Brain ageing and dementia: what makes the difference?

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The boundaries between non-pathological brain ageing and the dementias are unclear and contentious. Neuropathological examination can detect occasional individuals in whom the microscopic features typical of late-onset Alzheimer's disease are present yet a clinical history of dementia is absent. On other occasions, the converse seems true: individuals seriously disabled in life by dementia show at death only mild pathological features of Alzheimer's disease. Observations of this type, although often made by experienced neuropathologists, are not widely discussed by molecular neurobiologists, among whom the assumption has largely prevailed that Alzheimer's disease is a well-validated nosological entity, discontinuous with ageing and with its own discrete molecular pathology. This reasoning extends to the repeated proposition that understanding the pathogenesis of amyloid deposition will provide a sound and sufficient basis from which to develop novel therapies for Alzheimer's disease (Selkoe, 1999).

Findings from the Medical Research Council Cognitive Function and Ageing Study (MRC–CFAS) now challenge these assumptions on at least two fronts. First, they encourage dementia researchers to re-examine the basis for the belief that there are valid boundaries between non-pathological ('normal') ageing in the absence of dementia and the dementias. Second, they suggest that the central role often assigned to amyloid deposition requires review. Longitudinal follow-up studies such as the MRC–CFAS raise important issues about the nature of the phenomena to be explained. This editorial considers the early contributions to brain development as influences on cognitive decline in later life. In turn, this approach requires a deeper understanding than is as yet available of those brain mechanisms and processes most affected by ageing.

Until Margaret Esiri and her colleagues (Esiri *et al*, 2001) described their large community-based neuropathological study of the distinction between dementia and brain ageing in the absence of dementia, there was a shortage of data. It was impossible to accept the validity of contemporary neuropathological criteria for dementia, or the definitions of the boundary, if any, that existed between the dementias and 'normal' ageing. The study showed that in 209 old people weighted to contain 100 people who met clinical criteria for dementia before death, the majority showed mixed Alzheimer and vascular pathologies. At postmortem examination the brains of dementia and non-dementia subjects overlapped in neuritic and diffuse plaque density and no single pathological criterion reliably distinguished between groups. Coexistent vascular lesions did not provide sufficient explanation for the presence of dementia, but did encourage the view that interactions between Alzheimer and vascular pathologies may be critical determinants of progression to clinical dementia.

The MRC–CFAS data provide the strongest evidence yet that the relationship between 'normal' brain ageing and the dementias is best represented by a continuum. They also do much to weaken the pivotal position claimed for amyloid deposition in the pathogenesis of Alzheimer's disease. Without the inclusion of some other factor or factors, the 'amyloid cascade' hypothesis of Alzheimer's disease is no longer tenable. The MRC–CFAS programme may yet identify such factors. Not until their sample size has more than doubled and there are improved descriptions and quantifications of vascular lesions will it be possible to begin to disentangle the pathological processes that contribute to clinical presentations of dementia and, critically, to establish their true relationships with age.

RATE OF COGNITIVE CHANGE OR 'CASENESS'

Longitudinal psychological studies of cognitive ageing do not identify a single point of transition between 'normal' ageing and dementia. When several cognitive domains are used to predict later onset of dementia, cognitive decline is typically non-uniform across those domains, with the exception of early memory impairment – largely because of its inclusion among criteria for dementia (Chen *et al*, 2001). These pre-symptomatic patterns of cognitive decline are not reliably distinguished from 'normal' variation in cognitive function in late life, almost half of which is attributable to original childhood IQ (Deary, 2000).

Psychologists and psychiatrists alike are familiar with problems of this type and are comfortable with a search for antecedents that may extend into earlier developmental epochs. Links between increased late-life dementia risk and lower educational attainment suggest the association between dementia and childhood IQ reported by Whalley *et al* (2000). Explanations of associations of this type are complex and not mutually exclusive. Not least are the strong intergenerational and lifelong continuities of material advantage, which award entry to a safer, healthier environment to the mentally more able youngster. More usual is the concept that the mature brain possesses sufficient 'reserve' (or redundancy) to withstand age-related pathologies as described by Esiri *et al* (2001) and that this reserve is determined by early life experiences. The belief that childhood educational attainment or mental ability could determine a threshold which brain ageing or dementia pathology must be sufficient to exceed to cause dementia was supported by the data reported by Whalley *et al* (2000). The association between lower childhood IQ and dementia was confined to late-onset cases and was most marked in those presenting after age 72 years.

