Understanding normal and pathological declines in cognitive function and how they can be influenced by genetic and dietary factors

Professor Keith A. Wesnes
Wesnes Cognition Ltd, Streatley on Thames, UK

Department of Psychology,
Northumbria University, Newcastle, UK

Centre for Human Psychopharmacology
Swinburne University, Melbourne, Australia
Disclosures

• I am the developer of the CDR System
• Some of the data I shall be presenting is from the CDR System
• From 2009 until February 2014 I was employed by Bracket who provide the CDR System as a service to clinical trials
• I am a stockholder in Bracket
• Since March 2014, I own and run Wesnes Cognition Ltd which provides consultancy services to the clinical trials industry
Current Folklore

Sperling et al 2011 based on –
Relevant ILSI Publications

Evaluation of techniques to identify beneficial effects of nutrition and natural products on cognitive function

Keith A Wesnes

© 2010 ILSI Europe Nutrition Reviews® Vol. 68(Suppl. 1):S22–S28

Special Article

Criteria for validation and selection of cognitive tests for investigating the effects of foods and nutrients

Celeste A de Jager, Louise Dye, Eveline A de Bruin, Laurie Butler, John Fletcher, Daniel J Lamport, Marie E Latulippe, Jeremy PE Spencer, and Keith Wesnes

Vulnerable Domains of Human Cognitive Function

• Attention
  • Focussed, selective & sustained
• Information processing
• Working Memory
  • Verbal, numeric, spatial
• Episodic Memory
  • Verbal, visual
• Executive Function
• Psychomotor skills
Cognitive Declines in Normal Ageing
Declines in Cognitive Function in Normal Ageing

In an extensive research program over 20 years Salthouse & colleagues have convincingly demonstrated that all major domains of cognitive function decline from the 20s to the 90s in healthy individuals.

Timothy Salthouse. What is normal cognitive aging?
Alzheimer’s Association Research Roundtable: Early Risk Assessment for Alzheimer’s Disease
Washington, November 13, 2007
Common Assumptions about Cognitive Aging

- Only late in life
- Primarily memory
- Small effects
- Only some people

Declines in a measure of focussed attention and information processing in healthy volunteers (n=5989)

100 msec = 1 SD
Declines by percentiles

Ability to Focus Attention & Speed of Information Processing

Age-Group Years
18-25 26-30 31-35 36-40 41-45 46-50 51-55 56-60 61-65 66-70 71-75 76-80 80-87

msec
5th Percentile
25th Percentile
50th Percentile
75th Percentile
95th Percentile

Age-Group Years
18-25 26-30 31-35 36-40 41-45 46-50 51-55 56-60 61-65 66-70 71-75 76-80 80-87
CDR System Data from 5989 healthy individuals and >800 MCI & AD patients

Pattern comparable in a range of other measures

2002 onwards – Testing via the Internet
Declines in very healthy individuals (n=5989) and a opportunistic sample (n=93,334) who were tested remotely via the internet.
Declines in internet testing by percentiles

Age Group Years

18-25
26-30
31-35
36-40
41-45
46-50
51-55
56-60
61-65
66-70
71-75
76-80
81-87

msec
1000
1100
1200
1300
1400
1500
1600
1700
1800

5th Percentile
25th Percentile
50th Percentile
75th Percentile
95th Percentile
Are cognitive declines in normal ageing worthy of treatment?
Have either science or regulatory authorities recognised this decline and attempted to classify it as a treatable condition?

Benign Senescent Forgetfulness - The Beginning

Senescent Forgetfulness: Benign and Malignant

V. A. KRAL, M.D., Montreal
A unitary process?

This does not necessarily mean that one is dealing with two different processes. One might speculate that the senile atrophic process, when it affects the brain only mildly, and particularly when it relatively spares the hippocampal-fornix-mammillary system, may be accompanied by the benign type of memory dysfunction. When, however, these structures are affected more severely, the malignant memory dysfunction may result. In favour of such a unitarian pathogenetic hypothesis would seem to be the fact that the neuropathological findings do not permit a strict differentiation between the brains of people who had died in possession of their mental capacities from those who had died from senile dementia. Cerebral atrophy, fibrillary degeneration and senile plaques are found in both groups, although they are somewhat more pronounced in the latter than in the former. On the
1986 NIMH criteria for Age-Associated Memory Impairment

Age-Associated Memory Impairment: Proposed Diagnostic Criteria and Measures of Clinical Change – Report of a National Institute of Mental Health Work Group

Thomas Crook
Memory Assessment Clinics, Inc.

