Cognitive reserve is used to explain individual differences in the use of active processes to preserve cognitive function in the presence of brain pathology. Cognitive reserve is difficult to quantify experimentally and studies rely largely on the use of proxy measures such as premorbid IQ, education and occupation. Nevertheless, powerful longitudinal study designs suggest that premorbid IQ modifies the neurodevelopmental process in schizophrenia and modulates the impact of neurodegeneration in dementia. Evidence from intelligence research suggests that dysfunction of a fronto-parietal network has explanatory power for the effect of cognitive reserve in both disorders.

Address
Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London, United Kingdom

Corresponding author: Joyce, Eileen (e.joyce@ucl.ac.uk)

Current Opinion in Behavioral Sciences 2015, 4:142–416
This review comes from a themed issue on Cognitive enhancement
Edited by Barbara J Sahakian and Arthur F Kramer
For a complete overview see the Issue and the Editorial
Available online 21st May 2015
http://dx.doi.org/10.1016/j.cobeha.2015.05.003
2352-1546/© 2015 Elsevier Ltd. All rights reserved.

Introduction
The term ‘reserve’ refers to an unused capacity that can be called upon in times of need and is a concept that has been adopted to explain individual differences in the behavioural response to equivalent brain abnormalities [1]. ‘Cognitive reserve’ is used to explain individual differences in the recruitment of active neural processes to preserve cognition in the face of brain dysfunction. This was initially distinguished from ‘brain reserve’ which refers to individual differences in brain structure, such as brain size, dendritic branching or synapse count, that can affect the threshold for the clinical expression of brain abnormalities [2]. Recent evidence from the study of neural plasticity suggests that this distinction is less clear-cut. Active engagement of cognitive processes has been shown to modify synaptic structure and function beyond the age when the brain is fully developed [3,4]. Brain reserve is therefore not fixed but can accrue with experience thus providing the neural substrate for the employment or even improvement of cognitive reserve throughout life. Stern [2] introduced the term ‘neural reserve’ to refer to the dynamic process by which neural networks mediating cognitive function can be shaped by individual differences not only in genetic endowment but also in life experiences. He suggested that people with high neural reserve may be more efficient in the use of existing cognitive networks to compensate for the impact of neuropathology. A related concept is that of ‘brain maintenance’ proposed by Nyberg and colleagues [5]. This suggests that there are individual differences in the ability to stave off brain changes, the distinction here being one of resilience rather than compensation. Another mechanism that may contribute to cognitive reserve, also proposed by Stern [2], is ‘neural compensation’, which is the ability to activate alternative neural processes in order to overcome the impact of neuropathology.

The concept of cognitive reserve, as an active brain mechanism to preserve cognitive function, emerged from the study of dementia but has subsequently been invoked as an explanation of the variability in outcome for other brain disorders such as multiple sclerosis [6] and acquired brain damage [7–9]. Cognitive reserve also has explanatory power for understanding prognosis in disorders thought to have their roots in abnormal or derailed brain development, such as schizophrenia and affective disorders [10]. In the following sections we focus on recent research as to how cognitive reserve influences the presentation and course of neuropsychiatric disorders at both ends of the life span.

Measuring cognitive reserve
Although the concept of cognitive reserve is intuitively appealing, it remains difficult to quantify experimentally. Early studies linking greater educational attainment, occupational complexity and current leisure activity to lower incident dementia [11,12] suggested that certain life achievements or experiences render individuals more capable of compensating for developing neuropathology. Two meta-analyses incorporating studies up to 2004 suggested that the risk of dementia is decreased by 46% in people with high cognitive reserve defined by these parameters [13,14]. Consequently questionnaires capturing these facets of life experience were developed as measures of cognitive reserve [15–18]. Such tools are useful as they provide a methodology for the uniform collection of pertinent variables across studies. However they are confounded because levels of education, occupation and leisure activity may render individuals more or less susceptible to dementia for other reasons. For example lower education is associated with lifestyles that lead to high blood pressure and type 2 diabetes which in turn increase the risk of cerebrovascular disease and thus
dementia [19**]. In addition, these measures do not help us understand if and how the putative neural processes underpinning cognitive reserve, outlined above, contribute to the variability in outcome in brain disorders.

Acknowledging this, a recent study devised a statistical approach to the measurement of cognitive reserve using the longitudinal cognitive data of over 300 elderly participants from diverse backgrounds [19**]. Cognitive reserve was defined as ‘the difference between an individual’s expected cognitive performance, given a particular level of brain pathology, and their actual cognitive performance’. Latent variable modelling produced a baseline ‘residual’ measure (Mem-R) of episodic memory which was not attributable to individual differences in demographics or MRI brain volumes and accounted for ~50% of the variance in memory function. This measure also fulfilled the predictions of the cognitive reserve hypothesis: Mem-R correlated with premorbid IQ independently of the influence of education and in individuals with higher Mem-R there was a lower risk of converting to dementia and a weaker relationship between cognitive decline and an MRI index of neuropathology (brain atrophy). Importantly, this finding has been replicated and extended in a different cohort [20]. These two studies therefore provide a promising unconfounded method for defining and measuring cognitive reserve which can be used in future to investigate the neural mechanisms underlying individual differences in outcome in various brain disorders.