The MRC–CFAS programme represents the successful application of epidemiological and neuropathological methods to the study of distinctions between clinical cases and non-cases, and the ages at which disease onset does (or does not) occur. It is the most usual contemporary approach to age-related disease, where the disease of interest (in this case dementia) is defined as present or absent. It contrasts with a second and potentially more powerful research method, which investigates the rate of change in premorbid characteristics over a specified age interval (National Institute of Aging Working Group on Aging and Genetic Epidemiology, 2001). Here, risk factors for dementia are examined not

simply as contributing to duration of survival up to becoming a 'case' of dementia, but as possible determinants of rate and timing of change in parameters believed to be closely linked to the pathogenesis of dementia.

Age-related abnormalities of glucose metabolism are just one of these hypothetical parameters. Diabetes mellitus is a risk factor for stroke and a possible risk factor for Alzheimer's disease and vascular dementia (Luchsinger et al, 2001). Mature-onset (type 2) diabetes is also associated with cardiovascular risk factors that include hypertension and hyperlipidaemia, which may cause or accelerate unrecognised progressive cerebrovascular disease. There are at least two plausible biological mechanisms to link enduring age-related abnormalities in glucose metabolism with neuronal death: the formation of advanced glycation end-products (AGEs); and hyper-insulinaemia. Separate strands of evidence link foetal growth, adult hypertension and impaired glucose tolerance at age 64 years (Hales et al, 1991). Taken together, these observations advocate longitudinal studies on individual differences in glucose metabolism and age-related cognitive variation. When studies of this type extend across the life span, they are subsumed under the title 'life course approaches' to late-onset dementia and dementia-associated traits. They sometimes suggest parallel experimental routes to better understanding of mechanisms of age-related cognitive impairment (Strachan et al, 1997).

Explanations of associations between suboptimal foetal and infant growth and late-onset disease include failure to acquire lasting control of complex central regulatory systems. In brain development, foetal nutritional and hormonal environments are also important because of their critical roles in the expression of specific genes (Dauncey et al, 2001). Major differences in the foetal and infant nutritional environment induce large differences in expression of hormonal receptor isoforms and may provide the means whereby dietary micronutrients affect cognitive functions across the life span. Nutritional influences can be as apparently diverse as the contributions of folate and vitamin B_{12} to neurodevelopment and the greater age-related cognitive impairment linked to dietary and plasma folate concentrations (Miller, 2000; Duthie et al, 2002).

Diversity in timing and nature of single nutritional influences represents an important obstacle when taking a life course approach to understanding dementia. It can obscure the best route to elucidate the molecular mechanisms by which early nutritional experience affects neurodevelopment and later cognitive performance. For example, observational studies in late life suggest hyperhomocysteinaemia (attributed to reduced transformation of homocysteine to methionine by folate and vitamin B_{12}) as a possible risk factor for cerebrovascular disease (Miller, 2000) and dementia (Seshadri et al, 2002). Polymorphisms in the gene encoding methylenetetrahydrofolate reductase (MTHFR, an enzyme essential to folate metabolism) are, therefore, possible susceptibility factors for age-related cognitive decline; however, they possess the potential to influence brain metabolism throughout life. Similar critiques can be made of studies of interactions between genes and early nutrition. These may be as specific as their influences on peripheral insulin sensitivity and neurodevelopment, when the same factors might influence synaptogenesis in late life.

BRAIN AGEING AND COGNITIVE DECLINE

The association between brain ageing and age-related cognitive decline is uncertain. Largely because ageing studies are only just beginning, brain ageing is yet to be linked informatively to what is known about the neurobiological basis of cognitive decline. Higher brain functions comprise abilities like language, learning, memory, planning, abstract reasoning and self-awareness; most of these are impaired as age-related cognitive decline progresses to dementia. The neural foundations of higher functions are supported by the complex organisation of synaptic connections. One current paradigm attaches a central role to modulation of synaptic functions, some of which are enduring but the majority of which (especially in brain areas serving higher functions) require constant remodelling to respond optimally to environmental demands.

Brain areas that provide higher functions appear most susceptible to the effects of ageing and Alzheimer's disease. In one disease model, progression of age-related cognitive decline to dementia is best represented by a reversal of corticogenesis (Arendt, 2001). To develop such models further requires better understanding of ageing processes than is now available. Biological components of ageing certainly involve complex interplay between intrinsic (mostly genetic) and extrinsic (mostly environmental) factors. Recent progress encourages some optimism that a small number of highly conserved genes affect life span and do so through a similarly small number of metabolic processes. This view contrasts with the previous 'degenerative' position that held biological ageing to be haphazard and not amenable to study. Generation of metabolites of oxygen termed 'reactive oxygen species' (ROS) is an important cause of oxidative stress and ROS are intimately involved in the biology of ageing (Finkel & Holbrook, 2000). There are some parallels between ageing and altered metabolic states induced in lower organisms by adverse circumstances that are surprisingly similar in yeasts, nematodes, fruit flies and mammals (Guarente & Kenyon, 2000). They permit postponement of reproduction during unfavourable environmental conditions, and control expression of genes that protect against ROS damage and genes involved in insulin signalling (Finch & Ruvkun, 2001). Reduced expression of ageing genes involved in insulin-like receptor signalling extends life span, and this may be a specific property of neurons (Boulianne, 2001).

