Brain reserve and the prevention of dementia
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Introduction
‘Use it or lose it!’ is a maxim which captures public imagination when applied to almost any physiological system and particularly in relation to the brain and dementia. ‘Brain reserve’ has been invoked to explain this phenomenon; however, as a scientific concept it has suffered from overuse and lack of rigorous definition. Competing terms such as cognitive reserve and neural reserve only serve to further confuse the area. In this review, we first draw distinctions between different notions of brain reserve before settling on a straightforward behavioural account based on participation in complex mental activities. This allows us to then evaluate its aetiological status within a large body of epidemiological research. Significantly, there are now a series of clinical trials demonstrating that mental exercise can slow the rate of cognitive decline in late life. When coupled with a rich neurobiological literature implicating multiple potential mechanistic pathways, the possibility of delaying dementia onset via community-based mental activity programmes is emerging as a practical and empowering preventive strategy.

What does brain reserve mean?
One of the earliest references to ‘reserve’ was by Katzman et al. in 1988 [1], who in a seminal study noted that those individuals with high levels of Alzheimer’s disease pathology post mortem who otherwise remained nondemented in life had almost double the number of large pyramidal neurones throughout their neocortex in comparison with those who expressed clinical symptoms:

...these people might have started with a larger brain and more neurons and thus might be said to have a greater reserve ... [these individuals] had incipient Alzheimer’s Disease but did not show it clinically because of this greater reserve. [1] (p. 144)

This so-called ‘hard’ neurocentric version of brain reserve hence emphasizes a genetically endowed advantage based on increased neuronal numbers. It also implies the action of a linear threshold mechanism [2], whereby either a larger static lesion or the more protracted course of a progressive lesion was required before the individual crossed below a hypothetical functional threshold.

One of the obvious challenges for this version of brain reserve lies in its operationalization. How do we estimate an individual’s neuronal numbers, especially retrospectively when faced with an older individual? Use of a gross measure such as brain volume risks confusing a putative predictor variable with a known outcome variable.
(i.e. cerebral atrophy) and is thus unacceptable. An alternative that has been explored in relation to dementia is intracranial volume (ICV) as a proxy for maximal brain volume, and even head circumference [3] or head girth [4] as more basic measures. In general, these studies have failed to show a general association with dementia incidence across the full range of ICV, but rather an increased risk only when in the low to very low ranges [5], or when in the presence of an additional risk factor such as apolipoprotein E4 [3].

A more conceptual problem faced by the hard neurocentric proposition relates to the implication that brain reserve is nonmodifiable. Maximum ICV and head circumference are generally achieved by puberty [6] and reflect genetic variance in neuronal quantum as well as developmental, nutritional and environmental factors in early life [7]. More importantly, since these measures do not change after the onset of adulthood, does this mean that underlying brain reserve cannot change? As will be reviewed below, the vast weight of results from the epidemiological, clinical and neuroplasticity literature suggests quite the opposite. Dementia risk appears to be highly modifiable by experience even well into late life. For these reasons a hard neurocentric version of brain reserve is not tenable, although this probably reflects current technological limitations rather than any underlying conceptual flaw.

An alternative conceptualization has been championed which emphasizes ‘how well we use what has been left behind rather than how much of it remains’ and uses a software analogy in contradistinction to the hard neurocentric definition (aka cognitive reserve [8] or intellectual reserve [9]). Putting aside unhelpful dualistic tendencies in this approach, two nontrivial explanations have been suggested. First, we could replace ‘neuronal numbers’ with ‘neuropsychological competence’ or ‘intelligence’, and so apply a similar threshold mechanism whereby high brain reserve individuals simply perform better on neuropsychological tests, are more likely to remain within normal limits for longer despite the parallel progression of underlying disease. Alternatively, high brain reserve individuals may not only have a wider repertoire of conscious and preconscious cognitive strategies at their disposal, but also a greater number of potential neural pathways for execution of these same cognitive processes, thus allowing maintenance of function despite neurological insult:

In essence, an individual who uses a brain network more efficiently, or is more capable of calling up alternative brain networks or cognitive strategies in response to increased demand may have more cognitive reserve. [8] (p. 451)

Theoretically this approach is attractive because brain reserve has now been identified with a more specific neurocomputational mechanism, yet problems with operationalization again arise. Do we simply assess ‘cognitive flexibility’ psychometrically and so potentially confuse a predictor variable with outcome (i.e. with age-related decline in frontal lobe functions), or somehow attempt to estimate neurocomputational factors such as network efficiency, redundancy and dynamic range experimentally via some type of functional neuroimaging ‘stress test’? Whilst of high interest value, a general working definition of brain reserve along these lines remains impractical.