**Dementia**

Despite the caveats over the use of proxy measures, advances in study design have provided support for the protective effect of cognitive reserve in dementia. Longitudinal cohort studies of middle-aged or elderly participants with normal or mildly impaired cognition can control for confounders and provide a powerful means of determining factors that predict the transition to dementia and how they interact. Additionally, the availability of known biological markers of dementia risk (decreased CSF abeta42, presence of an APOE e4 allele, reduced MRI hippocampal volume and increased uptake of the PET amyloid ligand Pittsburgh compound B) has enabled putative mechanisms of action of cognitive reserve to be explored.

Longitudinal studies have found that more years of education and higher premorbid IQ are associated with a later onset of dementia symptoms [21–23] and, following onset, cognitive decline is faster in those with these indices of higher cognitive reserve [22]. The latter phenomenon has been hypothesised to reflect increasing neuropathological load eventually overriding the protective effect of cognitive reserve. This has now been directly supported by a study showing that more years of education was related to lower CSF abeta42, an index of underlying brain pathology, both at the time of symptom onset and 2 years later [24].

Cross-sectional studies of cortical amyloid binding provide support for the hypothesis that cognitive reserve delays the behavioural expression of Alzheimer neuropathology by finding that a proportion (19%) of cognitively normal elderly adults can have levels of brain amyloid binding as high as people with overt dementia and that years of education can modify the impact of cortical amyloid on the clinical diagnosis of Alzheimer’s disease [25]. The relationship between cortical amyloid binding and cognitive function has also been shown to be weaker in people with greater education level and higher IQ [26].

Whether high cognitive reserve actually modifies Alzheimer’s disease pathology before symptom onset has also been addressed but the evidence is equivocal. Higher premorbid IQ, education and occupation were found in one study to be associated with a slower rate of CSF abeta42 decline over 3 years in elderly cognitively normal people [27] but not in another study using similar measures of cognitive reserve over the same time course [23]. Studies examining the effect of life-long engagement with cognitively stimulating activities, rather than education and IQ, have also produced mixed results. One has found a correlation with hippocampal volume as assessed by serial MRI over 3 years: those with higher scores showing less hippocampal atrophy over time [28]. Greater participation in cognitively stimulating activities, especially in early and middle life, has also been associated with reduced cortical amyloid binding in a cross-sectional study [29]. Although these support the view that cognitive stimulation can modify the Alzheimer pathological process this must be tempered by the finding of another study showing that mid/late life cognitive activity is not associated with either the degree of cortical amyloid deposition or future cognitive decline; better education and occupational attainment did ameliorate the effect of cortical amyloid on cognitive decline but again it did not modify the absolute level of cortical amyloid pathology [30**].

Longitudinal studies agree that indices of cognitive reserve do not modify the impact of the APOE e4 allele on increased risk of Alzheimer’s disease [27,31,32] although one study found that cognitive reserve interacted to enhance the protective effect of the APOE e2 allele [32], an effect in a relative small number of participants that requires replication.

Overall, the existing results from longitudinal studies suggest that high cognitive reserve, albeit assessed by proxy measures, operates at the early stages of dementia by delaying the clinical expression of cognitive impairment. When these studies come to fruition with greater numbers it may be possible to answer the question
of whether life achievements or life style factors impart resilience to the progress of neuropathology as opposed to the ability to compensate for it. Until then the evidence is at best equivocal.

The results of studies which have included autopsies to ascertain the severity of dementia have been systematically and critically reviewed [33] in order to examine the relationship between life style factors, cognition and dementia. This failed to find a direct association between experiential factors, including education, and the degree of Alzheimer or vascular pathology except for one study linking early linguistic ability with the density of neurofibrillary tangles [34]. They found more evidence for a modulatory effect of cognitive reserve in that education, social networks, purpose in life and conscientiousness modified the clinical expression of Alzheimer and cerebrovascular pathology. They also found some support for a mechanism whereby life experiences have an impact on the expression of dementia irrespective of the degree or type of pathology; these included early and late cognitive activity and self-reported social isolation/loneliness. This could be interpreted as support for the neural reserve mechanism. Like the longitudinal studies, autopsy studies are more supportive of the hypothesis that cognitive reserve compensates for underlying dementia pathology rather than slows neuropathological process.

**Psychiatric disorders**

Barnett et al. [10] were the first to hypothesise that cognitive reserve might be an important explanatory factor for the variability in risk, clinical expression and functional outcomes of adult mental illness. Since then several studies have tested this using pre-morbid IQ as an index of cognitive reserve.

