# Cognitive reserve in ageing and Alzheimer's disease

*Yaakov Stern*

*Lancet Neurol* 2012; 11: 1006–12

Cognitive Neuroscience Division, Department of Neurology and Taub Institute, Columbia University College of Physicians and Surgeons, New York, NY, USA (Y Stern PhD)

Correspondence to: Dr Yaakov Stern, 630 W 168th Street, P&S Box 16, New York, NY 10032, USA
ys11@columbia.edu

**The concept of cognitive reserve provides an explanation for differences between individuals in susceptibility to age-related brain changes or pathology related to Alzheimer's disease, whereby some people can tolerate more of these changes than others and maintain function. Epidemiological studies suggest that lifelong experiences, including educational and occupational attainment, and leisure activities in later life, can increase this reserve. For example, the risk of developing Alzheimer's disease is reduced in individuals with higher educational or occupational attainment. Reserve can conveniently be divided into two types: brain reserve, which refers to differences in the brain structure that may increase tolerance to pathology, and cognitive reserve, which refers to differences between individuals in how tasks are performed that might enable some people to be more resilient to brain changes than others. Greater understanding of the concept of cognitive reserve could lead to interventions to slow cognitive ageing or reduce the risk of dementia.**

## Introduction

The possibility of a connection between life experience and the prevalence of dementia has long been discussed. In 1981, Gurland[1] wrote "It is still an open matter whether there is an important sociocultural contribution to the prevalence of Alzheimer's and other forms of dementia occurring in the senium, but evidence now available is sufficiently intriguing to warrant further study of the issue". Kittner and colleagues[2] suggested that adjustment should be made for level of education when screening for dementia to avoid ascertainment bias, whereas Berkman[3] suggested that we must remain open to the view that "educational level and/or socioeconomic behavior correlated with it may be a genuine risk factor for senile dementia and are worthy of scientific exploration in their own right". Zhang and colleagues[4] reported that a low level of education was associated with increased prevalence of Alzheimer's disease and dementia in a probability sample survey of 5055 older people not admitted to care facilities in Shanghai, China. These observations sparked my interest in studying the association between aspects of life experience and dementia; subsequently I have undertaken a long-term research programme to investigate cognitive reserve. In this Personal View I present a theoretical account of cognitive reserve, summarise epidemiological research that has lent support to the concept, and describe imaging studies that have attempted to identify the neural substrates of cognitive reserve. I will also discuss the potential clinical implications of the concept of cognitive reserve. Although I discuss cognitive reserve in the context of Alzheimer's disease and normal ageing, it has also been reported to provide benefit in patients with vascular injury,[5–7] Parkinson's disease,[8] traumatic brain injury,[9] HIV,[10] neuropsychiatric disorders,[11] and multiple sclerosis.[12]

## Brain reserve and cognitive reserve

The concept of reserve has been put forward to account for differences between individuals in susceptibility to age-related brain changes and pathology, such as that seen in Alzheimer's disease. Reserve is purported to act as a moderator between pathology and clinical outcome, thus accounting for the discontinuity. A convenient, although somewhat artificial, way to view cognitive reserve is to separate it into two main features: brain reserve and cognitive reserve.

The original concept of brain reserve was quantitative, for example the number of neurons or synapses available to be lost differs among individuals. This idea was supported by study findings that suggested the prevalence or incidence of dementia was lower in individuals with larger brains than in those with smaller brains.[13,14] I suggest that this is a passive model of brain reserve—ie, a large brain might simply be able to tolerate more pathology before it reaches the critical threshold for clinical symptoms to appear. By contrast, cognitive reserve is an active form of reserve in which brain function rather than brain size is the relevant variable. The concept of cognitive reserve suggests that the brain actively attempts to cope with pathology by using pre-existing cognitive-processing approaches or compensatory mechanisms.[15,16] Therefore, an individual with high cognitive reserve would cope better with the same amount of pathology than an individual with low cognitive reserve, even when brain size is the same.

Although the initial concept of brain reserve was entirely quantitative, several studies have suggested wider underlying biological features. For example, stimulating environments have been associated with neurogenesis[17–19] and upregulation of BDNF, which fosters neural plasticity and could impart reserve.[20] Brain reserve and cognitive reserve, therefore, seem to make independent and synergistic contributions to our understanding of individual differences in clinical resilience to brain pathology. Whether the two components of reserve interact remains unresolved.

Cognitive reserve was initially posited as a moderator between brain change and clinical outcome, but life experience may also prevent or minimise brain pathology. On a simple level, physical exercise has long been recognised to help prevent vascular disease. Likewise, participation in cognitively stimulating activities has been suggested to slow the rate of hippocampal atrophy in normal ageing,[21] and perhaps even to prevent

accumulation of amyloid plaques.[22] However, although these ideas are promising and intriguing, they are beyond the scope of this Personal View.