Another strategy has been to adopt a more behavioural focus, and simply ask how mentally active and engaged is a person in relation to the average? It is therefore motivated in establishing a reliable definition at the level of day-to-day observable and verifiable facts related to complex mental activity. The types of proxies used in this version of brain reserve include level and duration of formal education, the nature and complexity of occupational history, and the diversity, frequency and cognitive challenge of past and present leisure activities. We have recently combined this into a validated assessment tool, the Lifetime of Experience Questionnaire (LEQ) [10*], which takes 15 min to complete and is now available online for research use (http://train.headstrongcognitive.com/leq.aspx). Higher LEQ scores, for example, independently predict not only attenuated cognitive decline over time, but also a reduced rate of hippocampal atrophy. This approach also benefits from an extensive body of work linking complex mental activity with dementia risk (see next section). The main advantage from such a straightforward formulation is therefore the provision of an operational definition which is clinically relevant.

One can criticize the behavioural definition for remaining agnostic as to the ‘brain’ part of brain reserve; however, in reality the underlying construct reflects a number of interacting mechanisms at different temporal and spatial scales [11*] (Fig. 1). In my opinion there is no one brain
reserve, but a number of brain reserves. The choice of a working definition at the behavioural scale is therefore essentially for pragmatic reasons as it is arguably more amenable to reliable characterization and general utility.

Population evidence linking complex mental activity and dementia

Dozens of international, population-based cohort studies have now examined the link between complex mental activity and dementia risk. We conducted a metaanalysis of 22 such studies based on data from over 29,000 individuals. The results showed an overall risk reduction of 46% for high mental activity levels compared with low [odds ratio (OR) 0.54; confidence interval (CI) 0.49–0.59]. Interestingly, the separate effects of education (OR 0.53; CI 0.45–0.62), occupational complexity (OR 0.56; CI 0.49–0.65) and cognitive lifestyle activities (OR 0.50; CI 0.42–0.61) were similar in magnitude. The relatively narrow confidence intervals around each point estimate reflect the high concordance level between studies.

The issue as to what extent such mental activity-related dementia risk remains modifiable in late life has been addressed in more recent studies. These have analysed longitudinal dementia incidence as a function of participation in cognitive and social lifestyle activities in later life independent of either education or occupational experiences in earlier life [13–18]. After adjustment for covariates all have found significant protective risk ratios for higher mental activity individuals in the range of 0.41–0.67. In addition, a number of these studies point to dose-dependent effects [14,17,19]. One group, for example, found that the risk for dementia in a group with a moderate level of leisure activities was 50% compared with the low-activity group, whilst those with the highest activity levels had their risk reduced to 33% [18].

Could these effects simply reflect the fact that individuals with higher brain reserve start at a higher neurocognitive level, a type of ascertainment bias [20]? This is unlikely because almost all of the more recent epidemiological studies have adjusted for baseline cognitive status in their multivariate models. We also conducted a separate independent metaanalysis [21] of studies focused on cognitive decline rather than dementia incidence. Individuals with high levels of mental activities were found to have significantly less cognitive decline than those with lower activity levels. Passive mechanisms cannot therefore explain why complex mental activity is linked to both a slower prospective rate of cognitive decline and reduced dementia risk.

A critical assessment of epidemiological evidence linking complex mental activity and dementia can be made against six key aetiological criteria posed by Hill in 1965 [22]:

(1) association,
(2) consistency,
(3) dose dependency,
(4) biological plausibility,
(5) coherency,
(6) temporal primacy.

Metaanalysis has clearly shown a robust association between mental activity and dementia incidence, and this is a highly consistent finding across cohorts and countries and despite differences in the precise variables used. More recent studies have furthermore pointed to a dose-dependent pattern in this association. In terms of biological plausibility, there is an embarrassment of riches from animal and human studies indicating the action of several potential mechanisms. These have been reviewed in detail elsewhere [11] in conjunction with the introduction of a more coherent theoretical framework for their interpretation. Potential mechanisms will be briefly summarized in the final part of this paper.

