The Practitioner®

Normal cognitive decline or dementia?

Ebmeier KP. Normal cognitive decline or dementia?
Practitioner 2010;254(1725): 23-27

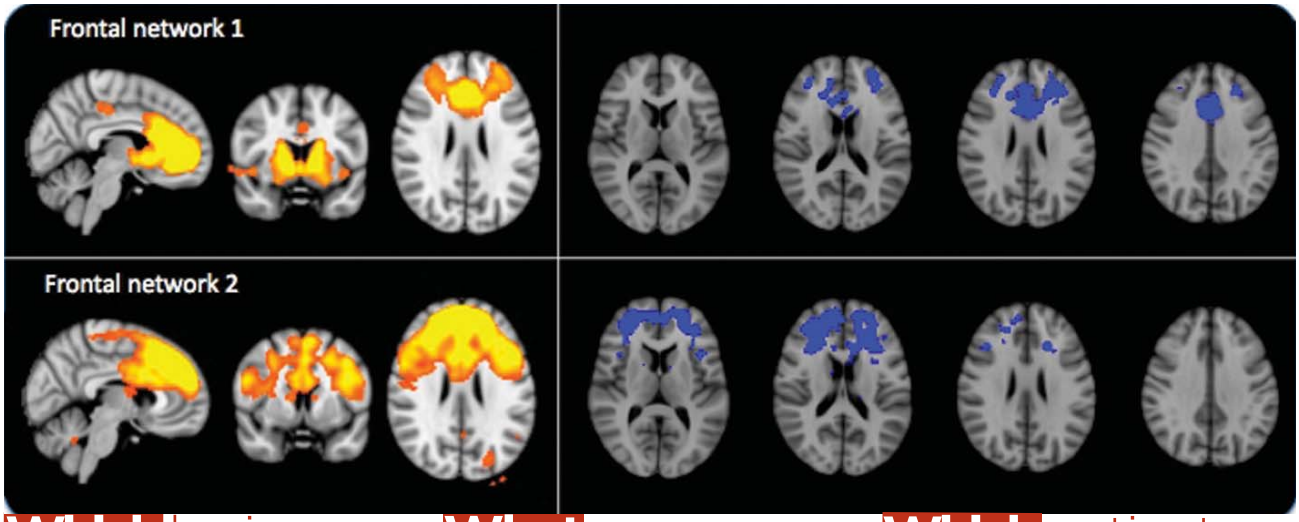
Professor Klaus P. Ebmeier MD
Foundation Professor of Old Age Psychiatry, University of Oxford

Practitioner
Medical Publishing Ltd

©Practitioner Medical Publishing Ltd.
Reprint orders to *The Practitioner*, 10 Fernthorpe Road, London SW16 6DR, United Kingdom. Telephone: +44 (0)20 8677 3508
www.thepractitioner.co.uk

Normal cognitive decline or dementia?

AUTHOR
Professor Klaus P. Ebmeier
MD
Foundation Professor of Old Age Psychiatry, University of Oxford



Courtesy of Dr Clare Mackay, University of Oxford

FIGURE 1
The left column (yellow) shows two frontal functional networks derived from resting functional MRI scans in 44 healthy volunteers. The right column (blue) shows the areas where older adults have greater coherence than younger adults (possible evidence of prefrontal scaffolding of other brain functions)

Which brain functions decline with age?

BRAIN AGEING IS GENERALLY THOUGHT OF AS ATROPHY, A MORE OR LESS PATHOLOGICAL loss of neurones, leading to cognitive deficits and functional impairment, if not clear-cut symptoms and signs of dementia. This model is likely to be relevant for the dementias,[2] or for brain changes associated with systemic, especially vascular pathologies.[3,4] There are, however, also physiological reductions in cell numbers, connectivity and brain plasticity during the life span, right from birth, that may play an important role in the adjustment of brain function to the changing roles of the individual (see box 1, right).[1]

‘Cognitive speed, inhibitory function, and memory decline with age’

What measures can be taken to halt decline?

