SCIENTIFIC COMMENTARIES

Educational attainment and mid-life stress as risk factors for dementia in late life

The prevalence of dementia doubles every 5–7 years after the age of 60–65 years, affecting approximately 50% of the population aged ~90 years. With the continuing demographic shift towards greater longevity in developed and developing nations, the human tragedy and already huge public health burden of these diseases will be monstrous within a few decades. Effective strategies for primary and secondary prevention must be developed. To accomplish this goal, we must accurately discern the specific disease processes leading to dementia, understand their essential determinants and identify environmental factors and experiences that can be targeted for primary and secondary preventive interventions.

Molecular, pathological and neuroimaging methods are being used to examine what appears to be the most important pathological processes responsible for the common dementing illnesses. Epidemiological methods are employed to define clinical features linked to specific pathogenic processes, and to identify risk factors associated with clinical illnesses, early clinical indicators, and structural and metabolic biomarkers. Despite many efforts, research to identify risk factors has been relatively disappointing. The current issue of Brain includes complementary epidemiological reports focusing on two informative but non-specific risk factors: mid-life stress and pre-morbid educational attainment.

In a clearly presented report from a longitudinal community study of 1462 women, Johansson and co-workers present convincing evidence for an association between self-reported mid-life stress and an increased risk of developing dementia decades later (Johansson et al., 2010). The authors recognize that the underlying mechanisms mediating the association cannot be determined, but suggest a number of alternatives. If, as may be the case, the adverse influences of stress are attributable to years of increased inflammatory, oxidative or cerebrovascular dynamic processes, the impact on ageing-related erosions of neural resources or the accumulation of neurotoxic materials might be ameliorated by dietary adjustments or pharmacological treatments during the periods of stress. These could have a substantial impact on the public health burden of the late-onset dementing illnesses (Komulainen et al., 2008; Schmidt et al., 2008; Sterlemann et al., 2008; Rothman and Mattson, 2010; Solas et al., 2010; Sterlemann et al., 2010). While the validity of mid-life stress as a risk factor seems likely, the lack of understanding of the underlying pathogenic processes does not yet justify such recommendations. What the study does make clear, however, is that at least some of the determinants of risk of late life dementia are discernible and operable many years before cognitive declines become apparent.

The second report, by the EClipSE collaborative members, addresses the role of education as a risk factor for late-onset dementia (EClipSE, 2010). The association between years of schooling (usually in childhood) and performance on nearly all neuropsychological tests employed in the assessment of life cognitive decline is well known and robust. Since test scores are used in the evaluation of cognitive impairment and the screening for dementia, an association between education and dementia in clinical settings would not be surprising. The key questions, of great relevance to primary and secondary prevention questions, are: is less educational attainment truly a significant risk factor for dementia? And, if it is, does it work through a direct influence on the development of structural brain lesions, or through neurocognitive mechanisms related to clinical expression?

The role of brain reserve may be central to mechanisms underlying both low childhood educational attainment and mid-life stress as possible risk factors for the development of dementia in late life. The concept and role of reserve was introduced and elaborated by Robert Katzman and colleagues (Katzman et al., 1988; Zhang et al., 1990; White et al., 1994). Their suggestion was based on the idea that neuronal and functional brain resources needed for complex cognitive functioning varied among individuals, and that more luxuriant resources might maintain functioning in the face of greater neuron and synaptic losses. The relevance of this concept to dementia has been supported by others (Hall et al., 2007; Koepsell et al., 2008). The term ‘brain reserve’ has been employed to represent structural resources while ‘cognitive reserve’ includes what might correspond in computer parlance to ‘software’ resources, i.e. learned cognitive methods and strategies utilizing redundant, default and interacting multi-synaptic ‘programs’ to accomplish complex tasks.

The relationship of education to brain reserve is itself complex. Depending on the culture and society, children with greater neuron numbers and connectivity, or who enjoyed the special advantages of a specific ethnic or cultural subset of the population,
might be availed of greater educational opportunities (Manly et al., 2005). To complicate matters, the cognitive ‘exercise’ implicit in educational experiences might simultaneously enhance these structural and cognitive reserves. If multisynaptic ‘programs’ involved in specific cognitive functions are encoded in diverse cortical regions (some in areas involving language, others involving spatial and temporal modelling, and still others involving complementary or alternative regions in the two hemispheres), losses in some regions might be tolerated by virtue of learned supplementary or alternative programs in other regions—contiguous, remote and contralateral. Such phenomena appear to be involved in post-stroke recovery of language and motor function (Sasanuma and Monoi, 1975; Winhuisen et al., 2005; Heiss and Thiel, 2006). The relevance of these phenomena to cognitive function and dementia in late life is currently the object of great interest and optimism, as witnessed by the generation of several useful conceptual frameworks, including those of ‘functional plasticity in cognitive ageing’ (Greenwood, 2007; Carlson et al., 2009; Hall et al., 2009); and ‘neurocognitive scaffolding’ (Goh and Park, 2009).

The relationship of education, intellectual factors and linguistic facility to Alzheimer’s disease was dramatically influenced by a 1996 publication from the ‘Nun Study’, linking linguistic complexity (idea density in a writing sample) in early adult life with cognitive facility and structural brain lesions in old age (Snowdon et al., 1996). Autopsied nuns, whose autobiographic essays (written at an average age of 22 years) demonstrated greater idea density, not only retained better cognitive functioning into later life, but also showed less brain atrophy and fewer Alzheimer neuropathological lesions at death. These observations are not consistent with the reserve hypothesis, which would have predicted early adult cognitive reserve (indicated by greater idea density) to have been protective, even in subjects whose brains showed structural brain lesions.