Yet perhaps the most important unresolved question has been direction of causality – whether active cognitive lifestyle is a prospective predictor of dementia, or low activity levels in fact an early sign of preclinical disease [23]. In order to disentangle this issue of temporal primacy, we must therefore turn to data from longitudinal clinical trials of complex mental exercise.
Mental exercise to prevent age-related cognitive impairment: emerging clinical trials

There is a long history of psychological study about the effects of cognitive training in late life [24,25]. Training on a specific cognitive task does indeed improve subsequent proficiency in that task. In the context of ageing and dementia, however, two major limitations have been recognized. First is the issue of transfer of effect: does training in a specific task generalize to other tasks within the relevant cognitive domain, and to other domains and general mental function? Second is the challenge of effect durability; in other words, is constant training required in order to maintain an advantage, or can a circumscribed intervention be sufficient to produce long-lasting effects? A sceptical viewpoint has reigned in the area of dementia care because of limited transfer of gains or persistence in earlier studies. The nature and efficacy of cognitive rehabilitation has, however, changed dramatically in recent years [26]. Even more exciting are those emerging clinical trial results which indicate that discrete mental programmes can generalize to slow not only the rate of decline within the trained mental faculty, but also the rate of decline in more general indices of function relevant to dementia.

The ACTIVE study has been highly influential in re-formulating thinking in the area [27]. This trial examined the effect of 10 weekly sessions of cognitive training on 2832 healthy older individuals initially divided into four different intervention groups: memory training, reasoning training, processing speed training and a wait-and-see control. The first round of follow up at 2 years found, as expected, that performance in the trained domain was maintained at a superior level to that the control group. At this stage, however, no evidence of transfer of gain to other domains was observed.

A recently reported 5-year follow up to the ACTIVE study examined not only change in cognitive performance, but also in instrumental activities of daily living (IADLs) [28]. Reasoning training more than any other type specifically protected against IADL functional decline over this extended period. This is therefore the first major clinical trial to show that a discrete ‘dose’ of directed mental activity can produce reliable long-term benefits on a general functional outcome, one that happens to form a core part of the dementia diagnosis. Evidence of transfer of gain and durability of effect are now available in a series of controlled trials which have used both normative and preclinical groups (Table 1) [27,29*,30**,31–35].

The relative effect sizes from randomized controlled trials of mental activity with long-term follow up are shown in Table 1. Considerable variability in intervention details, durations, follow-up periods and outcome measures makes a straightforward integration problematic. Nevertheless, the studies are all in agreement that mental activity training can have a positive protective effect on longitudinal cognitive change, with a mean effect size of 0.6. Whether cognitive exercise programmes of this type could produce equivalent reductions in dementia incidence is yet to be confirmed through a well designed trial. Issues that require careful attention include cohort selection to avoid ‘supernormal’ elderly with marginal natural change over time (as witnessed in the ACTIVE study), choice of the control condition to account for nonspecific factors, and specifics of the intervention itself. Beyond this, researchers need to expand the breadth of outcome measures to include the assessment of mood, quality of life and biomarkers. One study [33], for example, found that cognitive training was even more efficacious for maintaining mood than cognitive ability. Mental activity programmes can therefore aspire to a wider ambition that includes the empowerment and engagement of elders into the community.

One of the stronger effect sizes in the literature was from a study which used 8 weeks of daily computer-based cognitive exercises, allowing individuals to face more challenging versions of each task as their competency increased [29*]. It can be speculated that such a personalized and escalating training regime may be more effective in maintaining cognitive abilities than a one-size-fits-all approach. Use of computer-delivered and even online training may therefore allow for practical, standardized and effective interventions, and we have begun our own clinical trial to examine this option in the context of an at-risk cohort [the Study of Mental Activity and Resistance Training (SMART) trial].

What could be the mechanisms of action?

Environmental enrichment has been used for over four decades in order to examine the effect of mental activity on the mammalian brain [36]. Enrichment involves extra opportunities for exploration of novel toys and mazes, more contact with other animals and additional opportunities for voluntary exercise [37*,38].

