies, it is clear from the literature that these measures have also been shown to be modifiable through intervention and the environment. For example, McEwen has suggested that repeated stressors result in decreased dendritic branching and a reduction in the number of neurons. It has recently been suggested that early-life experience has a significant association with late-life brain size and may also be considered as a lifelong proxy of cognitive reserve. Therefore, brain reserve may represent, at least in part, the integration of life experience and environmental factors that overlap with the proxies of cognitive reserve. For example, a common proxy for cognitive reserve is education. Education is not only associated with premorbid ability but is influenced by childhood socioeconomic status, which in turn may reflect individual differences in diet and early-life stimulation. Moreover, education may influence late-life socioeconomic status and intellectual engagement, which may have an impact through passive and/or active routes. These structural, probably causal, paths between potential measures of reserve that extend across all models would suggest that reserve is unlikely to be optimally described by a single factor that can be measured directly.

Brain Reserve and the Passive Model

The passive reserve model can be summarized by the phrase “the more you have the more you have to lose before deficits appear.” “Having more” brain reserve, such as more synapses, will lead to sufficient residual capacity after accounting for pathology for function to continue unaltered. Insufficient reserve will lead to inadequate capacity, and functional loss will occur. There is considerable observational evidence that is consistent with the passive reserve model. Studies have reported higher levels of reserve proxies, such as brain size, neuronal number, and neuronal density in individuals with brain changes associated with dementia and disease but little or no cognitive deficits.
Cognitive Reserve and the Active Model

The active reserve model proposes that individual differences in processing mechanisms and the ability to compensate by actively adapting these mechanisms (and using new ones) is responsible for protecting an individual against the detrimental cognitive effects of aging and disease. A person’s premorbid intelligence as well as educational and occupational attainment have been suggested as proxies for measuring this ability. These measures are assumed to reflect the neural efficiency, or the ability to recruit alternative brain networks to compensate, when faced with pathology. Epidemiologic evidence supports the active or cognitive reserve hypothesis, with lower baseline intelligence scores, less education, and lower occupational attainment being risk factors for dementia and cognitive decline.23,24

A processing mechanism that is less susceptible to pathology is a potential source of cognitive reserve. Consider two individuals who perform identically through different neuronal routes because they have different brain structures or different expertise and training, or who might have used different cognitive strategies. One may be considered to have reserve if the mechanisms used are less susceptible to aging and disease. Evidence for individual differences such as these has been considered in a review article by Deary and colleagues.25 An alternative source of active reserve has its origins in an individual’s ability to compensate for detrimental pathology. This reserve could be realized by upregulation of an existing mechanism (working harder) or by the recruitment of alternative or more extensive neural networks (doing different). A recent review by Eyler and colleagues into the functional brain imaging correlates of successful cognitive aging reported “frequent support for the notion that increased brain responsiveness is associated with better cognitive performance” in aging samples. However, it is unclear whether this increased responsiveness is a consequence of the better performers’ mechanisms of working harder or doing different, or whether better performers had increased responsiveness before the onset of pathologic burden and established mechanisms that are less susceptible to disease and aging. Or is it the case that a combination of all possible sources and mechanisms of reserve is required to cope with the onset of disease and aging? It is difficult to test for the presence of one strategy versus another using a cross-sectional, observational approach predominantly used in the field. For example; Persson and colleagues27 compared the frontal cortex functional (fMR) imaging response during a verbal encoding task between those who had stable memory performance and those who had declined. Greater response was found in the right ventral prefrontal cortex among decliners than in those with stable performance. Is this evidence of a declining person working harder or are those that develop more efficient mechanisms being less susceptible? Cabeza and colleagues found that young adults and poorer performing older adults recruited similar right prefrontal cortex (PFC) regions, whereas higher performing older adults engaged PFC regions bilaterally. The investigators concluded that poorer performing older adults recruit a network of brain regions similar to those of young adults, but use these inefficiently, whereas higher performing older adults compensate for age-related neural decline by reorganizing brain functions, that is to say, doing different in that face of aging. An alternative explanation would be that higher performing adults develop this alternative mechanism before the onset of aging pathology and are therefore less susceptible.