In a large epidemiological birth cohort study, the impact of childhood IQ (measured at ages 7, 9, and 11) on mental health outcomes at age 32 was assessed [35]. There was a significant association between lower childhood IQ and higher risk of schizophrenia, major depression and several anxiety disorders. Lower childhood IQ was also found to be a predictor of greater co-morbidity in adulthood. Other large longitudinal cohort studies have examined the effect of IQ measured in young adults when they are drafted into the army and these have consistently found that IQ is associated with the later risk and severity of a range of psychiatric disorders [36–38]. There remain areas of controversy as to the association between pre-morbid IQ and adult substance abuse and bipolar disorder [35,36,39,40].

The inverse relationship between risk for schizophrenia and pre-morbid IQ is well established [41] and recent studies find that this effect is stronger than for other forms of mental illness [35,36]. A meta-analysis [42] of methodologically sound cohort studies found a robust linear relationship between pre-morbid IQ and the development of schizophrenia therefore showing that this effect operates across the entire range of intellectual ability. The risk was calculated as an increase of 3.8% for each IQ point decrement. The almost exact same finding of linear risk for schizophrenia with IQ (3.7%) has recently been reported in a single large army conscript study [43**]. This study, which included siblings, also found that high IQ attenuated the impact of genetic liability on schizophrenia risk and that the risk effect of IQ on schizophrenia was stronger in the lower IQ range. Regarding this latter observation, a different large cohort study found a similar effect of low IQ on schizophrenia risk but differed in that there was no effect at all of IQ above the learning disability range [44*]. It is important to resolve this discrepancy as the demonstration of a linear relationship between pre-morbid IQ and risk of developing schizophrenia implies that IQ is a proxy for a fundamental neurobiological process relevant to the causation of schizophrenia.

Over and above the possibility that cognitive reserve contributes to the absolute risk of schizophrenia, other studies suggest that it can moderate outcome. For example, out of a range of variables, IQ at onset of psychosis was shown to be the best predictor of functional outcome 4 years later [45]. More recently this has been supported by a study [46] showing that a cognitive reserve proxy consisting of pre-morbid IQ, educational, occupation and leisure activities, best predicted cognitive performance 2 years following the first episode of psychosis. Previous studies have found that lower pre-morbid IQ is associated with a lower age of schizophrenia onset, suggesting that cognitive reserve can play a role in delaying the onset of schizophrenia which is important because younger onset is associated with worse prognosis. An exception to this comes from recent research into cannabis use. Cannabis users have an earlier age of onset of psychosis than non-users. However they also have a higher pre-morbid IQ than those without a history of cannabis use [47–49]. These findings indicate that cannabis use may be a precipitating factor in the development of psychosis and that it counteracts the normally protective effect of cognitive reserve in delaying onset [47,50].

**Discussion**

The balance of evidence outlined above suggests that cognitive reserve may influence the outcome of brain disorders presenting at the extremes of the lifespan in different ways. For example, pre-morbid IQ appears to modify the neurodevelopmental process in schizophrenia and modulate the clinical expression of neurodegenerative process in Alzheimer’s disease. IQ may be a better reflection of the neural processes implied by the concept of cognitive reserve than, say, occupation or education. Duncan has found that IQ is related to the structure and function of a specific fronto-parietal neural network that
provides the processing requirements for the efficient execution of diverse cognitive tasks [51]. Functional imaging studies of schizophrenia are compatible with this network being dysfunctional in relation to cognitive impairment [41]. Thus a greater understanding of the core functions of this network and how it is influenced genetically and by experience may help elucidate causative mechanisms of schizophrenia [41]. The function of this network may also be relevant to the impact of cognitive reserve on dementia. Duncan and colleagues have shown that when part of this system is damaged there is an increase in activity throughout the system which they suggest reflects either the use of different strategies or the recruitment of more cortex to compensate [52]. Thus although IQ may effect outcomes in different ways in these two disorders, it may still reflect the function of the same neural system. An understanding of whether there is plasticity in the fronto-parietal system that can be modified by life experience would illuminate approaches to the cognitive remediation of both schizophrenia and dementia and have implications for health maintenance in the general public.

**Conflict of interest**
Nothing declared.

**Acknowledgement**
EMJ is supported by the UCLH/UCL Biomedical Research Centre.

**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

20. This study describes a new principled method of defining cognitive reserve.
This is a large longitudinal study which includes biological risk factors for dementia and brain imaging markers of dementia pathology. It refines measures of cognitive reserve by using factor analysis and in the analysis treats early predictors (age, education, occupation) differently from middle and late life cognitive stimulation.


This large cohort study of the effect of IQ in early adulthood on future risk of schizophrenia. The data are enriched by the inclusion of siblings and the interaction between cognitive reserve and genetic liability is addressed as well other question concerning the mechanism of action of IQ in schizophrenia risk.


This study finds that low premorbid IQ confers risk for schizophrenia only in the learning disabilities range with no protective effect in those with above-average IQ.