Mental stimulation is a strong signal for the induction of brain-derived neurotrophic factor and nerve growth factor [36,39]. These are vital for neural cell survival and proliferation, and knockout of these genes leads to impairment in learning and synaptic plasticity [40,41]. Synaptic plasticity is also augmented following a few weeks of enrichment [42]. Similarly, enrichment induces striking increases in synaptogenesis, by as much as 150–200% [43]. This effect is especially salient to clinical dementia, since synaptic density is perhaps the most accurate biophysical correlate of cognitive impairment [44,45]. Furthermore, dozens of studies have now shown...
<table>
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<th>Study</th>
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<td>Derwinger et al. (2006) [32]</td>
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<td>0.77</td>
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<td>Olazaran et al. (2004) [33]</td>
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<td>Scogin and Bienias (1988) [35]</td>
<td>Manual completion focusing on learning mnemonic skills, increasing encoding time and practice exercises</td>
<td>No contact</td>
<td>27 healthy elders with self-report memory complaints</td>
<td>36</td>
<td>Benton visual retention test</td>
<td>-0.06</td>
<td>-0.31</td>
<td>0.25</td>
</tr>
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Mean 0.6

Intervention and control z-scores = (post-pre raw scores)/pooled variance. Effect size estimate is Cohen's D = (intervention z-score) − (control z-score). IADL, instrumental activity of daily living; MCI, mild cognitive impairment; ADAS-cog, Alzheimer’s Disease Assessment Scale – cognitive subscale.
that enrichment can increase neurogenesis in the adult hippocampus [46**].

Pioneering studies in animals found that the mass and girth of the brain increased after a period of mental stimulation [47]. Remarkably, similar regional effects have been found in humans using volumetric MRI techniques after a period of behavioural training [48*] or physical exercise [49]. Whether cognitive training can retard the rate of hippocampal atrophy in Alzheimer’s disease is unknown, yet we have shown that lifetime levels of mental activity are inversely related to rate of hippocampal atrophy in healthy older individuals over time (M. Valenzuela, P. Sachdev, H. Brodary, et al., in preparation). Complex mental activity may also favour the establishment of redundant and alternative processing pathways in order to maintain computational function despite underlying pathology, commonly referred to as compensation (for a review, see Valenzuela et al. [11*]). Cognitive training does indeed induce a number of complex time-dependent changes in brain functioning, as revealed by functional MRI [50] and magnetic resonance spectroscopy [51].

Arguably the most intriguing data have come from studies showing that enrichment may directly interfere with Alzheimer’s disease pathophysiology. Enrichment has been associated with decreased development of amyloid pathology in a number of transgenic murine models, by as much as 50% [52,53**,54]. Conflicting results from animal [55] and postmortem studies [56*] means that replication of this kind of disease-modifying mechanism using in-vivo molecular imaging is a high priority. Intriguingly, as little as 3 h of enrichment affects no fewer than 50 genes related to synaptic plasticity, cell survival and intracellular cell signalling [57]. Both amyloid-dependent and independent mechanisms are therefore clearly plausible at the molecular level [53**].

**Conclusion**

Differential exposure to and participation in complex mental activity is a simple yet powerful way to conceive of and measure brain reserve. There is compelling and consistent epidemiological research linking it to reduced dementia risk. This effect is now starting to be replicated in clinical trials of mental exercise which have monitored long-term cognitive change. The neurobiological underpinnings of this effect are multifarious, with no likely single or universal mechanism. Brain reserve findings therefore appear to meet several of the key criteria proposed for the establishment of causal agency. In this way, there are realistic expectations that mental activity programmes could be a practical and effective primary preventive weapon against the development of dementia. New clinical trials designed to address this question are therefore of high importance and results will be keenly awaited.

**Acknowledgement**

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**References and recommended reading**

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

- of special interest
- **extremely outstanding interest**

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 314).


Integration of animal, preclinical, epidemiological, neuroimaging and computational research related to complex mental activity, ageing and dementia. Introduces a multiscalar spatial temporal framework for explaining brain reserve mechanisms.


First metaanalysis of effects of education, occupational complexity and cognitive lifestyle activities on incident dementia. Found a 46% reduction in dementia risk in those with higher complex mental activity levels.


Neuropsychiatry

25 Comprehensive review of cognitive training studies in older individuals.
29 Found strong positive effects for computerized cognitive training on longitudinal memory abilities in healthy elderly.
31 Pivotal first major randomized controlled trial of mental exercise for the prevention of longitudinal cognitive decline. Found limited transfer of gains across cognitive domains in original report at 2 years’ follow up. This 5-year follow-up found generalization of effect in reasoning training group to include relative conservation of instrumental activities of daily living.
48 May A, Hajek O, Steffens T, et al. Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. Cerebral Cortex 2007; 17:205–210. Primary evidence that behavioural intervention can change macroscopic structural brain characteristics such as regional brain volume.