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 **Foresight**

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

**State-of-Science Review: E14  
Determinants of Normal Cognitive Ageing:  
Implications for Mental Capital**

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*This review has been commissioned as part of the UK Government's Foresight Project,  
Mental Capital and Wellbeing. The views expressed do not represent the policy of  
any Government or organisation.*

## Summary

**This brief review describes the phenomenon of normal cognitive ageing. Especially, it addresses the individual differences in non-pathological cognitive ageing in humans. It discusses some key methodological issues and core theoretical constructs. It provides an overview of some of the determinants of individual differences in normal cognitive ageing. These influences include genetic variation, brain white matter pathology and integrity, health and fitness and disease states with an emphasis on vascular pathology, and psychosocial and lifestyle factors. Finally, it addresses the issue of identifying a multivariate recipe for relatively successful cognitive ageing.**

## 1. Background

Research into how older individuals can maintain their functional abilities in old age is extremely important. It helps us to understand how they might live independently for as long as possible, and can help to sustain quality of life. Cognitive functional ability is a salient and consistently-cited element in definitions of successful ageing. In addition to supporting independence and quality of life, retaining cognitive function has importance *per se*: how we think and remember is core to the self, how we interact with the world, and the access we have to our past. The variance between individuals in successful ageing might not only reflect individual differences in the ageing process, but also the expression of a range of factors acting in numerous domains (Andrews et al., 2002; Berkman et al., 1993; Jorm et al., 1998a; Rowe and Kahn, 1987).

With increasing age, the general trend is toward declines in some cognitive abilities (Hedden and Gabrieli, 2004). Some verbal and numerical abilities, and general knowledge, are well retained as people grow older. On average, aspects of memory, reasoning, speed of information processing, and executive functioning decline in a fashion that is similar to the age-related changes in physical functioning (Schaie, 2005). Thus, even apparently healthy elderly individuals are expected to show a degree of mental decline, just as their lung function and muscle strength have changed from their primes in young adulthood. This is often termed normal, usual or non-pathological cognitive ageing. However, there is a caution against dubbing any process of decline 'normal', for at least two reasons. First, the changes might be caused by pre-clinical pathology. Second, 'normal' can be associated with passive acceptance of the changes, whereas these processes may still be preventable or open to amelioration (Hendrie et al., 2006). For current purposes, the presence of 'normal' in the term normal cognitive ageing reflects the fact that the range of cognitive change being discussed is age-related, but it falls short of the diagnosable pathological entities of the dementias and mild cognitive impairment.

Far from being inevitable, one of the striking aspects of human cognitive ageing is the large variation between individuals: some people decline far more, and some far less than the average (Deary, et al., 2004; Salthouse, 2006; Schaie, 2005). A further striking observation concerns whether individual differences in ageing trajectories are specific to cognitive domains. Largely, it appears not. Both cross sectional and longitudinal studies support the view that ageing substantially affects cognition in general: when one cognitive ability starts to decline in a person, so do the others (Salthouse and Ferrer-Caja, 2003; Wilson et al., 2002). However, there also appear to be smaller, specific effects of age on individual cognitive domains.

The substantial variation in cognitive ageing trajectories between individuals is the focus of this review. It seeks to understand why otherwise healthy people show such differences in their age-related cognitive changes. There is unanimity in the field that a number of disparate factors are likely to be responsible for these observed individual differences (e.g. Christensen et al., 2004; Schaie, 2005; Hendrie et al., 2006). Identifying these factors is a research priority, because they could subsequently be promoted or discouraged – as appropriate – or manipulated, as part of interventions for delaying, ameliorating, or even reversing an individual's age-related cognitive decline. The potential outcome envisaged is future

generations in which a larger proportion of people maintain a satisfactory level of cognitive function. Potential risk and protective factors for normal cognitive ageing have been identified from within genetic, medical and biological, and psychosocial and lifestyle domains.

## **2. Some important methodological and theoretical considerations**

### **2.1. Cognitive ability *trait* and cognitive ageing *trajectory***

In humans, individual differences in cognitive function are relatively stable, and trait-like. Even from age 11 to almost age 80, about half of the reliable variance is stable (Deary et al., 2004). Therefore, when cognitive function is measured in older people it is not, *per se*, an index of cognitive ageing. Any mental test score reflects both the level from which the person started in young adulthood (the trait level, often called premorbid or prior cognitive ability), and the amount of decline, if any, that has taken place since then (the trajectory). It is important, if possible, when seeking factors that influence cognitive ageing, to have actual measures of cognitive change, which implies that the better studies are longitudinal (e.g. Schaie, 2005). It is also important to adjust for baseline cognitive functioning.