Box 2. Diagnostic criteria for age-associated memory impairment (Crook et al, 1986)

Aged over 50 years
History of gradual memory dysfunction apparent in activities of daily life
Subjective memory complaints substantiated by objective evidence of deficits as measured by performance on a well-standardised memory test at least one standard deviation below the mean established for young adults
Intact global intellectual function
Absence of dementia as determined by a score of 24 or higher on the Mini-Mental State Examination
Part of the Problem with AAMI

Overall, the merits of AAMI as a diagnosis remain unclear and some see its main purpose as a label to justify pharmacotherapy for what are essentially age-related memory changes experienced by the majority of the population.
Age-Related Cognitive Decline (ARCD)  
A Temporary Solution?

• DSM-IV identified Age-Related Cognitive Decline (ARCD) as a condition which may be a focus of clinical attention (diagnostic code 780.9).

• The advantage of ARCD is that it extended the range of impairments from simply memory to cognitive functioning in general, thus encompassing attention, information processing and a range of other aspects now known to deteriorate with ageing.

  • The definition was for:

    • A decline in cognitive functioning consequent to the ageing process that is within normal limits given the person’s age.
    • ‘Individuals with this condition may report problems remembering names or appointments or may experience difficulty in solving complex problems’.
Perceived problems with treating age-related cognitive decline
The elephant in the room — healthy brains in later life, epidemiology and public health

Carol Brayne

‘Adding life to years as well as years to life’
Light at the end of the tunnel
Sting of Alzheimer’s failures offset by upcoming prevention trials

Three prevention trials in asymptomatic Alzheimer’s disease patients will attempt to validate the amyloid hypothesis, evaluate biomarkers and set the stage for drug approvals.

Asher Mullard

Table 1 | Summary of upcoming prevention trials in Alzheimer’s disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Main patient population</th>
<th>Number of subjects*</th>
<th>Drugs (all versus placebo)</th>
<th>Primary aim and trial duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Asymptomatic PSEN1 E280A carriers, within 15 years of expected age of onset</td>
<td>216</td>
<td>Crenzumab</td>
<td>Cognition at 5 years</td>
</tr>
<tr>
<td>DIAN</td>
<td>Asymptomatic ADAD mutation carriers, 15 years before and up to 10 years after expected age of onset</td>
<td>160</td>
<td>Three undisclosed drugs</td>
<td>Target engagement at 2 years; a subsequent trial will assess cognition 3 years on</td>
</tr>
<tr>
<td>A4</td>
<td>Asymptomatic elderly patients with PET-amyloid positivity</td>
<td>1,000</td>
<td>An undisclosed drug</td>
<td>Cognition at 3 years</td>
</tr>
</tbody>
</table>

*Only including mutation carriers and positron emission tomography (PET)-amyloid positive patients; all trials will also enrol negative biomarker patients for ethical reasons. A4, anti-amyloid treatment in asymptomatic Alzheimer’s disease; ADAD, autosomal-dominant Alzheimer’s disease; API, Alzheimer’s Prevention Initiative; DIAN, Dominantly Inherited Alzheimer Network; PSEN1, presenilin 1.
Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease

Reisa A. Sperling a,*, Paul S. Aisen b, Laurel A. Beckett c, David A. Bennett d, Suzanne Craft e, Anne M. Fagan f, Takeshi Iwatsubo g, Clifford R. Jack, Jr. h, Jeffrey Kaye i, Thomas J. Montine j, Denise C. Park k, Eric M. Reiman l, Christopher C. Rowe m, Eric Siemers n, Yaakov Stern o, Kristine Yaffe b, Maria C. Carrillo q, Bill Thies q, Marcelle Morrison-Bogord r, Molly V. Wagster f, Creighton H. Phelps r
The pathophysiological process of AD is thought to begin many years before the diagnosis of AD dementia. This long “preclinical” phase of AD would provide a critical opportunity for therapeutic intervention. ...even this preclinical stage of the disease represents a continuum from completely asymptomatic individuals...

Similarly, additional work is required to identify and validate neuropsychological and neurobehavioral measures to detect the earliest clinical manifestations of AD. Longitudinal studies of older individuals, perhaps combining biomarkers with measures sensitive to detecting very subtle cognitive decline, are clearly needed.

...it is important not to lose sight of the potential that behavioral markers hold for early identification. It is likely that measured change in cognition over time will be more sensitive than any one-time measure.

...to biomarker-positive individuals who are already demonstrating very subtle decline but not yet meeting standardized criteria for MCI. Normal aging is accompanied by declines in speed of information processing, executive function (working memory, task switching, inhibitory function), and reasoning.
For patients whose disease is at an even earlier clinical stage, so that functional impairment would be more difficult to assess, it might be feasible to approve a drug through the FDA’s accelerated approval pathway on the basis of assessment of cognitive outcome alone.”
Is EFSA more flexible on age-related cognitive declines?