ACQUIRING RESERVE GENETICALLY

There is of course no randomized, double-blind longitudinal intervention study to identify the elements or life experiences that contribute to reserve. Evidence that reserve can be acquired is observational in nature, and causality is inferred rather than proved. It may well be that the proxies attributed to reserve are not causal but correlative and have, at least in part, a common origin. Examining the acquisition of brain or cognitive reserve separately is difficult because the parameters that describe a life course are interconnected. A genetically endowed advantage leading to greater neuronal numbers and a larger brain will also influence early-life intelligence, the education one receives, one’s occupational attainment, and the intellectual and physical pursuits one chooses to undertake. The influence of this life-course description of reserve is further complicated by the potential of the avoidance of pathologic burden by the educated and/or affluent. That is, those in privileged positions may avoid the potential risk factors for dementia, such as toxic exposures and risks encountered by manual workers, and are better able to act on public health advice by taking regular exercise and not smoking.

Genetic and environmental factors will influence an individual’s response to aging and disease. The combination of genes and environmental factors influencing brain development may also influence reserve and may be just as important, either alone or in combination, in early life as they are later. Identifying the genetic risk factors for dementia is
a rapidly growing field, with most (but not all) candidate genes having a likely hypothesized mechanism from genotype, through pathology, to disease.29

Identifying the genetic contributions to reserve holistically is difficult because of the absence of a directly measurable reserve quantity. There is considerable evidence that heritability is responsible for brain (and thus head) size, measures considered as proxies of passive brain reserve. Bartley and colleagues,30 examining twins using structural MR imaging, concluded that human cerebral size is determined almost entirely by genetic factors, but that overall cortical gyral pattern, though significantly influenced by genes, is determined primarily by nongenetic factors. Pfefferbaum and colleagues,31 examining twins using APOE polymorphisms, recently demonstrated an association between apolipoprotein E (APOE) polymorphisms and dementia, with multiple pathways that may explain the pathogenic nature of APOE.35 These factors include its role in the formation of AD neuropathology but also its role in modifying synaptic plasticity and repair. Reduced plasticity may well influence age-related neural reorganizing of brain functions, a postulated compensatory mechanism of reserve (doing different).

The genetic influence of brain connectivity has recently been examined by Fornito and colleagues,36 who used fMR imaging to study twins and identified genetic influences on anatomic connectivity. Extrapolating from this work, it is reasonable to suggest that different levels of connectivity may facilitate more robust and/or different mechanisms that maintain cognition in the face of pathologic burden. Examining the influence of APOE genotype, Dennis and colleagues37 found that in the absence of demographic or performance differences, carriers of APOE epsilon 4 (ε4) allele exhibited greater bilateral medial temporal lobe activity relative to noncarriers (working harder) while accomplishing the same encoding task. In addition, APOE ε4 carriers demonstrated a greater functional connectivity to some regions, but overall reductions in connectivity were found across the anterior and posterior cortices. Brain regions implicated in this investigation are known to incur structural and functional changes in mild cognitive impairment and AD. The investigators attribute these differences in connectivity patterns to the APOE-driven pleiotropism in functional brain organization in early life. These individual differences may enable mechanisms that are less susceptible to aging and disease burden, or may facilitate compensatory mechanisms (doing different) in the face of pathologic burden.

**ACQUIRING RESERVE ENVIRONMENTALLY**

Without considering genetic predisposition, risk factors for cognitive decline and dementia are interrelated, and probably have an impact on both the accumulation of dementia-related neuropathological burden and the acquisition of reserve. Experiences during life that are considered to promote reserve are socioeconomic status,38 social engagement,39 education, occupational status,3 mental engagement, and physical activity.40

A complete model for the interconnectivity and structure has yet to be established but, using a life-course approach, childhood socioeconomic status has been shown to influence childhood cognitive ability, education, occupational attainment, and cognition in late middle age in a variety of direct and indirect causal pathways.41 Similarly, Hirvensalo and Lintunen42 have suggested that socioeconomic status influences physical activity and, subsequently, health. Social engagement is related to cognition throughout adulthood, and is an important factor to consider in relation to efforts to promote optimal cognitive development and cognitive aging.43

