Box 1

Brain changes with ageing

Massive pruning, particularly of frontal connections, takes place in adolescence. Pruning makes neuronal function more specialised and predictable, also presumably more robust and effective in the environment for which the selective pruning was an adaptation. In this sense, age-dependent loss of brain plasticity may have an important role to play in normal brain development.

Mechanisms of adolescent brain maturation that involve nerve growth factor, brain derived neurotrophic factor, serotonin, oestrogen, growth hormone, Ca++-synaptic plasticity, or reactive oxygen species may play a similar, but deleterious role in cognitive ageing.[1]

Table 1

Established beneficial effect on cognitive function

Remedy	Method (Year)	Results (significant ● and non-significant ●)
Alcohol consumption as a risk factor for dementia and cognitive decline[14, 15]	Meta-analyses of 23 studies (2008)/ 15 prospective studies (2009)	● Pooled RR of Alzheimer's disease for light to moderate drinkers compared with non-drinkers 0.57 to 0.72 ● Pooled RR of vascular dementia for light to moderate drinkers compared with non-drinkers 0.75 to 0.82 (ns) ● Pooled RR of any dementia for light to moderate drinkers compared with non-drinkers 0.63 to 0.74 ● Pooled RR of cognitive decline for light to moderate drinkers compared with non-drinkers 0.89 (ns)

Table 3

Established absence of beneficial effect on cognitive function

Remedy	Method (Year)	Results
HRT to improve cognitive function or delay or prevent dementia[18-21]	Cochrane reviews of 16/7 studies (2008; 2009)	● Good evidence of NO beneficial effects on cognitive function in demented and non-demented women
DHEA supplementation for cognitive function in healthy elderly people[22]	Cochrane review: meta-analysis of 3 studies (2006)	● NO beneficial effect of DHEA supplementation on cognitive function of non-demented middle-aged or elderly people[22]
BP lowering in patients without prior cerebrovascular disease to prevent cognitive impairment and dementia[23, 24]	Cochrane review: meta-analysis of 4 studies (2009)	● NO significant difference between treatment and placebo (236/7767 versus 259/7660, OR = 0.89, 95% CI: 0.74 to 1.07) ● Changes in MMSE indicated NO benefit from treatment. Weighted Mean Difference (WMD) = 0.42, 95% CI: 0.30 to 0.53
Statins for the prevention of dementia[9]	Cochrane review: meta-analysis of 2 studies (2009)	● Good evidence from RCTs that statins given in late life to individuals at risk of vascular disease have NO effect in preventing Alzheimer's disease or dementia[9]
Vitamin B_6 and cognition[26]	Cochrane review: meta-analysis of 2 studies (2003)	● NO short-term benefit on cognition

key points

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Cognitive speed, inhibitory function, and memory decline with age while crystallised, particularly verbal, abilities remain largely intact. Poor health, fewer years of education, lower activity, the presence of the APOE ε4 allele, and high BP appear to predict faster cognitive decline.

Dementia is diagnosed in the presence of objective cognitive impairment, both long- and short-term memory, plus at least one additional (cortical) cognitive deficit, such as dysphasia, dyspraxia, agnosia, or disturbance in executive functioning (e.g. planning, organising, sequencing). In addition, patients have to show significant impairment in social or occupational functioning and a significant decline from previous levels.

Both smoking and diabetes increase the risk of all types of dementia, not smoking or even stopping smoking reduces this risk, but better control of type 2 diabetes does not appear to have a measurable effect. Drinking small to moderate amounts of alcohol appears to confer some benefit in ameliorating cognitive decline. However, there is some evidence that HRT, DHEA, BP lowering in patients without prior cerebrovascular disease, statins, vitamin B_6 and procaine are NOT helpful. The usefulness of exercise, treatment of type 2 diabetes, omega-3 fatty acids, folic acid with or without vitamin B_{12}, antioxidant vitamins, or ginkgo biloba remains controversial as there is insufficient evidence to establish or refute a beneficial effect.

In the community, depressive symptoms are more prevalent than dementia. Clinical (major) depression can present with cognitive deterioration, often associated with subjective complaints. Any sign of low mood is suggestive of depressive aetiology, but also evidence of diurnal variation, especially with worse symptoms in the morning, psychomotor slowing, anxiety and agitation, disturbance of sleep, appetite and motivation. Disproportionately severe deterioration particularly with complaints of poor memory or 'something wrong with the brain', in the absence of signals of underlying physical illness should prompt a review of depressive symptoms.