SCIENTIFIC OPINION

Guidance on the scientific requirements for health claims related to functions of the nervous system, including psychological functions

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)², ³

European Food Safety Authority (EFSA), Parma, Italy
Clear opportunity to study the declines which occur in normal ageing

With respect to the study population, results from studies conducted in subjects with mild cognitive decline, without clinical diagnosis of dementia or other psychological or neurological diseases which may be responsible for the impairment, could be used for the scientific substantiation of claims on cognitive function, as long as the methods and inclusion/exclusion criteria used to characterise the study group are clearly defined. The rationale for extrapolation of the results obtained in patients with clinical diagnosis of a cognitive disease (e.g. dementia) to the target population for the claim (e.g. subjects without the disease) should be provided, and will be considered on a case-by-case basis (e.g. evidence that the mechanism by which the food constituent may exert the claimed effect on cognition in subjects with the disease is also relevant for subjects without the disease). Where appropriate, the confounding role of medication should be considered (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect).
Do we have the right tools?
ADNI Normal Control Group

- Data downloaded from the ADNI database
- 249 non-cognitively impaired individuals
- Mean age 76 years (range 60-90)
- Mean MMSE 29 (range 24-30)
- Repeatedly performed a variety of neuropsychological tests for up to 6 years
- Population comparable to those who will participate in preclinical AD trials

Wesnes KA, Schneider LS (2012) Are neuropsychological tests such as those used in ADNI suitable for long-term trials of cognition enhancers for preclinical Alzheimer’s disease? Journal of Nutrition, Health & Aging 16: 810
Tests Administered

• Rey AVLT
• WMS Logical Memory I/II
• Category Fluency
• DSST
• Digit Span
• Boston Naming Test
• Trail Making Test
• Clock Copying Task
• Clock Drawing Task

Wesnes KA, Schneider LS (2012) Are neuropsychological tests such as those used in ADNI suitable for long-term trials of cognition enhancers for preclinical Alzheimer’s disease? *Journal of Nutrition, Health & Aging* 16: 810
Ceiling Effects on Clock and Boston Naming

Clock Drawing & Copying Tasks (range 0 to 5) % ADNI scoring 0 to 5 at baseline

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drawing</td>
<td>0</td>
<td>0.8</td>
<td>0.4</td>
<td>4.4</td>
<td>17.6</td>
<td>76.7</td>
</tr>
<tr>
<td>Copying</td>
<td>0</td>
<td>0</td>
<td>0.4</td>
<td>1.6</td>
<td>8.9</td>
<td>89.1</td>
</tr>
</tbody>
</table>

Boston Naming Test (range 0 to 30) % scoring 25 to 30

<table>
<thead>
<tr>
<th></th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>5.6</td>
<td>6.8</td>
<td>12.4</td>
<td>16.5</td>
<td>21.3</td>
<td>28.5</td>
<td>91.2</td>
</tr>
</tbody>
</table>

Wesnes KA, Schneider LS (2012) Are neuropsychological tests such as those used in ADNI suitable for long-term trials of cognition enhancers for preclinical Alzheimer’s disease? Journal of Nutrition, Health & Aging 16: 810
Data show persistent training effects

Decline from year 0

Wesnes KA, Schneider LS (2012)
Plus non-eqivalent parallel forms

Decline from year 0

AVLT - Immediate Recall
ADNI Controls
LSMeans with 95% Confidence Intervals

AVLT - Delayed Recall
ADNI Controls
LSMeans with 95% Confidence Intervals

Wesnes KA, Schneider LS (2012)
Effect Sizes of peak improvements for measures on which significant training effects were seen

<table>
<thead>
<tr>
<th>Measure</th>
<th>Years</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails A</td>
<td>0.5, 1, 2</td>
<td>0.22 - 0.31</td>
</tr>
<tr>
<td>Trails B</td>
<td>1</td>
<td>0.28</td>
</tr>
<tr>
<td>DSST</td>
<td>1, 2</td>
<td>0.19 - 0.20</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>0.5, 1, 2, 3, 5</td>
<td>0.31 - 0.48</td>
</tr>
<tr>
<td>Rey AVLT Delayed</td>
<td>1, 2</td>
<td>0.2 - 0.31</td>
</tr>
<tr>
<td>Logical Immediate</td>
<td>1, 2, 3, 4, 5, 6</td>
<td>0.43 - 0.72</td>
</tr>
<tr>
<td>Logical Delayed</td>
<td>1, 2, 3, 4, 5, 6</td>
<td>0.25 - 0.53</td>
</tr>
</tbody>
</table>
No test showed any consistent evidence of decline over 6 years, although:

- 11% developed aMCI
- Plus over the period
  - Cortical thickness declined steadily
  - Hippocampal volume decreased steadily
Had such effects been seen previously?

n= 694  
Mean age 75.9 years (SD 6.9)  
MMSE 28.3 (SD 1.7)  
Tested yearly over 6 years

<table>
<thead>
<tr>
<th></th>
<th>Baseline to next 6 years</th>
<th>Year 1 to next 5 years</th>
<th>Year 2 to next 4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Story retention</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word retention</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word generation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Word knowledge</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Individual differences in rates of change in cognitive abilities of older persons.  
A major problem with cognitive tests – practice/training effects

Cross-sectional assessments

Repeated assessments

Fig. 1. Estimates of cross-sectional differences and longitudinal changes over 7 years in two variables from the Seattle Longitudinal Study. Cross-sectional data from Table 4.2 and longitudinal data from Table 5.1 of Schaie (2005). The figures in the top two panels portray results of cross-sectional (dotted lines) and longitudinal (solid lines) comparisons in T-score units. The figures in the bottom two panels portray the same data as differences or changes over a 2.5-year interval in standard deviation units.
Practice Effects: A major limitation to the sensitivity of cognitive tests

Repeated testing of cognitive function in clinical trials is essential if the effects of a treatment are to be identified. Although such practice effects have long been known, and clear recommendations have been made for pres Study training in order to overcome them training is rarely done, particularly with pencil and paper tests. However, to avoid such potential problems, future work with cognitive tests should utilise tests with established training profiles. Computerised cognitive test systems are widely available, some with established training profiles. Such computerisation can improve the ease and quality of data collection, even in populations of patients with dementia.

Practice effects on cognitive tests are not a minor nuisance but a major potential problem that must be overcome by appropriate pres study training. Wesnes KA, Pincock C (2002). Practice effects on cognitive tasks: a major problem? The Lancet Neurology 1: 473.
Have there been no published guidelines on cognitive tests?

Objective Psychometric Tests in Clinical Trials of Dementia Drugs
Position Paper from the International Working Group on Harmonization of Dementia Drug Guidelines

Steven H. Ferris, *Ugo Lucca, †Richard Mohs, ‡Bruno Dubois, §Keith Wesnes, ¶Hellmut Erzigkeit, #David Geldmacher, and **Neil Bodick

NYU Medical Center, New York, New York, U.S.A.; *Instituto “Mario Negri,” Milan, Italy; †Mount Sinai School of Medicine, New York, New York, U.S.A.; ‡Groupe Hospitalier, Paris, France; §Cognitive Drug Research, Ltd., Reading, U.K.; ¶Universitat Erlangen–Nurnberg, Erlangen, Germany; #University Hospitals, Cleveland, Ohio, U.S.A.; and **Eli Lilly and Co., Indianapolis, Indiana, U.S.A.
Uniform Criteria/Requirements for Optimal Cognitive Assessment Instruments

*Sensitivity range*
- absence of ceiling and floor effects

*Practice effects*
- determines the need for practice sessions before the start of the trial

*Equivalent forms*
- for repeated testing over the course of the trial

*Validity*
- the instrument must measure the intended disease-relevant cognitive functions

*Longitudinal data*
- information should be available on expected change over the course of the trial, which is helpful for making power calculations

Ferris et al (1997)
Can computerised testing do any better?
Declines over 3 years for 777 individuals performing CDR System tests in Newcastle 85+ Study
Declines over 5 years in 256 non-demented subjects aged 70 to 90 performing CDR System tests

Wesnes K et al (2012). The year by year changes in cognitive function in a non-demented population aged 70 to 90 over a five year period. Journal of Frailty & Aging 1: 76.
Study shows reduced rate of cognitive decline over 5 years

Candesartan and cognitive decline in older patients with hypertension
A substudy of the SCOPE trial

257 older adults with hypertension (mean age 76) were treated with candesartan or placebo over 5 years.