### **2.2. Premorbid (prior) ability can confound causal attributions**

Although many longitudinal studies of cognitive ageing do attempt to adjust for baseline cognitive function, these 'baseline' assessments are often taken in old age. For two reasons, a true measure of premorbid ability from young adulthood is more helpful in seeking the determinants of cognitive ageing. First, prior ability may itself be a predictor of the amount of cognitive change. Some evidence shows that people who begin with higher ability tend to decline less as they grow older (Richards and Deary, 2005). Second, prior cognitive ability might have a confounding influence on the putative determinants of cognitive ageing. For example, one study appeared to find a protective effect on cognition in old age of taking food supplements (Whalley et al., 2004). Closer inspection of the results, however, shows evidence for reverse causality: that people with higher childhood intelligence are those who, at an older age, are both brighter and tend to take food supplements. Similarly, where education and occupation are thought to be influences on cognitive ageing, one must bear in mind that childhood cognitive function is a substantial predictor of both of these factors.

### **2.3. Cognitive reserve and cognitive capital**

These two theoretical concepts, derived from an economic metaphor of cognitive development and ageing, are currently popular. They can be traced back to two sources. First, there was Horn and Cattell's (1966) investment theory of cognition, whereby it was hypothesised that the brain's information processing capability (one's 'fluid' intelligence) was invested, via education and cultural experiences, to become stored knowledge and strategies ('crystallised' intelligence). Second, there was the observation that people with similar amounts of brain pathology did not always experience dementia, and this tended to be predicted by variation in some indicator of 'cognitive reserve' (e.g. education) (Stern, 2002).

Thus, the notion is that people with more cognitive reserve or capital start from a better position when it comes to ageing. They have some buffering against its effects. Richards and Deary (2005) have proposed modifying the term such that accumulation of 'reserve' must be apparent over and above the level of premorbid cognitive ability, and with a consideration of any brain pathology experienced: '*taking prior ability into account, the signature of the accrual of reserve is the identification of something that adds variance to later cognitive function*' (Richards and Deary, 2005, p.618). There is evidence that education and occupational social class do provide some cognitive reserve (Staff et al., 2004).

## 2.4. *The common cause hypothesis of cognitive (and other, bodily aspects of) ageing*

Cognitive ageing might occur in concert with other bodily functions. For example, it was found that sensory and cognitive systems might have shared age-related changes (Li and Lindenberger, 2002). The idea was broadened to include the possibility that wider physical functions might decline with a trajectory shared by cognition. That is, people whose cognitive ability is declining are also those whose general bodily frailty is increasing (Christensen et al., 2001). The importance of these considerations for cognitive ageing is that researchers can, therefore, investigate general bodily ageing processes as potentially relevant to changes in cognitive functions. These include inflammation (Zipp and Atkas, 2006) and oxidative stress (Halliwell, 2006). Measures derived from both of these processes have been associated with normal cognitive ageing (Rafnsson et al., 2007; Kachiwala et al., 2005).

## 3. Genetic influences on cognitive ageing

The broad sense heritability of cognitive ability rises from well below 50% in childhood to over 60% in adulthood, and is still probably at least this level in old age (Deary, Spinath and Bates, 2006). Although there are substantial genetic contributions to cognitive ability differences in older people, some of these influences will be those that contributed to differences in cognitive ability traits in youth. The key is to discover genetic contributions to cognitive change or trajectory: that is, those genetic influences present in old age but not earlier. For example, possession of the E4 allele of the gene for apolipoprotein E contributes significantly to verbal reasoning ability in 79-year-olds, but not to variance in the same test in the same sample at age 11 (Deary et al., 2002). Notwithstanding this clear example of a contribution to life-long cognitive change, and some others described below, an important and sophisticated study of ageing Swedish twins showed that cognitive change within old age might have very little genetic foundation (Reynolds et al., 2005). The researchers also found increased absolute variation in cognitive function as people grew older, the major influence being non-shared environment, which probably means that stochastic contributions are a major source of variation in cognitive ageing trajectories within old age.