## Epidemiological evidence for cognitive reserve

My colleagues and I first investigated the concept of cognitive reserve in a study of incident dementia, based on the assumption that Alzheimer's disease pathology slowly develops over time independently of cognitive reserve, and that the pathology begins to accumulate many years before the onset of clinically diagnosed Alzheimer's disease (figure 1).[23] Because people with greater reserve should be able to tolerate more Alzheimer's disease pathology, the onset of clinical dementia in these individuals should be delayed. 593 non-demented individuals aged 60 years or older were followed up for more than 4 years. Individuals with less than 8 years of education had 2·2 times higher risk of developing dementia than those with more years of education. Occupational attainment was also assessed, based on US census categories and classified as low (unskilled, semiskilled, skilled trade or craft, and clerical or office worker) or high (manager, business or government, and professional or technical) occupational levels. Participants with low lifetime occupational attainment were at 2·25 times greater risk of developing dementia than those with high lifetime occupational attainment. The implication of these findings was that educational and occupational experiences created a reserve against the effects of Alzheimer's disease pathology. Self-reported participation in various leisure activities in the preceding month were assessed by interview in a set of non-demented elderly participants.[24] The effects of participation in 13 groups of activities were assessed: knitting, listening to music, or other hobby; walking for pleasure or excursion; visiting friends or relatives; being visited by relatives or friends; physical conditioning; going to movies, restaurants, or sporting events; reading magazines, newspapers, or books; watching television or listening to the radio; doing unpaid community volunteer work; playing cards, games, or bingo; going to a club or centre; going to classes; and going to church, synagogue, or temple. Participants were allocated according to low (six or fewer activities) or high (more than six activities) participation in leisure activities. Those who engaged in more than six leisure activities had 38% lower risk of developing dementia than participants who partook in fewer activities. The authors of a review[25] of 22 cohort studies of the effects of education, occupation, premorbid IQ, and mental activities in incident dementia found that most of the studies reported a significant protective effect of these lifetime exposures, and calculated that the protective effect of higher cognitive reserve decreased the risk of developing dementia by 46%.

By contrast, after clinical presentation of Alzheimer's disease, patients with high cognitive reserve show more rapid decline than those with low cognitive reserve.[26,27] We matched patients with Alzheimer's disease according to clinical severity:[26] those with greater educational and occupational attainment died sooner than those with lower attainment. In a subsequent analysis, those with greater educational or occupational attainment had more rapid cognitive decline.[27] On average, scores on memory tests following diagnosis decline by about one point every year in patients with low attainment, but by two points in those with higher attainment.[27,28] A more rapid decline in cognitive function was also seen in patients with Alzheimer's disease who engaged in more leisure activities before the onset of dementia than in those who engaged in few activities.[29] Our theoretical explanation for these findings is that individuals with high cognitive reserve can tolerate more pathology and, therefore, the point at which cognitive functions begin to be affected will be later than in those with lower cognitive reserve. However, in all people a common point is reached when the pathology is so severe that function cannot be maintained (figure 1). According to these assumptions, individuals with the greatest cognitive reserve will have more advanced pathology at the onset of cognitive decline, less time until they reach the point when pathology overwhelms function, and thus a more rapid rate of decline.

Although these epidemiological studies support the concept of cognitive reserve, the evidence is not definitive. Only controlled studies can truly establish whether interventions or experiences are beneficial.

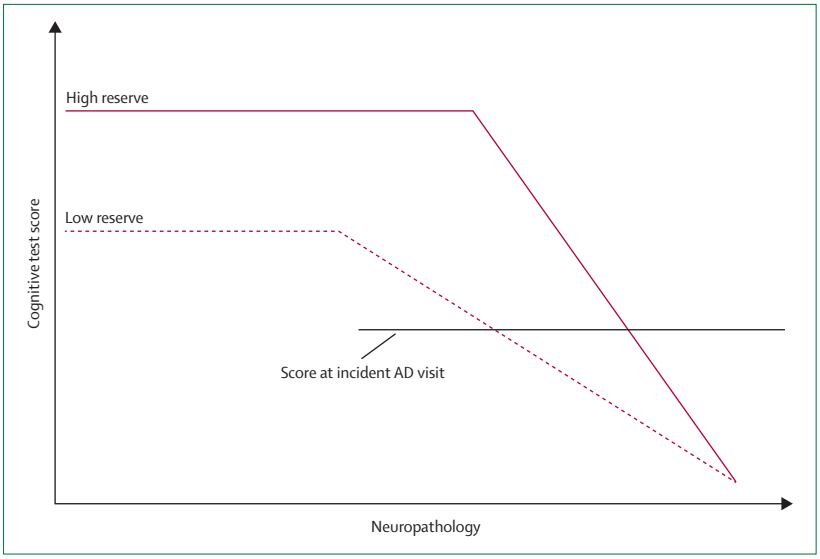


***Figure 1*: Hypothesised change in memory function over time in individuals with high and low cognitive reserve**

AD pathology begins to advance before changes in memory performance are observed. Decline is seen later in individuals with high cognitive reserve because pathology is tolerated longer than by people with low cognitive reserve. The figure shows a hypothetical point at which pathology is so severe that memory performance is nil. This point is the same for individuals with high and low reserve. The rate of decline, however, differs between groups, and is more rapid in individuals with high reserve than in those with low reserve. According to this model, the differential rate of decline is seen irrespective of whether individuals have been diagnosed as having AD before memory has begun to decline. AD=Alzheimer's disease.

