The concept of reserve is well-recognized in medicine. Various organs of the body, for example the kidney and the liver, manifest reserve such that significant damage can occur to the organ without impacting on clinical function. The very fact that an individual can donate one kidney and yet remain healthy attests to this fact. The glomerular filtration rate (GFR) is generally considered to be a measure of the excretory function of the kidney, with the normal GFR being $>90 \text{ mL/min/1.73 m}^2$. Significant kidney damage can occur without affecting GFR, and the GFR is generally $<30 \text{ mL/min/1.73 m}^2$ before features of chronic renal failure are manifest.\(^1\)

The brain is recognized to demonstrate a similar reserve capacity. It is known that degeneration of dopamine cells in the substantia nigra starts long before the symptoms of Parkinson’s disease develop, and the absolute number of pigmented neurons has been reported to be reduced to about one-third in patients.\(^2\) Individuals with brain injury appear to have different thresholds at which they will develop clinical symptoms. This reserve capacity has received the greatest attention in the case of Alzheimer disease. An early report showed that some individuals with high levels of Alzheimer’s type pathology in their brains escaped dementia during life, and that this was related to higher counts of large pyramidal neurons in their cerebral cortices.\(^3\) This led to the more commonly held conceptualization of brain reserve, that is, the so-called “hard” or “neurological” brain reserve.

According to the hard brain reserve concept, individuals differ in their reserve capacity depending upon some characteristics of the brains they are endowed with. Early support for this came from studies that related greater head size, measured as head circumference or intracranial volume, to a reduced risk of dementia.\(^4\) The argument presented was that larger brains were able to tolerate a greater extent of pathology before they reached the functional threshold at which symptoms became clinically manifest, that is, they had further to fall before reaching the disorder threshold. Head size is a proxy measure for brain size before the onset of pathology, but its appeal is limited by the fact that its association with intelligence or cognitive capacity is generally poor. Further studies showed that the relationship between head circumference and dementia was restricted to those in the low to very low range of head girth,\(^5\) or to an interaction with the polymorphism on the apolipoprotein E gene.\(^6\) It was also not clear what constituted the basis of a large brain. Was it large neuronal numbers, increased dendritic proliferation, greater synaptic density, more white matter connections, or simply large ventricles?

A major limitation of the “large brain” concept of reserve is that it is a static and passive viewpoint. An approach that Perneeczky et al.\(^7\) take in this issue is to relate the brain’s reserve capacity to its metabolic activity rather than the size. They use $^{18}$fluoro-2-deoxy-glucose positron emission tomography to examine relative metabolic activity in different brain regions. In previous studies, metabolic activity has been shown to be better related to functional capacity than brain size,\(^8\) and Perneeczky et al. have again demonstrated a significant association between glucose hypometabolism and impaired activities of daily living, especially for the right temporoparietal cortex.

Furthermore, their study takes the concept of brain reserve as being dynamic and active, and subject to
modification by experience. In fact, this is the dominant theme of the set of papers included in this issue; that brain reserve is modifiable and the brain is a highly plastic organ. Experience-related modification of brain structure is well-illustrated by the study of Nithianantharajah et al. Previous research has shown that environmental enrichment can produce a number of positive brain effects in rodents, which include greater dendritic length and branching, an increase in the number and size of synapses, formation and maturation of new neurons and circuits, increased expression of neuronal signaling molecules, and greater synaptic plasticity. In the current study, the authors have shown that effects of environmental enrichment are region-specific. They have demonstrated decreased spine density in neurons of the dentate gyrus, but no effect on neuronal density in the CA1 region or the somatosensory and motor cortices. In addition, enrichment increased dendritic diameter in the dentate gyrus and CA1 regions of the hippocampus but decreased soma area of layer V pyramidal cells in the somatosensory cortex. This work is further support for the concept of an adaptive brain, and underlies the dynamic nature of what was considered to be hard brain reserve.

The morphological consequences of environmental enrichment raise the possibility that this might produce disease modification itself. Previous research in a mouse model has shown that an enriched environment can delay the onset of Huntington’s disease. The study reported in this issue showed different results, suggesting variability in response, possibly due to different enrichment methods or other methodological differences. This is important to remember when translating these findings to humans—rigorous human studies are necessary before these findings are to be accepted and translated into clinical intervention. The implications are of great importance, as the morphological changes reported may be sufficient to rescue dysfunctional circuits and restore deficient memories or other cognitive functions. There is even the possibility of slowing the progress of disease, that is, individuals with high brain reserve might have slower disease progression in the presence of similar pathomechanisms.

