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Review

Cognitive reserve and successful ageing

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Background. The concept of cognitive reserve was introduced in the neurological field to account for the observation of individual discrepancies between the level of brain pathology and the observed cognitive/functional deficits. The notion of brain reserve provides a strong foundation for the recent increase of interest in modifiable risk factors as a strategy for brain health promotion.
Strategies. There is now evidence of protective effects on cognitive decline and dementia for physical activity, Mediterranean diet, cognitive training and social engagement, which may all be considered as contributing to brain and cognitive reserve mechanisms. Besides controlling risk factors, an area of great interest is the possibility to act positively on the reserve by means of active intervention. This possibility is suggested by the results of several cognitive training studies in healthy elderly subjects.
Conclusions. Even modest effects on the age of onset or the rate of cognitive decline would have an enormous positive impact on successful aging at the population level worldwide.

Key words: Cognitive reserve, Modifiable risk factors, Cognitive training, Social engagement, Mediterranean diet, Active interventions

The concept of cognitive reserve was introduced in the neurological field to account for the observation of individual discrepancies between the level of brain pathology and the observed cognitive/functional deficits [1]. The early observations at the roots of the concept came from neuropathological studies of Alzheimer's disease (AD), in which some individuals were found to demonstrate less cognitive impairment than others affected by a comparable degree of neuropathology [2]. The possibility to assess clinico-anatomical correlations *in vivo* opened new possibilities to the investigation of this intriguing phenomenon. An early study [1], based on the 2-dimensional technique of cerebral blood flow assessment, provided group level evidence for the role of education as a modulator of the brain pathology/clinical expression relation. Three groups of AD patients, with low, intermediate and high education were matched for clinical severity. Severity of hypoperfusion, which can be considered as an index of brain pathology, was inversely proportional to the level of education. In other words, the same level of clinical severity was associated with a more severe involvement of the brain in the more educated subjects, suggesting that education was providing some protection against cognitive decline. These pioneering observations, confirmed by many additional studies, led to the further development of the reserve concept. A proposed distinction is between a "passive" component of reserve (brain reserve), identified by quantitative indexes, such as brain size, neuronal number, density of synapses, and an "active" component, related to functional compensation and reorganization induced by environmental and lifestyle factors, indexed by education, occupational attainment and intellectual activities [3]. This is clearly an artificial distinction, given the strict intertwining of the two aspects as indicated by the notion of neuroplasticity, linking specific environmental experiences to brain changes. This is now supported by a large number of human studies, from the

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famous observation of increased hippocampal volume in London taxi drivers [4], to the short term gray matter associated to learning to juggle [5].

What is now generally accepted is that reserve can act as a modulator, resulting, in the case of progressive neurodegeneration, in delayed clinical expression, and, therefore, faster decline after reaching the diagnostic threshold. The original results reported by Stern et al. [1] have subsequently been replicated and expanded using positron emission tomography measurements of glucose metabolism [6]. In the latter study, the observations supporting the existence of reserve mechanisms were confirmed in a large sample of AD patients, and extended to the predementia condition of mild cognitive impairment (MCI). A significant association was found between higher education/occupation and lower regional metabolic rate of glucose in posterior temporoparietal cortex and precuneus, i.e. in areas typically affected in AD, both in demented patients and in MCI subjects, which were later found to progress to AD. The results suggest that education and occupation can be considered as surrogate measures of brain reserve, with an impact both on reducing the severity of dementia and on delaying the clinical expression of the brain pathology. Another interesting finding was subsequently reported, again using PET, but measuring a molecular marker rather than glucose metabolism [7]. The same reserve indicators, i.e. education and occupation, were correlated with acetylcholinesterase activity, measured voxelwise by [11C]-MP4A and positron emission tomography. In this case, a positive correlation was found between education and AChE activity in the hippocampus, bilaterally, and between occupation and AChE activity in the right posterior cingulate gyrus. These regions are part of the memory network, thus suggesting that stimulation of cholinergic neurotransmission may be a contributing factor to brain reserve.

The notion of brain reserve provides a strong foundation for the recent increase of interest in modifiable risk factors as a strategy for brain health promotion. There is now evidence of protective effects on cognitive decline and dementia for physical activity, Mediterranean diet, cognitive training and social engagement [8], which may all be considered as contributing to brain and cognitive reserve mechanisms. It is worth noting that this does not apply only to age associated cognitive disorders, but to a variety of neurological conditions, such as stroke or multiple sclerosis, where cognitive reserve appears to act as a powerful mediator between pathology and functional performance [9].

Besides controlling risk factors, an area of great interest is the possibility to act positively on the reserve by means of active intervention. This possibility is suggested by the results of several cognitive training studies in healthy elderly subjects. While the results of training in AD have largely been disappointing, a large-scale study in elderly subjects found a significant reduction of physiological cognitive decline in subjects engaged in working memory training [10]. Particularly remarkable are the results of a similar study [11], in which the positive effect of training was not limited to test performance, but extended to functional activities of daily living. The FINGER study in a large sample of at risk subjects, based on a comprehensive intervention on risk factors combined with cognitive training, reported significant effects on several cognitive variables [12]. The cognitive changes due to training in a sample of MCI patients were associated with changes in brain activity during a memory task measured with functional magnetic resonance [13].

The recent observations of a protective effect of bilingualism, resulting in a delayed age at onset of dementia [14] and in milder cognitive effects of stroke [15] has led to the hypothesis that learning a second language may be a privileged cognitive stimulating activity, an interesting concept that needs to be supported by experimental evidence.

Finally, neuromodulation approaches based on transcranial magnetic stimulation or direct current electrical stimulation, which have been shown to provide some performance enhancing effects in AD and MCI [16] may also be considered as a potential tool acting on cognitive reserve.

To summarize, the concept of cognitive/brain reserve is based on solid experimental evidence, and provides a useful theoretical framework for the development of programs aiming at the promotion of brain health in the elderly. While the benefits of such programs may not be apparent at the individual level, even modest effects on the age of onset or the rate of cognitive decline would have an enormous positive impact on successful aging at the population level worldwide.

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