Table 5
Comparison of change in cognition between the candesartan and placebo groups, as measured by coefficients of decline on five composite factor scores

<table>
<thead>
<tr>
<th>Cognitive factor</th>
<th>Coefficients of decline</th>
<th>Annual percentage change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candesartan, n = 112</td>
<td>Placebo, n = 116</td>
</tr>
<tr>
<td></td>
<td>Speed of cognition</td>
<td>2.3 (25.2)</td>
</tr>
<tr>
<td></td>
<td>Attention</td>
<td>0.004 (0.086)</td>
</tr>
<tr>
<td></td>
<td>Episodic memory</td>
<td>0.14 (1.38)</td>
</tr>
<tr>
<td></td>
<td>Working memory</td>
<td>0.0014 (0.0119)</td>
</tr>
<tr>
<td></td>
<td>Executive function</td>
<td>−0.0031 (0.0616)</td>
</tr>
</tbody>
</table>

Data shown are mean (SD). The Cohen D represents the effect size of treatment over placebo, based on the pooled SD. Adjusted for age, New Adult Reading Test errors, and baseline performance. Negative values indicate decline in performance over time.
Plasma homocysteine and cognitive decline in older hypertensive subjects

Sunil K. Narayan,1 Brian K. Saxby,1 Michael J. Firbank,1 John T. O’Brien,1 Frances Harrington,1 Ian G. McKeith,1 Monica Hansrani,2 Gerard Stansby3 and Gary A. Ford1

1Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK
2Department of Surgery, Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Newcastle upon Tyne, UK
3Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

<table>
<thead>
<tr>
<th>COGNITIVE DOMAIN</th>
<th>WHOLE GROUP n = 182</th>
<th>UPPER QUARTILE OF HOMOCYSTEINE</th>
<th>LOWER QUARTILE OF HOMOCYSTEINE</th>
<th>p</th>
<th>COHEN’S D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of cognition</td>
<td>−1.9 (17.6)</td>
<td>−7.3 (22.0)</td>
<td>4.1 (10.5)</td>
<td>0.02</td>
<td>−0.69</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.0007 (0.0477)</td>
<td>−0.018 (0.059)</td>
<td>0.0128 (0.0270)</td>
<td>0.02</td>
<td>−0.72</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>−0.03 (0.97)</td>
<td>−0.45 (1.28)</td>
<td>0.28 (0.79)</td>
<td>0.004</td>
<td>−0.69</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.0010 (0.0073)</td>
<td>0.0008 (0.0095)</td>
<td>0.0002 (0.0064)</td>
<td>0.79</td>
<td>0.07</td>
</tr>
<tr>
<td>Attention</td>
<td>0.005 (0.054)</td>
<td>0.007 (0.057)</td>
<td>0.009 (0.047)</td>
<td>0.82</td>
<td>−0.03</td>
</tr>
</tbody>
</table>

• “Computerised procedures are currently used extensively in general psychopharmacology, and some systems have been developed exclusively for use with demented patients

• “There is evidence that after initial familiarization, properly implemented computerised procedures can be perfectly acceptable to AD patients

• “Automated testing can have clear advantages for clinical trials in this field

• “Automated procedures have been shown to be more sensitive than the standard tests which are used in this field, and the sensitivity to anticholinesterases in AD also has been established

• “Given the previously noted importance of assessing attention and information processing speed in this field, computerised tests can provide optimal procedures for assessing changes in these functions. Some tests of attention and vigilance can only be run on computers

• “The Work Group concluded that computerised procedures should be used together with the established procedures in the field (e.g. the ADAS) so that the comparable utility and sensitivity of the two types of testing can be identified. If clear advantages of computerised procedures are demonstrated, such procedures might supersede existing methods.
Time to move on

Wesnes KA
2014
Moving beyond the pros and cons of automating cognitive testing in pathological aging and dementia:
The case for equal opportunity.
Alzheimer’s Research & Therapy, in press
Is it only drugs which can improve human cognition?
# Natural Products Which Enhance Cognitive Function