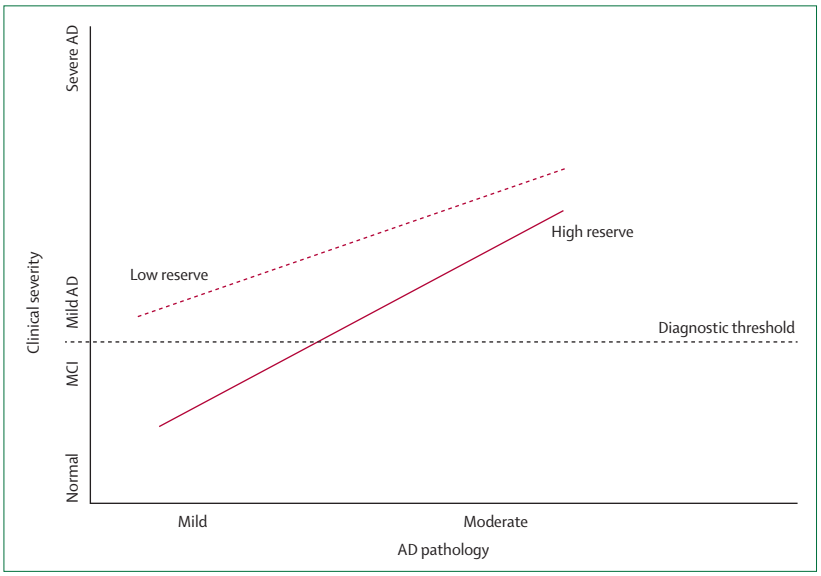


***Figure 2*: Clinical implications of cognitive reserve in patients with AD**
Individuals with low cognitive reserve might seem to be clinically demented when AD pathology is mild, whereas those with higher cognitive reserve might remain clinically normal. At higher levels of pathology, both groups might appear to be clinically demented. Still, those with higher reserve will appear to be less clinically severe than those with lower reserve. AD=Alzheimer's disease. MCI=mild cognitive impairment.

## Neuroimaging studies of cognitive reserve

### Resting regional cerebral blood flow

Epidemiological studies suggest that at any given level of clinical severity in Alzheimer's disease, the degree of pathology will be greater in individuals with higher cognitive reserve than in those with lower cognitive reserve (figure 2). This idea was tested by assessment of resting regional cerebral blood flow as a surrogate for Alzheimer's disease pathology.[30,31] In patients matched for clinical severity, an inverse relation was found between resting regional cerebral blood flow and years of education.[32] Higher level of education was associated with greater depletion of blood flow in the parietotemporal area (figure 3), where PET changes are seen in patients with Alzheimer's disease. This observation provided an initial indication that patients with higher cognitive reserve had more Alzheimer's disease pathology than those with lower cognitive reserve even though they appeared clinically similar. Similar associations have been shown for occupational attainment and leisure activities,[33–36] and a post-mortem study confirmed the relation with education.[37] The investigators examined at autopsy the brains of 130 elderly patients who had undergone cognitive assessment about 8 months before death. Education and a summary measure of Alzheimer's disease pathology (mean standardised density of neuritis and diffuse plaques and neurofibrillary tangles) were associated with cognitive performance, and education modified the association between Alzheimer's disease pathology and levels of cognitive function: for each additional year of education, the relation between Alzheimer's disease pathology and cognition was reduced by 0·088 standard units. Thus, at any given level of brain pathology, higher education was associated with better cognitive function.

### Neural mechanisms

The cognitive or neural mechanisms that might underlie the reserve against age-related or Alzheimer's disease-related pathology are unknown. Functional imaging has been used to try to identify networks that might mediate cognitive reserve. On the basis of these studies, I propose that neural implementation of cognitive reserve might take two forms: neural reserve and neural compensation.[16,38] Neural reserve is the idea that cognitive reserve could be associated with differences between individuals in the resilience of pre-existing cognitive networks, and neural compensation is the idea that some individuals might be better than others at using compensatory mechanisms.