Patients with subjective or objective memory impairment, but without functional deterioration, can be referred to the local memory clinic (where available), while demented patients eligible for acetylcholinesterase inhibitor treatment, patients whose diagnosis is unclear and who may need some specific investigations, as well as patients who may benefit from a combined approach with psychotropic drugs and behavioural support should be referred to the local mental health team.

If patients are depressed, referral may be indicated if: the first or later line of antidepressant treatment fails; patients are acutely psychotic, suicidal or at risk of self-neglect; or if a specialist psychotherapeutic intervention appears warranted.

Table 2

Established detrimental effect on cognitive function

Risk factor or remedy	Method (Year)	Results
Smoking as a risk factor for dementia and cognitive decline[11]	Meta-analysis of 19 prospective studies with at least 12 months of follow-up (2007)	● Current smokers at baseline relative to never smokers: Pooled RR for incident Alzheimer's disease 1.79 (95% CI: 1.43 to 2.23) Pooled RR for incident vascular dementia 1.78 (95% CI: 1.28 to 2.47) Pooled RR for any dementia 1.27 (95% CI: 1.02 to 1.60). Greater yearly declines in MMSE over the follow-up period (β=-0.13, 95% CI: -0.18 to -0.08). ● Current smokers at baseline compared with former smokers: Pooled RR of Alzheimer's disease 1.70 (95% CI: 1.25 to 2.31). Increased decline in cognitive abilities (β=-0.07, 95% CI: -0.11 to -0.03)
Diabetes and the risk of multisystem ageing phenotypes[12, 13]	Systematic review and meta-analysis of 15 studies (2009)	● Pooled RR for Alzheimer's disease comparing persons with diabetes with those without was 1.39 (CI: 1.16 to 1.66) ● Pooled RR for vascular dementia comparing persons with diabetes with those without was 2.38 (CI: 1.79 to 3.18) ● Pooled RR for all dementia when persons with diabetes were compared with those without was 1.47 (95% CI: 1.25 to 1.73)
Procaine for cognition and dementia[31]	Cochrane review: meta-analysis of 2 controlled studies (2008)	● Detrimental effect of procaine (20/208 active versus 3/207 placebo, OR 7.30, 95% CI: 2.13 to 25.02, P = 0.002)

Table 4

Insufficient data to establish or refute a beneficial effect on cognitive function

Remedy	Method (Year)	Results
Physical activity programmes for persons with/without dementia[16, 17]	Cochrane review: meta-analyses of 4/11 studies (2008; 2009)	● Insufficient and inconsistent evidence of effect on cognitive function
Treatment of type 2 diabetes[10]	Cochrane review: meta-analysis of 5 studies (2002)	● NO convincing evidence relating type or intensity of diabetes treatment to the prevention or management of cognitive impairment in type 2 diabetes (no recent update)
Omega-3 fatty acids for the prevention of dementia[25]	Cochrane review: meta-analysis (2006)	● No suitably controlled data available, recent controlled trials have been negative
Folic acid ± vitamin B_{12} for prevention and treatment in healthy elderly and demented people[27]	Cochrane review: meta-analysis of 8 studies (2008)	● There is no adequate evidence of benefit from folic acid supplementation with or without vitamin B_{12} on cognitive function and mood of unselected healthy elderly people. ● In healthy elderly people with high homocysteine levels, 800 mcg/day folic acid supplementation over three years was associated with significant benefit in terms of: **a. global functioning** WMD 0.05, 95% CI: 0.004 to 0.096, P = 0.033 **b. memory storage** WMD 0.14, 95% CI: 0.04 to 0.24, P = 0.006 **c. information-processing speed** WMD 0.09, 95% CI: 0.02 to 0.16, P = 0.016 ● In people with cognitive impairment including Alzheimer's disease there was inconsistent benefit in measures of cognitive function from folic acid, with or without vitamin B_{12}. Folic acid plus vitamin B_{12} was effective in reducing serum homocysteine concentrations (WMD -5.90, 95% CI: -8.43 to -3.37, P < 0.00001)[27]
Vitamin, mineral and fatty acid supplements to prevent cognitive decline[28, 29]	Meta-analysis of 22 trials (2008)	"NO significant effect of taking B vitamins or antioxidant vitamins on global cognitive function. There was insufficient evidence to evaluate the effect of omega-3 fatty acids on any cognitive domains"[28]
Ginkgo biloba for cognitive impairment and dementia[30]	Cochrane review: meta-analysis of 36 controlled studies (2008)	The results from the more recent methodologically adequate trials show INCONSISTENT results for cognition, activities of daily living, mood, depression and carer burden[30]