Caffeine, Guarana, Oxygen & Glucose

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>n</th>
<th>Design</th>
<th>ATT &amp; IP</th>
<th>WM &amp; EF</th>
<th>EM / LTM</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine 100 mg</td>
<td>Young Vols</td>
<td>17</td>
<td>x-over</td>
<td>↑</td>
<td></td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Young Vols</td>
<td>30</td>
<td>x-over shift-work mod.</td>
<td>↑</td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>Caffeine 150 mg</td>
<td>Young Vols</td>
<td>24</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Caffeine 75 &amp; 150 mg</td>
<td>Young Vols non-caffeine users</td>
<td>24</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>34</td>
</tr>
<tr>
<td>Caffeine 75 &amp; 150 mg</td>
<td>Young Vols caffeine users</td>
<td>24</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>32</td>
</tr>
<tr>
<td>Caffeine 150mg &amp; L-theanine 250mg</td>
<td>Young Vols</td>
<td>24</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>32</td>
</tr>
<tr>
<td>Guarana 37.5 &amp; 75 mg</td>
<td>Young Vols</td>
<td>26</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>44</td>
</tr>
<tr>
<td>Guarana 75 mg</td>
<td>Young Vols</td>
<td>28</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>165</td>
</tr>
<tr>
<td>Red Bull</td>
<td>Young Vols</td>
<td>24</td>
<td>x-over single dose</td>
<td>↑</td>
<td></td>
<td>↑</td>
<td>91</td>
</tr>
<tr>
<td>Energy Drink Caffeine 75 mg &amp; glucose 37.5 g</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>110</td>
</tr>
<tr>
<td>Energy shot – caffeine 140 mg glucose free, B vitamins &amp; amino acids</td>
<td>Young Vols</td>
<td>91</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Glucose 40 g</td>
<td>Children 5-6 years</td>
<td>30</td>
<td>x-over acute</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
<td>103</td>
</tr>
<tr>
<td>Glucose 40 g</td>
<td>Young Vols</td>
<td>18</td>
<td>x-over acute</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>38</td>
</tr>
<tr>
<td>Glucose 25 g</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over acute</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>25</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Elderly Vols</td>
<td>20</td>
<td>x-over acute</td>
<td>↑</td>
<td></td>
<td>↑</td>
<td>71</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over acute</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>72</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over acute</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>93</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Young Vols</td>
<td>32</td>
<td>x-over acute</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>92</td>
</tr>
<tr>
<td>Oxygen</td>
<td>CFS</td>
<td>16</td>
<td>x-over acute</td>
<td>↑</td>
<td></td>
<td>↔</td>
<td>166</td>
</tr>
</tbody>
</table>

↑ = statistically significant enhancement  
↔ = no significant change  
↓ = significant impairment  
Empty box = domain not assessed  
ATT & IP = Attention & Information Processing  
WM & EF = Working Memory &/or Executive Function  
EM / LTM = Episodic Memory / Long-Term Memory
# OTHER NATURAL PRODUCTS WHICH ENHANCE COGNITIVE FUNCTION

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>n</th>
<th>Design</th>
<th>ATT &amp; IP</th>
<th>WM &amp; EF</th>
<th>EM/LTM</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacopa Monniera 300 mg</td>
<td>Vols 18-60 years</td>
<td>107</td>
<td>// group 90 days</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
<td>99</td>
</tr>
<tr>
<td>Breakfast Cereals Low v High GI</td>
<td>Children 6-11 yrs</td>
<td>64</td>
<td>x-over acute</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>37</td>
</tr>
<tr>
<td>Breakfast Cereals</td>
<td>Children 9-16 yrs</td>
<td>29</td>
<td>x-over acute</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>133</td>
</tr>
<tr>
<td>Breakfast</td>
<td>Children 6-16 yrs</td>
<td>1386</td>
<td>// group Internet</td>
<td>↑</td>
<td>↔</td>
<td>↑</td>
<td>134</td>
</tr>
<tr>
<td>Breakfast Isomaltulose enriched milk</td>
<td>Children 5-6 years</td>
<td>30</td>
<td>x-over acute</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>103</td>
</tr>
<tr>
<td>Chewing Gum</td>
<td>Young Vols</td>
<td>75</td>
<td>// group</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>155</td>
</tr>
<tr>
<td>Docosahexaenoic Acid (DHA)</td>
<td>Children 10-12 yrs</td>
<td>90</td>
<td>// group 8-weeks</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
<td>182</td>
</tr>
<tr>
<td>Docosahexaenoic Acid (DHA)</td>
<td>Elderly Vols</td>
<td>74</td>
<td>// group 90 days</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>180</td>
</tr>
<tr>
<td>Fat 16 g</td>
<td>Young Vols</td>
<td>18</td>
<td>x-over acute</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>38</td>
</tr>
<tr>
<td>Huperzine A, Vinpocetine &amp; Acetyl-L-Carnitine</td>
<td>Vols 22-60 years</td>
<td>74</td>
<td>// group 30 days</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>101</td>
</tr>
<tr>
<td>Melissa Officinalis 300- 900 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>46</td>
</tr>
<tr>
<td>Non-cholinergic binding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melissa Officinalis 600-1600 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>51</td>
</tr>
<tr>
<td>Cholinergic binding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peppermint Essential Oil</td>
<td>Young Vols</td>
<td>96</td>
<td>// group single dose</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>69</td>
</tr>
<tr>
<td>Protein 40 g</td>
<td>Young Vols</td>
<td>18</td>
<td>x-over acute</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>38</td>
</tr>
<tr>
<td>Pycnogenol 150 mg</td>
<td>Vols 60-85 years</td>
<td>101</td>
<td>// group 3 months</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
<td>87</td>
</tr>
<tr>
<td>Rosemary Essential Oil</td>
<td>Young Vols</td>
<td>96</td>
<td>// group single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>68</td>
</tr>
<tr>
<td>Rosemary 100% powder 750 mg</td>
<td>Vols 65-90 years</td>
<td>28</td>
<td>x-over single dose</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>79</td>
</tr>
<tr>
<td>Salvia Officinalis 167 &amp; 333 mg</td>
<td>Vols 65-90 years</td>
<td>20</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>90</td>
</tr>
<tr>
<td>Salvia Lavandulaefolia 50 &amp; 100 µl</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>106</td>
</tr>
<tr>
<td>Salvia Lavandulaefolia 25 &amp; 50 µl</td>
<td>Young Vols</td>
<td>24</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>106</td>
</tr>
<tr>
<td>Salvia Lavandulaefolia 25 &amp; 50 µl</td>
<td>Young Vols</td>
<td>24</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>107</td>
</tr>
<tr>
<td>Water</td>
<td>Dehydrated Young Vols</td>
<td>24</td>
<td>x-over single dose</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>179</td>
</tr>
</tbody>
</table>