Normal cognitive ageing, that is, life-long cognitive change, is a quantitative trait and, in common with others, its genetic origins are likely to be numerous and mostly small in effect size. For example, the significant *APOE* effect described above accounted for between 1% and 2% of the variance in cognitive change between age 11 and 79. Other genetic variants that contribute significantly to lifetime cognitive change, such as those within the *COMT* (Harris et al., 2005), *BDNF* (Harris et al., 2006), *DISC1* (Thompson et al., 2005), and *PRNP* (Kachiwala et al., 2005) have similar effect sizes. There are reports of associations between cognitive change within old age and genetic variation in, for example, the serotonin transporter gene (Payton et al., 2005), *PPAR-g* (Yaffe et al., 2008), *CETP* (Barzilai et al., 2006), and *MPO* (Pope et al., 2006). Though small in effect, most of these genetic differences have plausible mechanisms whereby they might influence cognitive ageing.

However, in an area where effect sizes are small and human cohorts with the appropriate phenotypes are rare, there is, as yet, insufficient replication of any individual contribution except, perhaps, *APOE*, which has a well-established association with normal as well as pathological cognitive ageing (Small et al., 2004).

To date, the limited literature on genetic contributions to normal cognitive ageing has mostly been driven by a candidate gene approach (Deary et al., 2004; Payton, 2006). Candidates are sought from, for example, genes known or thought to be associated with the dementias, general cognitive ability, learning and memory, cardiovascular disease, and oxidative stress. Among the next steps will be to complement further investigations using this rational approach with whole genome analyses and other sources of genetic variation, such as copy number variation and gene expression. These will all demand large samples, which will only become even larger if gene-environment and gene-gene interactions are to be considered.

The existence of genetic contributions to cognitive ageing does not mean that these are not amenable to intervention. Once the mechanisms are understood, genetic contributions might well be modifiable. Small effect sizes might militate against interventions being worthwhile. However, it might be the case that a genetic variant with a small effect size in the population has a larger effect within sub-groups.

#### **4. Contributions from white matter pathology and integrity**

Structural and functional changes in the brain are central to research on cognitive ageing, with a distinction often made as to whether these are pathological, or normal 'age-related' changes (Hedden et al., 2004). This distinction will have implications for treatment and intervention strategies. Both the grey and white matter of the brain shrink as people age. Though there is often a focus on grey matter, the integrity and volume of white matter and the extent of white matter lesions (WML – sometimes called leukoaraiosis or white matter abnormalities or hyperintensities, because they are especially bright in some magnetic resonance imaging modalities) have come under increased scrutiny as contributors to normal cognitive ageing. In older people, poorer cognitive outcomes are associated with having more WML severity (Gunning-Dixon and Raz, 2000).

These white matter changes, primarily in the frontal cortex, have been related to slowed information processing speed and memory, both immediate and delayed (Hedden et al., 2004). The contribution of WML to lifetime cognitive ageing is relatively large, and independent of prior cognitive ability (Deary et al., 2003a; Leaper et al., 2001). Therefore, lessening the burden of white matter lesions, by finding and combating their determinants, is one direction of intervention. This includes hypertension and other vascular risk factors, such as diabetes (Deary et al., 2003a; Murray et al., 2005).

The study of the state of the brain's white matter has progressed, with the development of diffusion tensor magnetic resonance imaging, to provide indicators of white matter integrity. Better retention of white matter integrity is associated with more successful cognitive ageing (O'Sullivan et al., 2001), though there is also some evidence of reverse causality (Deary et al., 2006). These studies are still small and require more replication, but better understanding of how to retain white matter integrity is a possibly fruitful avenue for interventions.