The key idea behind neural reserve is that cognitive reserve might be mediated by the same networks that are used by individuals in the absence of pathology related to age or disease. For example, the differential efficiency or capacity of these networks could account for variation between individuals in performance and the ability to cope with brain changes. In a functional MRI (fMRI) study, network efficiency and capacity were assessed in young (age 20–29 years) and old (age 60–69 years) adults.[39] The extrinsic difficulty of a task was manipulated by shortening of the response deadline. Covariance analysis of the imaging data showed a spatial pattern of activation in young and old adults that increased as the deadlines shortened. The spatial pattern was expressed to a greater degree by the older adults when the deadline was longest. By contrast, the young adults' pattern expression was greater than the older adults' at the shorter deadlines when the task was most difficult. This finding is consistent with the idea that network efficiency and capacity are reduced with increasing age. Differences in efficiency and capacity were also noted among individuals within each age group; therefore, individuals with more efficient or higher-capacity networks could have more resilience in the face of age-related or disease-related changes.

Neural reserve and neural compensation were also assessed in a series of imaging studies.[40,41] Young (mean age 25·1 years) and older (74·4 years) healthy adults were assessed with the letter Sternberg task. In this task, participants study one, three, or six letters for 3 seconds (stimulus phase) followed by a 7-second retention phase. They are then presented with a single probe letter and are asked to indicate whether it was included in the previously studied set. fMRI analyses were used to assess load-related activation: the aspects of activation that change as the number of letters studied increases. Multivariate linear modelling showed that load-related activation during the retention phase was characterised by two networks of brain regions that seemed to work together as the task got harder,[40] as inferred by an increase in fMRI signal. The

first network was used by both the young and elderly adults and involved areas often associated with working memory (eg, midline cerebellum and left insula/inferior frontal gyrus). The second network was primarily characterised by activation in parahippocampal areas and was used consistently only in the elderly group. The elderly adults who used the second network the most had the worst performance in the task. In a follow-up analysis atrophy in a key area within the first network (the left precentral gyrus) was associated with decreased efficiency in that network and increased use of the second network.[41] This observation might be an example of neural compensation—ie, as age-related changes limit the efficiency of the first network, the second network becomes increasingly used. Although those who rely more on the compensatory network can still perform the task, they do so less successfully than those who rely on the first network. A further analysis[42] identified two potential influences of cognitive reserve (as measured by intelligence quotient [IQ]) in these individuals. First, the individuals with high cognitive reserve could tolerate more atrophy in the first network and still preserve performance without having to resort to using the second network. Second, individuals with high cognitive reserve did better in the letter Sternberg task, even when they use the second network, than those with low cognitive reserve.[42] This finding suggests that patients with high cognitive reserve can make use of resources that are separate from those directly involved in task performance, and is consistent with the idea that generalised neural representation of cognitive reserve could impart protection across a wide range of tasks. To investigate the possibility of a generalised neural representation of cognitive reserve, imaging data acquired during the stimulus-presentation phase of two different tasks with different cognitive demands were analysed. In young adults, an activation network was identified, in which expression increased with increasing load-related activation and correlated with high cognitive reserve.[43] This type of network could be an example of the neural instantiation of cognitive reserve. In the future, identification of neural patterns of activation that are associated with generic cognitive reserve could provide direct ways of measuring the level of reserve in any individual. Furthermore, a quantifiable neural pattern for cognitive reserve might lead to stratification of outcomes in studies of pharmacological and non-pharmacological approaches to improve cognitive functioning.

## Application of cognitive reserve in clinical assessment

When cognition is assessed as part of a diagnostic work-up, the most appropriate validated indicators of cognitive reserve for each patient—such as educational or occupational attainment—should be used. In the event that an individual's level of education is not believed to be a good representation of his or her optimum cognitive functioning, assessment of IQ or consideration of occupation might be useful.

Individuals with high cognitive reserve, by definition, will present with disease-related clinical symptoms later than individuals with low cognitive reserve. This difference could be identified in individuals with high cognitive reserve by the use of more challenging tests or tests that are more specific for particular pathology (eg, associative learning tasks for the hippocampus). Clinicians must, however, be aware that even in individuals with underlying pathology there will still be a period during which sensitive measures cannot detect cognitive changes in patients with high cognitive reserve.