Although there is empirical evidence for these proxies of reserve, the biological mechanisms through which these environmental factors act to realize reserve are unclear. Staff and colleagues19 recently demonstrated an association between socioeconomic position in childhood and hippocampal volumes in late life, and suggested that childhood socioeconomic status brings about other individual differences, for example in education, occupation, diet, and mental stimulation, which result in restricted development of the hippocampus. Hippocampal volume is a risk
factor for conversion to AD. Hippocampal volume may then be considered a proxy of passive reserve (having more). Similarly, Rushton and Ankney showed in a cross-sectional study that brain size increased with socioeconomic status. This mechanism of passive reserve may explain the association between risk of dementia and socioeconomic position.

Alternatively, these proxies of passive reserve may bring about mechanisms and connectivity patterns that facilitate active mechanisms. This proposal is partly conjecture, but Corden and colleagues found that those with high social cognition scores activated a different network when compared with those with lower social cognition scores. Social cognition has been shown to be associated with social interaction/engagement. The causal direction is unproven; however, the reserve provided by greater social engagement may be a consequence of the use of different neuronal networks, with the high social cognition network being less susceptible to burden. Song and colleagues found that functional connectivity within the frontal lobe and between the frontal and posterior brain regions were both important predictive factors for intelligence. This connectivity may well facilitate the formation of less susceptible mechanisms through greater efficiency, or provide an individual with more compensatory options in the face of burden (doing different).

Waiter and colleagues, using fMR imaging response to the inspection time task in two groups aged 69 years who differed in terms of their lifelong cognitive trajectory, found that the group of individuals who maintained their cognitive ability, relative to their childhood ability, demonstrated a pattern similar to healthy young samples. It is reasonable to assume that maintenance of cognitive ability was brought about by factors such as education, occupation, and intellectual engagement, resulting in the network responsible for the task being less susceptible. In addition, the different pattern observed in those that had a less favorable lifelong cognitive trajectory may be evidence of a functional relocation of the network responsible for the task (doing different) in those experiencing preclinical cognitive decline, or possibly evidence that those with less intellectual enrichment throughout life had always relied on a different neuronal network that was more susceptible to decline.

TESTING AND MEASURING RESERVE

This article hypothesizes the potential links between proxies of reserve, differences in brain structure, functional architecture, adaptability, and the protection from functional loss. To test the reserve hypothesis requires a proxy estimate of reserve, a measure of pathologic burden in the brain, and a measure of cognitive change. This evaluation can only be accurately achieved using imaging in a longitudinal study design for a well-characterized sample. Although cross-sectional investigations still have a role to play in linking reserve proxies to brain differences and brain differences to cognitive change, the subtle interrelationships of reserve will best be exposed with long-term longitudinal studies.

Bolstering reserve is an obvious therapeutic target with which to counteract the effects of brain aging and dementia. The field, however, is limited by the use of proxy or surrogate measures for reserve, such as the participation in complex mental activities (education, occupation, social engagement) or crude biological markers (head size, brain volumes). The evolving imaging fields that measure anatomic and functional connectivity and the use of information/systems theory approaches to examine qualities such as robustness may provide more insightful biological measures of reserve. A true measure of reserve should explain a large proportion of the remaining variance in cognition, after adjusting for the influence of neuropathologic burden. The more variance it explains, the better the measure. A secondary feature should be that the environmental or biological proxy of reserve has biologically plausible mechanisms of action. Creating a practical measure that successfully aggregates the possible sources of reserve would enable identification of vulnerable groups for intervention, and enable researchers to better predict decline and subsequently quantify the influence of any intervention.

SUMMARY

Current evidence indicates that there are many roads to reserve, all of which are interconnected. It is likely that these have their origins in early life through genetic predisposition, but are modifiable throughout life. Simplifying the categories of having more, being more or less susceptible, working harder, and doing different have been used for convenience, and do not imply that they are discrete; indeed, having more neurons is likely to facilitate more than one mechanism of reserve. Despite the considerable literature on the subject, reserve remains a heuristic concept with only portions of the full picture currently understood.

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