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 **Foresight**

**Mental Capital and Wellbeing:  
Making the most of ourselves in the 21st century**

**State-of-Science Review: SR-E4  
Cognitive Reserve and Mental Capital**

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## Summary

**Cognitive reserve describes an individual's resistance to cognitive impairment that arises as a consequence of brain pathology caused by injury, disease or the normal ageing process. Concepts of reserve differ in their emphasis: some describe the 'hardware' of brain function such as brain size or the number of neurons; while others emphasise the importance of cognitive 'software' such as intelligence, experience and knowledge. Recent evidence has successfully demonstrated that cognitive reserve is not fixed. It can be increased through physical or mental activity, social stimulation, and potentially also through medication or dietary interventions. Cognitive reserve is, therefore, a key aspect of mental capital, which can be accumulated through education, work and other physically- or mentally-challenging activities. The biological basis of cognitive reserve, and the mechanisms by which these interventions may boost it, remain largely unclear. However, such interventions are of undoubted significance for the ageing population, where they may help reduce the personal, social and economic burden of both dementia and normal cognitive ageing.**

### 1. The concept of cognitive reserve

Cognitive reserve describes an individual's resistance to impairment in cognitive processes such as memory, reasoning and attention, which may arise as a consequence of brain pathology caused by injury, disease or the normal ageing process.

The concept arose from the observation that, in a number of neurological conditions including dementia and acute head injury, there is often no direct relationship between the extent of brain damage and the severity of clinical symptoms that emerge (Stern, 2002). So, a third factor is hypothesised to modify the relationship between pathology and clinical symptoms. This factor has been formulated in a variety of terms. These include general terms such as 'brain reserve' or 'brain reserve capacity' (Katzman, 1993; Satz, 1993), 'neuronal reserve' (Mortimer et al., 1981), and most recently, as 'cognitive reserve' (Stern, 2002; Stern, 2003; Whalley et al., 2004).

There are two broad models of reserve (Scarmeas and Stern, 2003; Stern, 2002) which vary to the extent in which reserve is seen as an active *versus* passive construct. The concepts are alike to the extent that high reserve is seen as a protective factor against the development or expression of a range of conditions, from Alzheimer's disease to the cognitive consequences of normal ageing. They also agree that low reserve is a vulnerability factor which lowers the threshold for the symptoms, functional impairment and clinical presentation that accompany neurological disorders.

These models differ, however, in the measures used, and in assumptions they make about the neurological basis of the reserve.

Cognitive reserve has been investigated primarily in dementia and acute brain injury, but the concept may be applicable to a broad range of neurological and psychiatric conditions. Some cognitive decline is a normal part of healthy ageing, and cognitive reserve may explain individual differences in this, as well as in the more severe memory loss associated with the onset of dementia, which is over and above normal decline with age, and for which help should be sought. Cognitive reserve is thus a key aspect of mental capital, which can be accumulated through education, work and other physically or mentally challenging activities.

Potential means of boosting cognitive reserve are of clear significance for the ageing population, where they may be crucial in helping reduce the personal, social and economic burden of both dementia and normal cognitive ageing.

## **2. Passive models of cognitive reserve**

Passive models of reserve concern individual differences in the 'hardware' of brain function. These may include structural differences in the number or density of neurons or synapses. In these models, increased brain reserve, such as a higher number of healthy synapses prior to pathology, leads to an increased number of remaining available synapses post pathology. If the reserve is sufficient, little or no loss of function will be seen despite pathology. If, however, reserve is low, the threshold at which clinical manifestations occur will be reached with relatively little pathology.

There is some clinical support for these models. Between 10-40% of individuals who show neuropathological markers of Alzheimer's disease (AD) during autopsy show no cognitive impairment (Mortimer, 1997). It has been reported that these non-demented individuals have larger brains and a greater number of neurons than elderly volunteers who do not show histopathological signs of AD (Katzman et al., 1988). Den Heijer and colleagues (2006) found that brain volumes were 17% smaller in cognitively-intact elderly people diagnosed with dementia within 2-3 years, and 5% smaller in those diagnosed six years after the initial assessment. Brain reserve may also be important with respect to the severity and timing of the onset of dementia (Mori et al., 1997).

## **3. Active models of cognitive reserve**

In contrast, active models consider individual differences in the 'software' of brain processing, and use proxy measures of brain functioning, such as intelligence test scores and educational and occupational attainment. These measures are assumed to reflect the efficiency of neural processing, or the ability to recruit alternative brain networks to compensate for the effects of pathology. In its narrow sense, 'cognitive reserve' is usually taken to mean the former, referring exclusively to healthy individuals or individuals prior to the onset of brain pathology.