Information on brain structure integrity could be integrated with cognitive data for diagnostic purposes. Neuroimaging tools have the potential to detect pathological changes when only slight impairment is indicated by neuropsychological testing, particularly in individuals with high cognitive reserve who maintain cognitive functioning for an extended period of time. For example, at a given level of clinical severity in patients with Alzheimer's disease, higher levels of

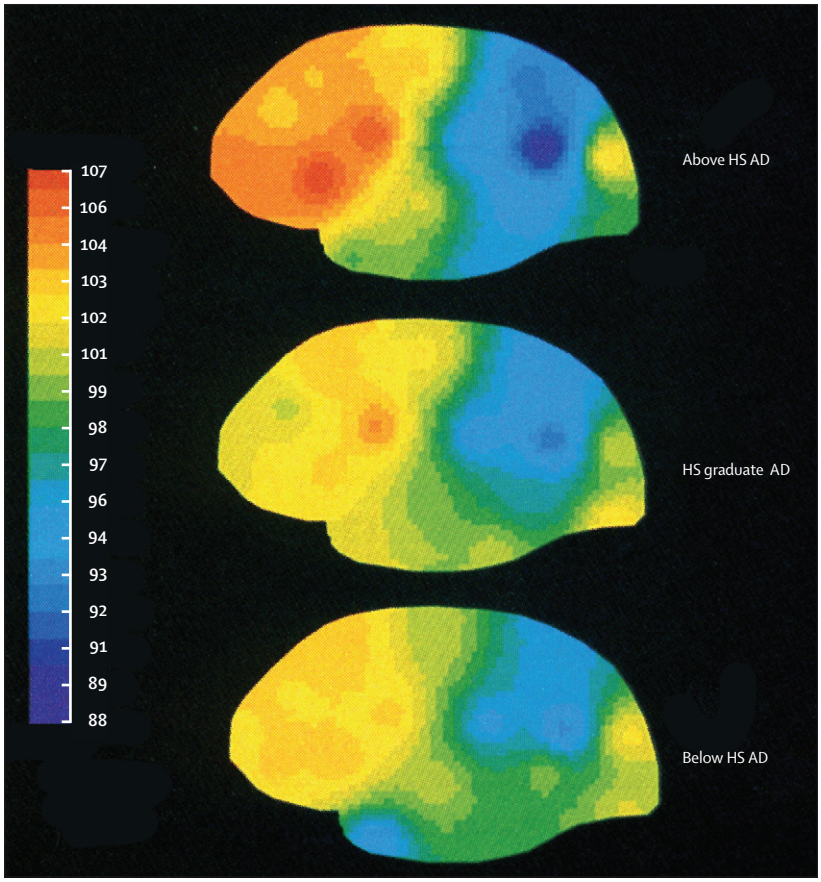


***Figure 3*: Cerebral blood flow as a proxy for AD pathology in patients with different levels of education**
Each group comprised 20 AD patients matched for clinical severity based on assessments of mental status and activity of daily living scores. The lowest blood flow (dark blue) was seen in the parietotemporal areas of patients with the highest educational level, which indicates the most advanced AD pathology. AD=Alzheimer's disease. HS=high school. Reproduced from Stern et al,[32] by permission of John Wiley and Sons.

education are associated with more severe disease-related changes on PET scans than seen for those with lower levels of education.[44,45]

Integration of the cognitive reserve concept into the interpretation of biomarker imaging, however, is premature. Although the presence of amyloid in the brain can be detected with PET or testing of CSF, the prognostic implications of these tests are not fully established. These biomarkers could, however, provide fruitful avenues for research into cognitive reserve.

Cognitive reserve should also be recognised as a factor that will affect the rate of cognitive decline after diagnosis. The rate of decline after clinical onset is more rapid in individuals with high reserve than in those with low reserve, even when other factors that might contribute to the disease course are taken into account.[27,28,46] This effect has direct relevance for assessing the efficacy of potential treatments in clinical trials, because the response to a particular medication might be altered by the degree of underlying pathology. Additionally, most clinical trials are designed to compare rates of decline between treatment and control groups. A mismatch in cognitive reserve across groups could lead to differences in the rates of decline that have nothing to do with the study drug.

Finally, epidemiological evidence that links specific life experiences and individual characteristics to reduced risk of dementia is insufficient to show definitively whether these have any direct preventive or delaying effects. Intervention studies are needed to firmly establish causal links between these features and cognitive reserve. In the meantime, patients should be recommended to engage in mental and physical activities that are unlikely to be harmful, and clinicians should be careful not to present these activities as established treatments or proven preventive strategies against dementia.

## Cognitive reserve in remediation and prevention

Epidemiological evidence suggests that experiences at all stages, even in later life, can contribute to cognitive reserve. Intervention might, therefore, be useful even in elderly patients to impart or maintain reserve, slow age-related cognitive decline, and prolong healthy ageing. The most successful remediation approach so far has been aerobic exercise. Controlled studies have shown that in elderly individuals with respiratory capacity below the median at baseline, aerobic exercise increases respiratory capacity and cognitive performance.[47,48] Cognitive intervention studies, however, have had mixed results. In one large study, participants received training in one of three cognitive domains: memory, reasoning, and speed of information processing. Training in one cognitive domain did not affect outcomes in the two other domains. Additionally, training did not result in any improvement in formal measures of everyday function.[49]