NORMAL AGEING

There is general agreement that cognitive speed, inhibitory function, and memory performance decline with age while crystallised, particularly verbal, abilities remain largely intact in those who survive for long-term follow-up.[5]

The following factors appear to predict faster cognitive decline:[5]

- poor health
- fewer years of education
- lower activity
- the presence of the APOE ε4 allele (which appears associated with age-related cognitive impairment, cardiovascular disease, Alzheimer’s disease, and poor outcome after brain trauma)
- high blood pressure

Age-related reductions in hippocampal function and particularly in plasticity may account for some of these changes.[6] Typically, however, the brain is not a passive organ that just shows local underactivity in the affected region. Compensatory additional recruitment of neurones occurs mainly in prefrontal brain areas (see figure 1, above) to back up »

Which patients should be referred?

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 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)

compromised functions.[7,8] This may explain the observation that older people may perform as well as their younger peers by using alternative strategies. How effectively such prefrontal scaffolding works, will affect the speed of functional deterioration. It is likely that compensatory mechanisms rather than the primary deficit associated with declining short-term memory are modified by training, so they should be the focus of remedial strategies against cognitive deterioration.[7]

HALTING DECLINE

What measures, if any, can be taken to halt decline in function? This question can only be answered by randomised controlled trials. There is a temptation to infer risks and benefits from association studies, but unfortunately there is often no correspondence between the results of cohort or case-control studies which may be confounded, and the properly controlled randomised studies.[9]

Tables 1-4, above and opposite, summarise recent reviews of studies examing risk factors and interventions to ameliorate cognitive decline.

'Both smoking and diabetes increase the risk of all types of dementia'

Evidence of benefit

Alcohol: Drinking small to moderate amounts of alcohol appears to confer some benefit (see table 1, above).

Stopping smoking: Both smoking and diabetes increase the risk of all types of dementia (see table 2, above), not smoking or even stopping smoking reduces this risk, but better control of type 2 diabetes does not appear to have a measurable effect (although the most recent review was carried out in 2002).[10]

Evidence of no benefit

There is some evidence that the following are NOT helpful (see table 3, opposite):

- HRT
- DHEA supplementation
- BP lowering in patients without prior cerebrovascular disease
- statins
- vitamin B_6
- procaine

Usefulness under debate

The usefulness of the following remains CONTROVERSIAL (see table 4, opposite) as there is insufficient evidence to establish or refute a beneficial effect:

- exercise
- treatment of type 2 diabetes
- omega-3 fatty acids
- folic acid with or without vitamin B_{12}
- antioxidant vitamins
- ginkgo biloba

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

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]

»

key points

SELECTED BY
Dr Peter Saul
GP, Wrexham and associate GP Dean for North Wales

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.

DIAGNOSING DEMENTIA

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
- 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[32]

Any evidence of the following may point towards alternative causes of cognitive deterioration:

- cerebrovascular disease
- Parkinson's disease
- Huntington's disease
- subdural haematoma
- normal-pressure hydrocephalus
- brain tumour

Thus, any localising neurological symptoms and signs require careful evaluation to exclude treatable disease.

DEPRESSION

Depressive symptoms are more prevalent than dementia in the community.[33] Clinical (major) depression can present with cognitive deterioration, often associated with subjective complaints. Obviously 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.

'Any localising neurological symptoms and signs require careful evaluation to exclude treatable disease'

'Depressive symptoms are more prevalent than dementia in the community'

DELIRIUM

The other cause of rapid cognitive deterioration, delirium, is characterised by evidence of underlying physical disease, sometimes trivial such as urinary tract infection, and psychiatric symptoms, such as (visual) hallucinations, anxiety, agitation, and disorientation.

CONCLUSION

Patients presenting with cognitive deterioration, i.e. subjective deterioration or decline observed by their family, require an estimation of degree of functional impairment relative to pre-morbid levels if any, and then a systematic evaluation of physical and mental state, with referral to memory clinics or other specialist assessment if necessary.[34]

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.[34]

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.[33]

REFERENCES

1 de Magalhaes JP, Sandberg A. Cognitive aging as an extension of brain development: a model linking learning, brain plasticity, and neurodegeneration. *Mech Ageing Dev* 2005;126 (10): 1026-33
2 Nelson PT, Braak H, Markesbery WR. Neuropathology and cognitive impairment in Alzheimer disease: a complex but coherent relationship. *J Neuropathol Exp Neurol* 2009; 68(1): 1-14
3 Schmahmann JD, Smith EE, Eichler FS et al. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. *Ann N Y Acad Sci* 2008; 1142: 266-309
4 Iadecola C, Park L, Capone C. Threats to the mind: aging, amyloid, and hypertension. *Stroke* 200; 40 (3 Suppl): S40-4
5 Christensen H. What cognitive changes can be