#### **5. Health – especially vascular disease - contributions**

Some, or even much of, normal cognitive ageing might be caused by overt or occult illness. Poor self-reported health is associated with more age-related cognitive decline (Anstey and Christensen, 2000). More objectively, worse cognitive ageing is associated with greater allostatic load, a compendium measure of 10 indicators, six of which are aspects of the metabolic syndrome and others related to HPA axis functioning (Seeman et al., 2001). In old age, physical fitness — as measured by a combination of lung function, grip strength and walking speed — contribute to cognitive ability, after adjustment for true prior ability (Deary et al., 2006). The specific example of vascular disease provides a good instance of helpful research avenues for clues to variation in normal cognitive ageing. Vascular problems are associated with the continuum of cognitive problems, from normal ageing to dementia (O'Brien et al., 2003). The individual disease entities of stroke, myocardial infarction and peripheral vascular disease are all associated with cognitive decline within old age in non-demented people (Rafnsson et al., 2007). The cardiovascular disease risk factor traits of blood pressure (Qiu et al., 2005) and ankle-brachial blood pressure index (Price et al., 2006) are associated with cognitive decline. There is also some reverse causality, with prior, even childhood, cognitive ability being associated with cardiovascular diseases and hypertension in later adulthood (Hart et al., 2003; Starr et al., 2004). Diabetes is associated with accelerated cognitive decline (Cukierman et al., 2005), as is the metabolic syndrome (Yaffe et al., 2007). Better control of Type 2 diabetes is associated with less cognitive decline (Ryan et al., 2006). There is evidence that both the vascular (Ferguson et al., 2003) as well as the metabolic (Gallacher et al., 2005) disturbances in diabetes affect cognitive function.

Some have advocated treating vascular risk factors as a way of slowing cognitive ageing, especially the slide into clinical cognitive ageing syndromes (Alagiakrishnan et al., 2006). An interesting aspect of this suggestion was that, in addition to more obvious chemical cardiovascular treatments and preventative measures, there were also broader suggestions concerning antioxidants, stress reduction, diet, exercise, and other aspects of lifestyle and social life. This again is a reminder that keeping a healthy mind does not occur in isolation from a healthy body.

## **6. Psychosocial and lifestyle factors**

Certain psychosocial factors and the choices that individuals make about their lifestyles have been identified as potentially important predictors of cognitive ageing. A review conducted as part of the NIH Cognitive and Emotional Health Project identified putative protective or risk factors ranging from educational experiences and socioeconomic status to physical activity, highlighting the varied nature of possible influences (Hendrie et al., 2006).

Smoking, for example, appears to have deleterious consequences for lifetime cognitive change (Deary et al., 2003b; Whalley et al., 2005). Dietary and nutritional factors have also been implicated. Fish, vegetables, and fish oil supplements are found helpful to cognitive ageing in some single observational studies (e.g. Morris et al., 2005; 2006; Whalley et al., 2004). Further replication is required, however, not least because of possible reverse causation, as mentioned earlier.

Using broad occupational classifications, it has been suggested that individuals employed primarily in manual or unskilled occupations may be at a higher risk of developing dementia and Alzheimer's disease (Seidler et al., 2004; Paykel et al., 1994; Qiu et al., 2003; Stern et al., 1994; Karp et al., 2004; Smyth et al., 2004). As mentioned in the cognitive reserve section above, there was still an effect, modest in size, for occupational classification in determining cognitive ability in later life, after controlling for premorbid ability (Staff et al., 2004). However, a dearth of studies with measured premorbid cognition means that replication is required. Educational attainment may also confound any association, although it is frequently used as a proxy for prior ability. This is insufficient. Educational attainment is not only predicted by childhood ability (which will partly determine later occupational attainment) but it also adds unique, independent variance to later life cognitive ability (Staff et al., 2004) and is thus cited as a cognitively protective factor.

Increasingly, skilled or professional occupations may require more cognitive effort to be exerted whilst on the job, thus preserving cognitive functions over the working life. Being situated within a safer, less hazardous working environment might lead to improved health and wellbeing compared to those in more harmful settings. Or, any beneficial effect could be indirect and act through the accrued advantages of higher status, which perhaps include reduced stress (McEwen, 2006). An increased focus on specific occupational characteristics – such as job complexity and the mental demands encountered, or the hazardous nature of tasks and situations – is required for a more thorough understanding of the factors that are detrimental or beneficial with respect to cognitive ageing (Bosma et al., 2003; Jorm et al., 1998b).

A systematic review (covering 15 longitudinal studies investigating the effects of lifestyle factors on normal cognitive ageing) concluded that there is evidence of a protective effect from social 'lifestyle components' against cognitive decline. However, the varied assessment of social networks, contacts, ties, (dis)engagement, integration and support (different terminology often covering very similar underlying constructs) makes summary statements of this kind largely uninformative (Fratiglioni et al., 2004). The cognitively beneficial effect of having close, supportive significant other(s) or a strong social network may act through health-related and physiological pathways or serve to encourage cognitive stimulation via increased contact and engagement. Whereas the impact of social support networks on normal cognitive ageing is of great interest, assessment of these factors is often amalgamated with that of engagement with others in more formalised

social activities, such as going to church or participation in social groups, so that disentangling any effect is problematic. However, it has been suggested that both social network indices and social activity may have independent effects on cognitive change, with increased social activity tentatively proposed as having a greater impact (Zunzunegui et al., 2003; Barnes, et al., 2004).