Studies that involve participants in complex gameplay have shown promise. For example, Basak and colleagues[50] assessed elderly people who played a complex role-playing computer game for fifteen 1·5-h training sessions in the laboratory in a period of 4–5 weeks, resulting in a total training time of 22·5 h. They reported improved performance in a wide range of cognitive tasks. Similarly, focused computerised training improved working memory capacity and extended working memory to tasks in which participants received no training.[51] The limitations and promise of various cognitive interventions in relation to lifelong learning and ageing have been set out by a working group.[52]

A complex computer game designed by human operations psychologists has been used to test different approaches to training young adults in complex tasks.[53] One approach, called emphasis-change training, improved gameplay and enabled extension of training to other tasks. Players were instructed to focus on all of the features of the game, but to give particular attention to one feature per game and to change to a different feature each time they played. For example, in some games they were instructed to control the ship that they were piloting, but in others they attended more to destroying mines that appeared occasionally on the screen. By shifting emphasis from game to game, participants did not fall into a fixed strategy. Rather, they developed the ability to deal with the task as a whole. This approach could be termed attention allocation or executive control. By using this approach, young adults were able to use the training to incorporate a demand and simultaneously do an additional task, while playing the game.[54] Ability in real-world training tasks (eg, performance in flight simulator training) was also improved.[55,56] In a preliminary study the ability of older adults (mean age 66 years) to learn to play the game, and the possibility that gameplay might improve cognitive performance were investigated.[57] 90 individuals were assigned to three groups: no playing, playing the game without emphasis-change training, and playing the game with emphasis-change training. In the two game groups participants played three times per week for 12 weeks. Although the game was challenging for the elderly participants, only six dropped out of the study and gameplay performance improved with time in those who completed the study. Players in the no-emphasis-change group were less focused on the key goals of the game than those in the emphasis-change group; they were more likely to respond to opportunities for bonus-point rewards than to consider strategy. By contrast, players in the emphasis-change group focused more on the central features of the game and on achieving the overall goal of attacking and destroying the fortress. The primary cognitive measures assessed were five tasks that involve executive control: trail-making test, letter-number sequencing test, Stroop colour and word test, set-switching task, and flanker task. On one of these tasks, a test of working memory, emphasis-change training was associated with greater improvement in working memory from baseline than in the other two training groups. On the basis of these findings, a study has

been started to assess the effects of playing complex games in conjunction with aerobic exercise, with the hope of showing a synergistic effect through a boost in brain reserve from exercise (eg, by improving plasticity via upregulation of BDNF) and a rise in cognitive reserve by increasing the efficiency of the cognitive networks underlying executive control.

How life experience contributes to the creation of cognitive reserve and protection against age-related and disease-related pathology remains unknown. Focused but large-scale studies are required to formulate specific recommendations. The most meaningful endpoints would be slowed rate of age-related decline in cognitive function or reduced risk of developing Alzheimer's disease. No study has yet shown effects on either of these endpoints. The optimum cohorts would include elderly people with intact cognitive function followed up for years. Studies could, and probably should, involve several interventions, including exercise, cognitive stimulation, and social stimulation. A drawback of such studies is that they would be very expensive, will require a large number of participants, and will have to be conducted over several years. In the meantime, a general recommendation is to continue educational and mentally stimulating activities throughout life.[58]

## Conclusions

The concept of cognitive reserve arose from epidemiological observations. Various life exposures seem to be associated with resilience against age-related or pathology-related impairment of cognitive function. The original observations indicated the involvement of easily measurable variables, such as education or occupational attainment, but other lifestyle factors, for instance behaviours that stimulate cognition, personality, and so on, also seem to be important. Overall contributions to reserve most likely come from multiple sources, and cognitive reserve might, therefore, change across an individual's lifespan dependent on exposures and behaviours. This idea suggests that changes in lifestyle and interventions might be useful to delay age-related cognitive decline or dementia. Epidemiological studies, however, only describe correlations and do not test causation, and carefully controlled studies will be required to assess the effects of practical interventions.

The desire to understand the neural basis of cognitive reserve has been a motivating factor behind functional imaging studies. The findings might contribute to the understanding of age-related changes in brain behaviour and could lead to targeted interventions. Direct neural measures of cognitive reserve, perhaps based on patterns derived from fMRI, would be very useful.

The concept of cognitive reserve could be applied during clinical assessment. The association between high cognitive reserve and rapid decline in patients with Alzheimer's disease makes it important to include this factor in diagnostic formulations and in clinical trials that compare rates of decline between drugs and control. Again, a directly measurable neural correlate of reserve, such as an fMRI pattern, would be useful. More generally, consideration of cognitive and brain reserve will be helpful in the development of systems-based approaches to understanding brain changes. Since the brain passively and actively attempts to cope with brain changes or pathology, the factors that contribute to resilience need to be understood.

### Search strategy and selection criteria

This Personal View focuses primarily on the work of the author and his group since 1992. It does not represent an exhaustive literature review on this topic. Other included articles were already known to the author and are intended to support points made in the discussion.