Once pathology is suspected or known, the term 'compensation' may be more appropriate, and could also be applied to the recruitment of alternate or more extensive neural networks to compensate for the cognitive effects of normal ageing (Richards and Deary, 2005).

A large body of epidemiological evidence supports active models of cognitive reserve in dementia. Lower intelligence scores, and lower education and occupational attainment, are all risk factors for dementia (Katzman, 1993; Letenneur et al., 1999; Schmand et al., 1997; Snowdon et al., 1996; Stern et al., 1994) although some have argued that this may reflect an ascertainment bias (Tuokko et al., 2003).

Highly educated individuals may also continue to benefit from cognitive reserve after the diagnosis of dementia, showing slower decline in at least some areas of cognition (Le Carret et al., 2005). That these findings are the result of active processes is supported by the evidence (discussed below) that high levels of physical, social and intellectual activities are all protective against dementia (Kramer et al., 1999; Scarmeas and Stern, 2003).

## **4. Cognitive reserve and mental capital**

Cognitive reserve underpins mental capital in a number of ways, in both the healthy population and among people with a range of illnesses.

In the general population, cognitive reserve may affect inter-related domains including cognitive ageing, wellbeing, health behaviours, and life span. Cognitive reserve can be thought of as an asset that can be

accumulated throughout life, through education, work, and leisure activities involving physical or cognitive exertion. This asset can be used throughout life to take advantage of opportunities and to maintain wellbeing in response to stress and other environmental challenges. Nonetheless, most evidence for its utility comes from circumstances where the brain is required to function beyond its maximum capacity. Whether limitations are reached because of ageing, illness, or injury, cognitive reserve can then be drawn upon to minimise functional impairment.

A concrete example of the importance of cognitive function in predicting health and wellbeing is the surprisingly large effect it has on longevity. On 1 June 1932, a general ability test was given to all children aged 11 in Scottish schools. Follow-up of children who took part has shown that childhood ability score clearly predicts the likelihood of surviving to age 79 (Whalley and Deary, 2001). A 15-point lower ability score in childhood reduces the likelihood of being alive 65 years later to 79%, and a 30-point lower score reduces it to 63%. (In fact, this is probably an underestimate of the magnitude of the effect, since many of the deaths in the cohort occurred during the Second World War, and are presumed unrelated to childhood ability).

Further analysis of these data has shown that lower IQ is linked to a range of causes of death, including cardiovascular and coronary heart disease, and lung cancer (Hart et al., 2003). These associations remain after controlling for socioeconomic status. Lifestyle and health behaviours such as diet, exercise and smoking are clearly likely to play a role (Gottfredson and Deary, 2004). This is supported by evidence that early-life physical activity is positively correlated with later-life cognitive performance (Dik et al., 2003).

The role of cognitive reserve has recently been studied in a wide-range of disorders including epilepsy (Oyegbile et al., 2004; Pai and Tsai, 2005), multiple sclerosis (Cader et al., 2005), and sleep apnea-related cognitive deficits (Alchanatis et al., 2005). While it has not yet been extensively investigated in neuropsychiatric conditions, it has been implicit, for example, in the large body of work assessing premorbid intelligence and risk for schizophrenia (Aylward et al., 1984). We have recently argued that cognitive reserve may also be relevant to understanding individual differences in symptomatology and functional outcome in schizophrenia (Barnett et al., 2006).

The role of cognitive reserve in disorders such as Alzheimer's disease may be different from its role in normal cognitive ageing. In AD, environmental factors such as diet (Luchsinger and Mayeux, 2004) and toxic exposures (Flaten, 2001) may affect the risk for disorder, while other factors such as education, affect the level of cognitive reserve. The degenerative nature of AD means that cognitive reserve is thought of primarily as a protection against the onset of dementia. However, in the case of acute brain injury, cognitive reserve may work both to protect against cognitive impairment, and as cognitive compensation, in recovery of function.

## **5. Fixed and changeable aspects of cognitive reserve**

Cognitive reserve is a component of mental capital that has both innate and malleable aspects.

Innate aspects include those features of 'hardware' that are genetically or neonatally programmed. For example, in the general population, larger head circumference is associated with less decline in memory in old age (Gale et al., 2003).

However, other aspects of reserve are clearly malleable: individuals with more education have been shown to have greater brain weight, larger neurons and increased arborisation of neurons (Katzman et al., 1988; Mortimer, 1997). The structure of the central nervous system is sensitive to functional factors such as occupation. This was recently demonstrated in a widely-reported study showing that taxi drivers, who use contextual spatial memory a great deal, exhibit changes in the topographical organisation of the hippocampus (Maguire et al., 2000).