The role of activity participation in shaping cognitive outcomes is, in itself, a fertile area of research. Numerous studies have supported the claim that greater activity in the social, physical or intellectual domain is predictive of better cognitive outcomes or reduced cognitive decline (Fratiglioni et al., 2004). With respect to physical activity, it need not be vigorous (walking, for example) to offer protection against cognitive decline (Weuve et al., 2004; Yaffe et al., 2001). As vascular disease has been linked to cognitive decline, increased physical activity may affect later life cognitive outcomes via a reduction in vascular risk factors (such as hypertension) and vascular disease (Hendrie et al., 2006). There may also be a direct effect of physical activity on brain physiology by 'facilitating neurogenerative, neuroadaptive, and neuroprotective processes' (Dishman et al., 2006, p.345). However, remaining mentally engaged is often seen as the most important activity for preserving cognitive ability into old age, frequently expressed as part of the 'use it or lose it' hypothesis (Orrell and Sahakian, 1995). In general, increased participation in intellectually stimulating activities has been related to the maintenance of cognitive function, or reduced cognitive decline (Fratiglioni et al., 2004):

*'[those] who engage in activities that make significant demands on their cognitive skills will show greater maintenance or improvement in their abilities...different patterns of participation in everyday activities may be associated with different trajectories of cognitive change in later life'*

(Hultsch et al., 1999, p.247)

A randomised trial involving extensive training in older people in a number of individual cognitive domains showed some improvement in functions specific to the mode of training, but not on others, and lasted up to five years (Willis et al., 2006). To reap rewards from cognitive training programmes, however, these may have to be tailored to individual requirements due to a lack of transfer of the effects (Fillit et al., 2002; Salthouse, 2006).

Although the activity participation hypothesis may be more appropriate for, and particularly relevant to, activities of a specifically cognitive nature, it is possible that any and all activities involve some form of mental stimulation – for example, in the planning stages or when carrying out physical and mental tasks. Use or disuse of mental abilities could lead to structural or functional changes in the brain. With an engagement model, however, the nature of causality is difficult to tease out, particularly as participation in cognitively demanding activities is likely to be determined by prior cognitive ability (Hultsch et al., 1999). Thus, reverse causality is a particular problem in this area of cognitive ageing, in which most studies are observational.

## **7. Identifying, validating and promoting a recipe for success**

This short overview could not be comprehensive. Its objectives were: to outline the field of research, describing the main basic findings and distinguishing it from dementia research; to outline some special methodological and theoretical issues in the field; to describe typical findings from a selected yet diverse range of influences on cognitive ageing; and to provide pointers to avenues of possible intervention. Aspects of mental ability generally deteriorate with increasing age, although the course of such change is highly variable. Consequently, it is possible to identify older individuals who are ageing 'successfully', with respect to cognition, in relation to their peers. By determining what predicts such individual differences, a recipe for successful cognitive ageing can be drawn up. This is necessary if the cognitive health and wellbeing of an increasingly aged population is to be promoted.

Although validation and replication is required, factors from diverse domains have been shown to predict cognitive ageing. Genetic factors linked to cognitive change and decline may highlight the mechanisms to target in any intervention, whilst the integrity and connectivity of white matter might reflect the accrued action of a range of psychosocial, lifestyle and health-related factors. The most proactive steps an individual can take to ensure cognitive vitality in later life are likely to include adopting cognitively-protective lifestyles, consisting of concerted effort to reduce cardiovascular risk factors and disease and increased activity and engagement.

For the practical researcher and those wishing to develop and influence policy, the pressing and growing problem of cognitive ageing presents special challenges. Among these are the facts that: the assessment of change is technically difficult and demands unusually burdensome studies; most studies are observational; the influences in cognitive ageing are heterogeneous, demanding collaboration amongst biomedical, physical and social scientists; and some of the theoretical constructs in the field are employed with insufficient clarity.

## Acknowledgements

*Ian Deary is the recipient of a Royal Society-Wolfson Research Merit Award.*

*Alan Gow is supported by a grant from Help the Aged (the Disconnected Mind project).*

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First published September 2008.

The Government Office for Science.

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