**Conflicts of interest**

I declare that I have no conflicts of interest.

**Acknowledgments**

This work was funded by NIA RO1 AG14671.

**References**

1 Gurland B. The borderlands of dementia: the influence of sociocultural characteristics on rates of dementia occurring in the senium. *Aging* 1981; **15:** 61–84.

2 Kittner SJ, White LR, Farmer ME, et al. Methodological issues in screening for dementia: the problem of education adjustment. *J Chronic Dis* 1986; **39:** 163–70.

3 Berkman LF. The association between educational attainment and mental status examinations: of etiologic significance for senile dementias or not? *J Chronic Dis* 1986; **39:** 171–74.

4 Zhang M, Katzman R, Salmon D, et al. The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender and education. *Ann Neurol* 1990; **27:** 428–37.

5 Elkins JS, Longstreth WT, Manolio TA, Newman AB, Bhadelia RA, Johnston SC. Education and the cognitive decline associated with MRI-defined brain infarct. *Neurology* 2006; **67:** 435–40.

6 Dufouil C, Alperovitch A, Tzourio C. Influence of education on the relationship between white matter lesions and cognition. *Neurology* 2003; **60:** 831–36.

7 Dufouil C, Alperovitch A, Ducros V, Tzourio C. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. *Ann Neurol* 2003; **53:** 214–21.

8 Glatt SL, Hubble JP, Lyons K, et al. Risk factors for dementia in Parkinson's disease: effect of education. *Neuroepidemiology* 1996; **15:** 20–25.

9 Kesler SR, Adams HF, Blasey CM, Bigler ED. Premorbid intellectual functioning, education, and brain size in traumatic brain injury: an investigation of the cognitive reserve hypothesis. *Appl Neuropsychol* 2003; **10:** 153–62.

10 Farinpour R, Miller EN, Satz P, et al. Psychosocial risk factors of HIV morbidity and mortality: findings from the Multicenter AIDS Cohort Study (MACS). *J Clin Exp Neuropsychol* 2003; **25:** 654–70.

11 Barnett JH, Salmond CH, Jones PB, Sahakian BJ. Cognitive reserve in neuropsychiatry. *Psychol Med* 2006; **36:** 1053–64.

12 Sumowski JF, Chiaravalloti N, Deluca J. Cognitive reserve protects against cognitive dysfunction in multiple sclerosis. *J Clin Exp Neuropsychol* 2009; **31:** 913–26.

13 Katzman R, Robert T, DeTeresa R, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol* 1988; **23:** 138–44.

14 Schofield PW, Logroscino G, Andrews H, Albert S, Stern Y. An association between head circumference and Alzheimer's disease in a population-based study of aging. *Neurology* 1997; **49:** 30–37.

15 Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 2002; **8:** 448–60.