↑ = statistically significant enhancement  ↔ = no significant change  ↓ = significant impairment
Empty box = domain not assessed
ATT & IP = Attention & Information Processing
WM & EF = Working Memory &/or Executive Function
EM / LTM = Episodic Memory / Long-Term Memory
## Ginkgo Biloba & Ginseng

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>n</th>
<th>Design</th>
<th>ATT &amp; IP</th>
<th>WM &amp; EF</th>
<th>EM / LTM</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo Biloba – Tanakan</td>
<td>MCI</td>
<td>54</td>
<td>// group 12 weeks</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>137</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 120 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>47</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 120 mg</td>
<td>Young Vols</td>
<td>87</td>
<td>x-over single dose</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>43</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 120 mg</td>
<td>Vols 50-70 years</td>
<td>11</td>
<td>x-over single dose</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
<td>176</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 120 mg</td>
<td>Vols 40-60 years</td>
<td>120</td>
<td>// group 8 weeks</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>112</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 240&amp;360 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>47</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 360 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>50</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 120 mg &amp; Bacopa Monniera 300 mg</td>
<td>Young Vols</td>
<td>12</td>
<td>x-over single dose</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>177</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 120 mg &amp; phosphatidyserine 360 mg</td>
<td>Young Vols</td>
<td>18</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>42</td>
</tr>
<tr>
<td>Ginkgo Biloba – GK501 120 mg &amp; phosphatidylcholine 360 mg</td>
<td>Young Vols</td>
<td>18</td>
<td>x-over single dose</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>42</td>
</tr>
<tr>
<td>Panax Ginseng G115 200 mg</td>
<td>Young Vols</td>
<td>28</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>44</td>
</tr>
<tr>
<td>Panax Ginseng G115 200 mg</td>
<td>Young Vols</td>
<td>18</td>
<td>// group 21 days</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>54</td>
</tr>
<tr>
<td>Panax Ginseng G115 200 mg &amp; 600 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>49</td>
</tr>
<tr>
<td>Panax Ginseng G115 400 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>49</td>
</tr>
<tr>
<td>Panax Ginseng G115 400 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>50</td>
</tr>
<tr>
<td>Panax Ginseng G115 400 mg</td>
<td>Young Vols</td>
<td>30</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>102</td>
</tr>
<tr>
<td>G115 200 mg &amp; Guarana 75 mg</td>
<td>Young Vols</td>
<td>28</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>44</td>
</tr>
<tr>
<td>GK501 120 mg &amp; G115 200 mg</td>
<td>Neurasthenia 40-65 years</td>
<td>64</td>
<td>// group 90 Days</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>123</td>
</tr>
<tr>
<td>GK501 120 mg &amp; G115 200 mg</td>
<td>Vols 40-66 years</td>
<td>256</td>
<td>// group 90 Days</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td>151</td>
</tr>
<tr>
<td>GK501 360 mg &amp; G115 600 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>50</td>
</tr>
<tr>
<td>GK501 360 mg &amp; G115 600 mg</td>
<td>Young Vols</td>
<td>20</td>
<td>x-over single dose</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>48</td>
</tr>
<tr>
<td>Pharmaton Capsules</td>
<td>Vols 18-75 years</td>
<td>622</td>
<td>Internet Users v Non-Users</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td>161</td>
</tr>
<tr>
<td>Pharmaton Capsules</td>
<td>Vols 20-45 years</td>
<td>31</td>
<td>// group 3 months Night Shift Model</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td>127</td>
</tr>
</tbody>
</table>

↑ = statistically significant enhancement  ↔ = no significant change  ↓ = significant impairment