Two recent, systematic reviews demonstrate the significance of various proxies of cognitive reserve, including education, occupation, premorbid IQ and mental activities. Valenzuela and Sachdev (2006c) compiled evidence from cohort studies involving more than 29,000 individuals and found that higher reserve was associated with a 46% decreased risk of dementia over a median of seven years follow-up. Interestingly, complex mental activity in later life was associated with lower dementia, independent of other lifelong predictors such as education and occupation, and according to a dose-response relationship. A second review of a further 47,000 individuals showed that multiple measures of reserve similarly predicted cognitive decline, as opposed to dementia (Valenzuela and Sachdev, 2006b). It should be noted that the overall magnitude of the effect in the general population may be substantially smaller than this, and is difficult to estimate since individuals who are at the highest risk of dementia are unlikely to be enrolled in, and likely to drop out of, complex mental activities or education. In addition, the cognitive benefits of complex activity are in reducing relative, rather than absolute, risk for dementia or cognitive decline. Nonetheless, even small effects may be important when considered at the population level, in that they would reduce the number of individuals who pass a threshold of cognitive impairment, and help to reduce the financial cost of dementia.

Although cognitive reserve can be manipulated in adult life, its development in early life may also be important. Studies from the 1946 British birth cohort (Richards et al., 2004) showed that both childhood IQ (measured at age 15) and adult verbal ability (measured with the National Adult Reading Test – NART – at age 53) were negatively correlated with decline in memory and processing speed between ages 43 and 53 years. These relationships were independent of the effects of educational attainment and social class and suggest that the protective effect of ability can both arise during childhood or be attained during adulthood.

Richards and Sacker (2003) attempted to model the relative contributions of childhood IQ, educational attainment and adult occupation to adult cognitive reserve, again defined using NART scores at age 53. They found the strongest relationship was with childhood cognition, with educational attainment showing an intermediate effect, and adult occupation the weakest. This pattern is probably not limited to IQ: similar relationships were found for verbal memory and psychomotor outcomes in adulthood.

Interestingly, while paternal occupation was a good predictor of childhood attainment, its effect on cognitive reserve was negligible, supporting the notion that individual ability is more important than socio-economic factors or background.

## **6. Methods for boosting cognitive reserve**

Epidemiological evidence (Verghese et al., 2003; Wilson et al., 2002) shows that taking part in cognitively stimulating activities benefits general cognitive functioning and reduces risk of dementia. However, these observational studies are limited because cognitive ability may influence an individual's choice of activities. Stronger evidence is therefore gained from intervention studies.

For example, a single-blind, randomised controlled trial in 2,832 independently-living volunteers aged 65 to 94 years found that cognitive training improved the targeted cognitive ability over a two-year period compared with the baseline performance. However, the effects appear limited to the targeted domain: there was no improvement in other cognitive capacities (Ball et al., 2002). This study is one of the largest yet published but it should be noted that some studies have found more modest effects (Spector et al., 2003), and that the short-term benefits of cognitive training have in some cases failed to persist (Orrell et al., 2005).

Cognitive functions decline at different rates (Singer et al., 2003). Any demonstration that programmes of complex mental activity can reduce cognitive decline must therefore be interpreted in the light of the generalisability of such results from specific domains to broader aspects of cognitive and global function.

Five-year follow-up of the Ball et al. trial showed that training in reasoning, but not processing speed or memory domains, was associated with less difficulty in the activities of daily living (Willis et al., 2006).

Longitudinal observational studies have shown that voluntary physical activity appears to protect against cognitive decline (Studenski et al., 2006). Again, such studies may be confounded by volunteer characteristics, unmeasured personality influences, and reverse causation. The stronger evidence, therefore, arises from studies where individuals are randomly assigned to a fitness intervention or a control condition, and the cognitive effects are subsequently assessed.

Colcombe and Kramer (2003) performed a meta-analysis of 18 such studies, comprising nearly 200 older individuals who undertook cognitive testing both before and after a fitness programme. Fitness training was found to have robust effects on cognitive function, but these were relatively selective, with the largest improvements found in executive control processes. The effects appeared larger in women and in 'middle old' individuals aged 66 to 70 years.

Another potential way to enhance cognitive function is by pharmacological means (Duka et al., 2007; Jones et al., 2007). While substances such as caffeine are routinely used by the general population for exactly this purpose, there are obvious ethical dilemmas regarding the acceptability and safety of any widespread use of cognitive-enhancing drugs (Turner and Sahakian, 2006).

Many substances, including common stimulants such as caffeine, show benefits for cognition in healthy volunteers (Academy of Medical Sciences, 2008; Turner et al., 2003). Evidence from neuroimaging studies suggests that they may act by inducing more efficient use of neural circuitry (Furey et al., 2000; Mehta et al., 2000). The long-term benefits of any currently-available or future drugs in those at risk of dementia is currently unknown and is at this point purely speculative. Nonetheless, the development of pharmacogenetics may enable targeting of genetically suitable individuals and minimisation of possible side-effects such that cognitive-enhancing drugs may one day prove a safe and viable approach to boosting mental capital (Academy of Medical Sciences, 2008).