Extrinsic contributions to brain ageing are poorly understood and lag some way behind elegant scientific studies of intrinsic components. Acquired defences against ROS damage are largely derived from dietary antioxidants which oppose ROS production. When ROS defences falter, additional burdens are placed on the brain's capacity to maintain structural integrity, most often threatened by increased peroxidation of neuronal lipid membranes, oxidative damage to DNA or large regulatory molecules (Whalley, 2001). Terminally differentiated cells such as neurons cannot dispose of DNA damage by cell division and must rely on their own DNA repair enzymes. This type of damage may not only compromise the performance of neuronal sub-populations that provide higher mental functions but also impair the capacity to make good or compensate for performance decrements.

Arendt (2001) has summarised much of the available evidence to support the hypothesis that age-related cognitive decline and Alzheimer's disease are best understood as progressive failure of synaptic remodelling. In his view, there is much compelling evidence to accept, first, that abnormal

dendritic sprouting occurs in Alzheimer's disease, and second, that 'morphoregulatory molecules' involved in neurodevelopment re-emerge as part of Alzheimer molecular pathology. He suggests, for example, that the conserved functions of amyloid precursor protein (APP), the presenilins and apolipoprotein E (all implicated in Alzheimer's disease) are the key roles of morphoregulatory molecules in synaptic formation, turnover and stabilisation. They are preferentially expressed in adult brain in areas that retain most capacity to modify synaptic function. Morphogenesis of neurons has been of enormous relevance in understanding neurodevelopment and differential survival of cell types. Arendt (2001) now extends their significance to late life. First, he argues that these molecular processes underpin the 'functional sculpting' used by the immature brain to 'self-organise' the acquisition of higher functions such as language. Second, he identifies among the detritus of dementia, features that imply reactivation of brain self-organising molecular machinery. In Arendt's view, it is this reactivation that triggers the cascade of events which results eventually in the selective loss of cortical neurons.

To this model, Arendt (2001) adds the lifelong accumulation of noxious influences on brain function from sources as diverse as malnutrition, neurotoxins and cerebrovascular disease. Age-related endogenous oxidative damage to neurons (summarised above) further stresses brain adaptive mechanisms. The gradual and pervasive result is to jeopardise the high investment made by those neurons that retain a capacity for synaptic remodelling after completion of brain maturation. Missing from Arendt's model are mechanisms that account for individual and gender differences in rate of change in traits associated with dementia. This dilemma is familiar to developmental neuroscientists and has a strong likeness to current research problems in the molecular genetics of cognition (Plomin & Craig, 2001). Potentially, hormonal and genetic contributions to synaptic remodelling could be relevant. For example, there is evidence that oestrogens induce synapse formation in rat hippocampus and that this induction is dependent on apolipoprotein E (Stone *et al*, 1998). Diversity in efficiency of self-organisation may contribute to variation in childhood mental ability; these differences may extend into late life, leading to the divergence between brain ageing and dementia.

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CONCLUSION

Understanding individual differences in age-related cognitive decline is beset with difficulty. Neuropathological evidence of the hypothetical discontinuity between 'normal' ageing and dementia is lacking; the best available evidence suggests that there is no boundary at all. Detection of sources of variation in rate of cognitive decline requires considerable investment in longitudinal, population-based studies. The MRC–CFAS findings are the outcome of a longitudinal study that will continue to be informative for many years. Quite rightly, the study has focused on dementia outcomes over an age interval when the risk of dementia is high.

The problem of the boundary between brain ageing and dementia remains. It will demand detailed attention in the analysis of current longitudinal databases and in future research design. Some clarification seems certain if the recommendations of the National Institute of Aging Working Group on Aging and Genetic Epidemiology (2001) come to influence brain ageing research goals and practice. As the precise tools of molecular biology are applied to the phenomena of ageing, so boundaries may be brought into focus. So far, it seems, those boundaries are not where the clinical data suggested they should be. If the ultimate research goal is to postpone or perhaps even to prevent dementia, research of this type is certain to inform the timing of successful intervention.

DECLARATION OF INTEREST

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