expected with normal ageing? *Aust N Z J Psych* 2001; 35(6): 768-7
6 Lister JP, Barnes CA. Neurobiological changes in the hippocampus during normative aging. *Arch Neurol* 2009; 66(7): 829-33
7 Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol* 2009; 60: 173-96
8 Han SD, Bangen KJ, Bondi MW. Functional magnetic resonance imaging of compensatory neural recruitment in aging and risk for Alzheimer's disease: review and recommendations. *Dement Geriatr Cogn Disord* 2009;27 (1): 1-10.
9 McGuinness B, Craig D, Bullock R, et al. Statins for the prevention of dementia. *Cochrane Database Syst Rev* 2009 (2): CD003160
10 Areosa SA, Grimley EV. Effect of the treatment of Type II diabetes mellitus on the development of cognitive impairment and dementia. *Cochrane Database Syst Rev* 2002 (4): CD003804
11 Anstey KJ, von Sanden C, Salim A et al. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol* 2007; 166 (4): 367-78
12 Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. *PLoS One* 2009; 4 (1): e414.
13 Wrighten SA, Piroli GG, Grillo CA et al. A look inside the diabetic brain: Contributors to diabetes-induced brain aging. *Biochem Biophys Acta* 2009;1792 (5): 444-53
14 Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *Am J Geriatr Psych* 2009; 17(7): 542-55
15 Peters R, Peters J, Warner J et al. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing* 2008; 37 (5): 505-12
16 Forbes D, Forbes S, Morgan DG et al. Physical activity programs for persons with dementia. *Cochrane Database Syst Rev* 2008 (3): CD006489
17 Angevaren M, Aufdemkampe G, Verhaar HJ et al. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev* 2008 (3): CD005381
18 Dunne L, Seaton TL. Does hormone replacement therapy (HRT) improve cognitive function or either delay or prevent dementia in postmenopausal women? *J Fam Pract* 2001; 50 (6): 547
19 Hogervorst E, Yaffe K, Richards M et al. Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev* 2009(1): CD003799
20 Kurt M, Bekci B, Karakas S. Hormone replacement therapy and cognitive function in postmenopausal women. *Maturitas* 2006 ; 53(1): 39-48
21 Lethaby A, Hogervorst E, Richards M et al. Hormone replacement therapy for cognitive function in postmenopausal women. *Cochrane Database Syst Rev* 2008 (1): CD003122
22 Grimley Evans J, Malouf R, Huppert F et al. Dehydroepiandrosterone (DHEA) supplementation for cognitive function in healthy elderly people. *Cochrane Database Syst Rev* 2006 (4): CD006221
23 McGuinness B, Todd S, Passmore P et al. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev* 2009 (4): CD004034
24 Duron E, Hanon O. Hypertension, cognitive decline and dementia. *Arch Cardiovasc Dis* 2008;101(3):181-9
25 Lim WS, Gammack JK, Van Niekerk J et al. Omega 3 fatty acid for the prevention of dementia. *Cochrane Database Syst Rev* 2006 (1): CD00537
26 Malouf R, Grimley Evans J. The effect of vitamin B6 on cognition. *Cochrane Database Syst Rev* 2003 (4): CD004393
27 Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. *Cochrane Database Syst Rev* 2008 (4): CD004514
28 Jia X, McNeill G, Avenell A. Does taking vitamin, mineral and fatty acid supplements prevent cognitive decline? A systematic review of randomized controlled trials. *J Hum Nutr Diet* 2008; 21(4): 317-36
29 Pratico D. Evidence of oxidative stress in Alzheimer's disease brain and antioxidant therapy: lights and shadows. *Ann N Y Acad Sci* 2008; 1147: 70-8
30 Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev* 2009(1):CD003120
31 Szatmari S, Bereczki D. Procaine treatments for cognition and dementia. *Cochrane Database Syst Rev* 2008(4): CD005993
32 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association. Washington, D.C. 1994
33 Gargiulo A, Ebmeier KP. Awareness key in managing depression in later life. *Practitioner* 2008; 252(1705): 32-39
34 Gargiulo A, Ebmeier KP. Managing Alzheimer's disease in primary care. *Practitioner* 2009 ; 253(1714): 19-22