16 Stern Y. Cognitive reserve. *Neuropsychologia* 2009; **47:** 2015–28.
17 Brown J, Cooper-Kuhn CM, Kemperman G, van Praag H, Winkler J, Gage FH. Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. *Eur J Neurosci* 2003; **17:** 2042–46.
18 van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA* 1999; **96:** 13427–31.
19 van Praag H, Kemperman G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 1999; **2:** 266–70.
20 van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. *Nat Rev Neurosci* 2000; **1:** 191–98.
21 Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS One* 2008; **3:** e2598.
22 Landau SM, Marks SM, Mormino EC, et al. Association of lifetime cognitive engagement and low β-amyloid deposition. *Arch Neurol* 2012; published online Jan 23. DOI:10.1001/archneurol.2011.2748.
23 Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 1994; **271:** 1004–10.
24 Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology* 2001; **57:** 2236–42.
25 Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. *Psychol Med* 2005; **25:** 1–14.
26 Stern Y, Tang MX, Denaro J, Mayeux R. Increased risk of mortality in Alzheimer's disease patients with more advanced educational and occupational attainment. *Ann Neurol* 1995; **37:** 590–95.
27 Stern Y, Albert S, Tang MX, Tsai WY. Rate of memory decline in AD is related to education and occupation: cognitive reserve? *Neurology* 1999; **53:** 1942–57.
28 Scarmeas N, Albert SM, Manly JJ, Stern Y. Education and rates of cognitive decline in incident Alzheimer's disease. *J Neurol Neurosurg Psychiatry 2006;* **77:** 308–16.
29 Helzner EP, Scarmeas N, Cosentino S, Portet F, Stern Y. Leisure activity and cognitive decline in incident Alzheimer disease. *Arch Neurol* 2007; **64:** 1749–54.
30 Friedland RP, Brun A, Budinger TF. Pathological and positron emission tomographiccorrelations in Alzheimer's disease. *Lancet* 1985; **325:** 228.
31 McGeer EG, Peppard RP, McGeer PL, et al. $^{18}$Fluorodeoxyglucose positron emission tomography studies in presumed Alzheimer cases, including 13 serial scans. *Can J Neurol Sci* 1990; **17:** 1–11.
32 Stern Y, Alexander GE, Prohovnik I, Mayeux R. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Ann Neurol* 1992; **32:** 371–75.
33 Stern Y, Alexander GE, Prohovnik I, et al. Relationship between lifetime occupation and parietal flow: implications for a reserve against Alzheimer's disease pathology. *Neurology* 1995; **45:** 55–60.
34 Scarmeas N, Zarahn E, Anderson KE, et al. Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. *Arch Neurol* 2003; **60:** 359–65.
35 Alexander GE, Furey ML, Grady CL, et al. Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. *Am J Psychiatry* 1997; **154:** 165–72.
36 Perneczky R, Drzezga A, Ehl-Schmid J, et al. Schooling mediates brain reserve in Alzheimer's disease: findings of fluoro-deoxy-glucose-positron emission tomography. *J Neurol Neurosurg Psychiatry* 2006; **77:** 1060–63.
37 Bennett DA, Wilson RS, Schneider JA, et al. Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology* 2003; **60:** 1909–15.
38 Stern Y, Habeck C, Moeller J, et al. Brain networks associated with cognitive reserve in healthy young and old adults. *Cereb Cortex* 2005; **15:** 394–402.
39 Stern Y, Rakitin BC, Habeck C, et al. Task difficulty modulates young-old differences in network expression. *Brain Res* 2012; **1435:** 130–45.
40 Zarahn E, Rakitin B, Abela D, Flynn J, Stern Y. Age-related changes in brain activation during a delayed item recognition task. *Neurobiol Aging* 2007; **28:** 784–98.
41 Steffener J, Brickman AM, Rakitin BC, Gazes Y, Stern Y. The impact of age-related changes on working memory functional activity. *Brain Imaging Behav* 2009; **3:** 142–53.
42 Steffener J, Reuben A, Rakitin BC, Stern Y. Supporting performance in the face of age-related neural changes: testing mechanistic roles of cognitive reserve. *Brain Imaging Behav* 2011; **5:** 212–21.
43 Stern Y, Zarahn E, Habeck C, et al. A common neural network for cognitive reserve in verbal and object working memory in young but not old. *Cereb Cortex* 2008; **18**: 959–67.
44 Garibotto V, Borroni B, Kalbe E, et al. Education and occupation as proxies for reserve in aMCI converters and AD: FDG-PET evidence. *Neurology* 2008; **71:** 1342–49.
45 Kemppainen NM, Aalto S, Karrasch M, et al. Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. *Ann Neurol* 2008; **63:** 112–18.
46 Hall CB, Derby C, LeValley A, Katz MJ, Verghese J, Lipton RB. Education delays accelerated decline on a memory test in persons who develop dementia. *Neurology* 2007; **69:** 1657–64.
47 Angevaren M, Aufdemkampe G, Verhaar H, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev* 2008; **2:** CD005381.
48 Kramer AF, Hahn S, Cohen NJ, et al. Ageing, fitness and neurocognitive function. *Nature* 1999; **400:** 418–19.
49 Jobe JB, Smith DM, Ball K, et al. ACTIVE: a cognitive intervention trial to promote independence in older adults. *Control Clin Trials* 2001; **22:** 453–79.
50 Basak C, Boot WR, Voss MW, Kramer AF. Can training in a real-time strategy video game attenuate cognitive decline in older adults? *Psychol Aging* 2008; **23:** 765–77.
51 Klingberg T. Training and plasticity of working memory. *Trends Cogn Sci* 2010; **14:** 317–24.
52 The Royal Society. Brain waves module 2: neuroscience: implications for education and lifelong learning. http://royalsociety.org/uploadedFiles/Royal_Society/Policy_and_Influence/Module_2_Neuroscience_Education_Full_Report_Printer_Friendly.pdf (accessed Sept 9, 2012).
53 Mane A, Donchin E. The space fortress game. *Acta Psychol* 1989; **71:** 17–22.
54 Fabiani M, Buckley J, Gratton G, Coles MGH, Donchin E. The training of complex task performance. *Acta Psychol* 1989; **71:** 259–99.
55 Gopher D, Weil M, Bareket T. Transfer of skill from a computer game trainer to flight. *Hum Factors* 1994; **36:** 387–405.
56 Gopher D, Weil M, Siegal D. Practice under changing priorities: an approach to the training of complex skills *Acta Psychol* 1989; **71:** 147–77.
57 Blumen HM, Gopher D, Steinerman JR, Stern Y. Training cognitive control in older adults with the space fortress game: the role of training instructions and basic motor ability. *Front Aging Neurosci* 2010; **2:** 145.
58 Orrell M, Sahakian B. Education and dementia. *BMJ* 1995; **310:** 951–52.