The report by EClinSE demonstrates a consistent association of fewer years of education with a higher risk for dementia across all three study cohorts, but fails to show a relationship with the occurrence or severity of structural brain lesions. These observations support a meaningful role of education as a determinant of cognitive reserve, possibly including a further association with structural brain reserve. Their findings also seem consistent with a summary report from the National Alzheimer’s Coordinating Centre, in which greater educational attainment was associated with better neuropsychological test performance when few or only mild Alzheimer’s lesions were observed at autopsy, but not when the structural changes were more severe (Koepsell et al., 2008).

Both low educational attainment (reflecting childhood experiences) and stress during middle adult life appear to be legitimate risk factors for late-onset dementia. While the protective influence of greater education appears to operate through a mechanism involving cognitive reserve, the adverse consequences of mid-life stress may be due to an aggravation of ageing-related atrophy, neurodegenerative processes or ischaemic cerebrovascular disease. With so few candidate targets for the development of public health strategies to prevent or ameliorate the processes that lead to late life dementia, these deserve special attention.

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Advance Access publication July 17, 2010
doi:10.1093/brain/awq201

Funding

The author’s efforts are supported by grants 5U01 AG19349 and 5UO1 AG017155 from the National Institute on Aging, National Institutes of Health, Bethesda, Maryland.

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Beneficial brain autoimmunity?

This issue of *Brain* contains two articles that, although coming from strikingly different backgrounds, seem to describe one common phenomenon: beneficial autoimmunity. *Beneficial autoimmunity?* Strict linguists would qualify this mere term as unacceptably paradoxical, in more than one sense: how can ‘immunity’, i.e. protection against potential danger, turn against self and cause disease, and furthermore, why should this be called ‘beneficial’?

Linguistics aside, the concept of beneficial autoimmunity has developed over the past decades. Initially, brain-specific T cell clones were first isolated from autoantigen-primed and subsequently even from completely normal, healthy rodents. When transferred into healthy recipients, these T cells caused severe encephalomyelitis (Ben-Nun *et al.*, 1981; Schluesselner and Wekerle, 1985). Later, it turned out that primates, in particular human beings, also have high numbers of autoreactive T cells in circulation. When activated ex vivo and re-injected into the same donor, the autoreactive T cells cause disease, as shown in monkeys (Meinl *et al.*, 1997).

But, why do we all harbour potentially pathogenic self-reactive immune cells in our immune repertoires? It is hard to accept that our self-reactive T cells just evolved to persist as vicious time bombs waiting for a trigger to detonate. Instead, could these cells be on a beneficial mission, which we still wait to appreciate fully? And, how could autoimmunity T cells function favourably? In their pursuit of infectious agents, immune responses commonly create collateral damage of previously intact tissues. But at the same time, they are supportive of tissue regeneration, for example, healing of skin wounds by releasing regenerative mediators (Jameson *et al.*, 2002). In addition, immune cells also produce neurotrophins, like brain-derived nerve growth factor (BDNF), which act in manifold ways on neural cells (Kerschensteiner *et al.*, 1999). Thus, it is not too far-fetched to assume that under particular conditions, autoimmune T cells could help regeneration of lesioned cells by depositing BDNF or other trophic factors.

One of the new *Brain* papers studies the role of BDNF in experimental autoimmune encephalomyelitis (EAE) and re-examines the question whether BDNF might have therapeutic applications as an anti-inflammatory, regenerative agent in diseases like multiple sclerosis. This work combined a classical EAE model (immunization of C57BL/6 mice against peptide representing sequence 35–55 of the myelin oligodendrocyte glycoprotein) with advanced transgenic technology to examine the effect of BDNF on CNS autoimmunity. While it is known that in the complete absence of BDNF, most global knockout mice die before birth, Gold *et al.* (2010) engineered ‘conditional’ knockout animals that are lacking BDNF in selected tissues. In some of the mice, BDNF expression was switched off exclusively in inflammatory cells, T cells or macrophages. In other animals, BDNF was knocked out in astrocytes. In contrast to the globally BDNF-deficient mice, the conditional knockout animals survive into adulthood so that they are available for EAE experiments.

In a first set of experiments, the investigators sought to reduce the physiological BDNF level in the CNS, the target tissue of EAE. Most of the intracerebral BDNF is produced by electrically active neurons, with a minor contribution from astrocytes (Zafra *et al.*, 1992). Remarkably, even targeted deletion of BDNF synthesis in astrocytes affected myelin oligodendrocyte glycoprotein-induced EAE. While the acute inflammatory response seemed largely unaffected, in later phases there was a trend towards increased axonal damage. Hence, the authors concluded that locally produced BDNF mitigates inflammation-dependent neuronal damage. Certainly, one would expect a dramatically enhanced effect after deletion of BDNF in its major source, neurons.

It should be kept in mind that BDNF is not only produced by autochthonous CNS cells, astrocytes and neurons, but also by inflammatory cells, including T cells and macrophages (Kerschensteiner *et al.*, 1999). How would deletion of BDNF in effector T cells and accessory macrophages (the cells responsible for inflammatory brain damage) affect pathogenesis? Deletion of the neurotrophin in either T cells or macrophages alone was without demonstrable