While most cognitive enhancers are currently used only experimentally, a more immediate innovation might be the introduction of food supplements as a means of boosting cognitive reserve in high-risk groups. A recent Dutch study following 818 men and women aged 50-70 years for three years showed that an 800mg daily folic acid supplement significantly reduced cognitive decline in memory, processing speed and sensorimotor speed (Durga et al., 2007).

## **7. Biological basis of cognitive reserve**

The neural basis of cognitive reserve is currently poorly understood. One idea is that cognitive reserve represents the ability to 'optimise or maximise performance through differential recruitment of brain networks' (Stern, 2002, p451). Indeed, imaging studies have shown differential neural activation in high *versus* low reserve individuals when performing cognitive tasks (Habeck et al., 2003; Scarmeas and Stern, 2003; Stern et al., 2003).

However, it is unclear whether these distributed patterns are specific to the particular task investigated or if they are more generalisable. Indeed, since cognitive reserve was developed as an explanation for the apparent lack of relationship between neural abnormality and outcome, it is perhaps unlikely that the mechanisms underlying cognitive reserve can be attributed to particular brain regions, systems or neurotransmitters, at least with the resolution of current techniques. Moreover, the neural basis of cognitive reserve may, by definition, change with age since it may involve the recruitment of alternative neural regions or networks to compensate for age-related cognitive decline (Cabeza et al., 2002; Scarmeas et al., 2003).

Studies in animals provide insight into the biological effects of enriched environments (analogous to increased mental activity), or enhanced voluntary physical activity (such as wheel-running in rodents). Rodents raised under these conditions appear to show increased neural and vascular cell proliferation, increased numbers and functioning of synapses (Studenski et al., 2006).

Recent studies have compared the growth of new nerve and stem cells in adult mice exposed to increased physical, social or mental activity. Compared with other activities, running promoted the greatest increase in stem cell proliferation and differentiation and increased the survival of new cells, as well as improving learning (van Praag et al., 1999a; 1999b). Cortical neurogenesis as a consequence of physical activity has also been demonstrated in rats and non-human primates (Studenski et al., 2006).

It is not yet clear to what extent these changes demonstrated in animal models can be directly translated to humans. Nonetheless, they are an important step in understanding the neural basis of interventions to enhance cognitive function.

One further avenue of exploration is that of the genetic basis of cognitive decline and, conversely, of cognitive reserve. While some candidate genes have been suggested (e.g. Deary et al., 2002), few have been universally replicated. Nevertheless, genetic variation is likely to play a contributing role both in itself, and through interactions with environmental exposures (Lee, 2003).

## **8. Applications and the future of cognitive reserve**

Increasing understanding of cognitive reserve has potential benefits in both health and illness. Improving an individual's cognitive ability, or reducing their cognitive decline, even modestly, could have significant long-term social and financial benefits by delaying dementia (Brookmeyer et al., 1998).

The concept of cognitive reserve has been described as a 'catalyst for research' (Stern, 2003). However, it is a relatively recent innovation, and further research is required to clarify many aspects of its utility and mechanisms.

The evidence presented above suggests a number of ways in which cognitive reserve could be boosted, at a population or individual level of intervention.

In terms of increasing mental capital by improving cognitive reserve, it is not yet clear which of the many interventions is most effective, nor which is the active component. In fact, multimodal interventions may prove beneficial in humans as they have in other species. In dogs, for example, a combination of behavioural and dietary supplements is more effective than either intervention alone, in terms of influencing both cognitive functioning and neuroanatomy (Milgram et al., 2006).

Large, multi-arm studies are necessary to assess the applicability of multimodal interventions in humans. Such studies would both inform the feasibility of widespread attempts to improve cognitive reserve, and help to pin down the active components of any such interventions.

Another need, currently being addressed, is for better means of measuring lifetime participation in physical and mental activities (Valenzuela and Sachdev, 2006a; Wilson et al., 2003). This may help to counter criticisms of the concept of cognitive reserve by providing more concrete means of measurement and, thus, more specific evidence of its effect.

The idea that, when it comes to cognitive capital, one must 'use it or lose it' (Orrell and Sahakian, 1995) appears to have gained great public acceptance, as evidenced by the speed at which companies have

marketed computer games that purport to keep ageing brains sharp (*Nature Neuroscience* editorial, 2007). Much research remains to be done in order to validate these products, as well as to clarify their mechanisms, but this is unlikely to deter potential customers.

A key challenge for the future is therefore to channel the public's interest in building their cognitive reserve into activities that are most likely to bring long-term benefit.

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