Activity or enrichment-dependent neuronal plasticity demonstrated in the mice experiments can be modeled on a computer using network theory, as is demonstrated by Rubinov et al. in this issue. These authors modeled a neural system as having small-world architecture with “nodes” connected by “edges.” Random node deletion, representing neuronal death, does not result in loss of local or global efficiency. This aligns with the notion of neuronal plasticity. Targeted deletion of central nodes leads to the loss of efficiency, which can be compensated by simulated neurogenesis. This article illustrates how neuroanatomical changes associated with brain reserve might translate into maintenance or loss of functional networks. It is likely that individuals with high reserve have greater neurocomputational flexibility and might use a range of information processing pathways for solving complex problems.

This brings us to another approach to brain reserve that emphasizes functional rather than structural reserve, the so called “cognitive reserve” or “intellectual reserve.” According to this conceptualization, individuals with high brain reserve perform better on cognitive tasks, and this provides them with a greater buffer in the process of their decline before they reach a threshold for diagnosis of dementia. The superior performance may be related to an efficient set of neural networks or a wider repertoire of conscious and preconscious cognitive strategies. These may be innate and/or enriched by environmental exposure. This repertoire arguably permits the high reserve individuals to compensate for loss more effectively than those with a limited repertoire.

In the dementia and ageing literature, various proxy measures have been used for cognitive reserve, and these include measures of intelligence, education, and occupation. The inference would be that those with high education would be able to accumulate more pathology before clinical deficits are manifest. A meta-analysis of the literature relating brain reserve to incident dementia, which included 22 studies comprising 29,000 individuals followed-up over a median 7.1 year, concluded that higher brain reserve was associated with a lowered risk for incident dementia (summary odds ratio, 0.54; 95% confidence interval, 0.49–0.59). Consistent with previous literature, Perneczky et al. very elegantly showed that well-educated patients with dementia with Lewy bodies could offset more brain damage, as measured by glucose metabolic rates, until they reached the same level of impairment on activities of daily living as the less educated comparison subjects. On the other hand, Christensen et al. did not find
an association between level of education indicators of brain reserve, such as brain volume and the extent of white matter hyperintensities, and high education was not a protective factor for cognitive decline. This discrepant finding may be related to a number of methodological issues, including the fact that this was a relatively young sample, being 60–64 years at index assessment, most had high levels of education and the neuropsychological assessments were limited in their scope. It can be argued that there might be a threshold above which education becomes protective, and the effect thereafter is probably not linear. The protective effect is therefore unlikely to be demonstrable in a well-educated population.

Occupation has been shown to have a protective effect, but whether the nature of work is important has been investigated to a lesser degree. The report by Karp et al. addresses this with data from the Kungsholmen Project in Sweden. In this study over 6 years, incident dementia was lower in those with higher complexity of occupation. Jobs that were associated with analyzing, coordinating and synthesizing data were the most protective, and these could compensate for low education in both men and women.

The final perspective on reserve in this issue relates to its potential in clinical and preventative medicine. Valenzuela and Sachdev review the literature on intervention trials for the protective effects of complex mental activity. These trials follow from the observational studies that complex mental activity delays the onset of dementia and slows the rate of decline of cognitive function, consistent with the Karp report. Of the 54 published intervention studies, seven met strict criteria for inclusion. The authors conclude that intervention with cognitive exercises produces a positive effect with a strong effect size in healthy older people compared to wait-and-see control conditions, and this effect does not appear to be diluted over 2 years. There is considerable neurobiological evidence that mental stimulation enhances brain function. Complex mental activity induces the production of neurotrophic factors, such as brain-derived neurotrophic factor and nerve growth factor, and increases neurogenesis, synaptogenesis and perhaps angiogenesis.

The concept of brain reserve appears to be moving rapidly from basic biology and epidemiology to clinical medicine. There are a number of trials currently underway to examine the relative benefits of mental and physical activity and whether the two have a synergistic effect. The protective effect of mental activity is a simple concept that appears to have captured the imagination of the lay press and the common person, and there is an emerging industry attempting to commercialize this knowledge. This issue of the Journal is a timely reminder that hard science must guide every step of this process so that the best and most meaningful interventions reach the clinic and the market.

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References