Empty box = domain not assessed  ATT & IP = Attention & Information Processing  WM & EF = Working Memory &/or Executive Function  ME / LTM= Episodic Memory / Long-Term Memory
Question

• There is no doubt that cognition can be improved in all age groups
• The question becomes are all these interventions competing for a small reserve of opportunity to improve function, or could they be additive
Other opportunities for enhancement-
Neurogenesis
The genesis of new cells, including neurons, in the adult human brain has not yet been demonstrated. This study was undertaken to investigate whether neurogenesis occurs in the adult human brain, in regions previously identified as neurogenic in adult rodents and monkeys. Human brain tissue was obtained postmortem from patients. We demonstrate that new neurons, as defined by these markers, are generated from dividing progenitor cells in the dentate gyrus of adult humans. Our results further indicate that the human hippocampus retains its ability to generate neurons throughout life.
Increased Expression of RbAp48 Restores Memory Capacity in Old Mice

A Major Cause of Age-Related Memory Loss Identified

Researchers are making strides in uncovering the low-level details of how memory operates in mammalian brains, just as they are making strides in all areas of biology. Sometimes the process of discovery comes hand in hand with a demonstration of utility, as is the case here. Putting to one side the consequences of an Alzheimer's-like build up of amyloid deposits and its associated neural dysfunction, the research quoted below demonstrates that the rest of the decline in memory function due to old age in mice can be mostly reversed by increasing the levels of one particular protein. This is very interesting, as it suggests that the processes of memory are not greatly inhibited by most of the forms of cellular damage that causes aging, at least in mice, and that this portion of mental decline occurs due to one of the epigenetic responses to that damage.

Editor's Summary

Try to Remember

We do not know why, but we think we know where: Age-related memory loss begins in the dentate gyrus of the brain. (Alzheimer's disease starts in nearby entorhinal cortex and other parts of the hippocampus.) To understand better why we forget more easily as we age, Pavlopooulos et al. gained access to eight human brains and looked carefully for proteins that rose and fell in the dentate gyrus with age. One was particularly notable, RbAp48, a histone-binding protein that regulates transcription and decreases in expression in older people. Exploring its function in mice led the authors to conclude that RbAp48 participates in the dentate gyrus dysfunction that becomes more prominent with aging and could potentially be a target for treatment of age-related memory decline.

By first searching for proteins that are modulated in an age-related fashion in the human brain, the authors firmly rooted their investigation in the translational space. Their subsequent experiments in mice were designed to examine the protein's function in ways that would have been impossible in humans. Key to validating RbAp48's function was a transgenic mouse line that carried a dominant-negative inhibitor of RbAp48, but only in the forebrain. The authors could manipulate expression of RbAp48 at will by switching it on and off with artificial triggers. Prematurely inhibiting RbAp48 in young mice resulted in memory deficits just like those seen naturally in older mice. Increasing RbAp48 in older, more forgetful mice restored their memory to its youthful vigor. And not only behavior was affected. Functional magnetic resonance imaging showed that the dentate gyrus in the artificially impaired young mice did not work properly, and molecular assays showed abnormal histone acetylation.

Further exploiting their transgenic mice, the authors also support the idea that RbAp48 acts through the protein kinase A (PKA) - cyclic adenosine monophosphate (cAMP) response element-binding protein 1 (CREB1) - CREB-binding protein (CBP), a well-understood signaling pathway. Agents that enhance signaling through PKA and CREB (cAMP signaling) are already known to improve age-related problems in hippocampal function in mice, so it is a logical next step to test these drugs for therapeutic use in treating age-related memory problems in people.
Figure 2. The hippocampal tri-synaptic circuit based on the rat brain. Neurons in layer II of the EC project to the DG, bypassing the subiculum, with additional collaterals projecting to the CA3 subfield (perforant path, pp). Granule cells in the DG project to the CA3 field of the hippocampus via the mossy fiber (mf) pathway.

**Special Issue: Hippocampus and Memory**

**Pattern separation in the hippocampus**

Michael A. Yassa\(^1\) and Craig E.L. Stark\(^2\)

\(^1\) Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD 21218, USA
\(^2\) Department of Neurobiology and Behavior, Center for Neurobiology of Learning and Memory, University of California, Irvine, CA 92697-3800, USA
Pattern Separation in the Human Hippocampal CA3 and Dentate Gyrus

Arnold Bakker\textsuperscript{1}, C. Brock Kirwan\textsuperscript{2}, Michael Miller\textsuperscript{3}, and Craig E.L. Stark\textsuperscript{1,4,*}

Fig. 3.
Bias scores in the MTL. A single bias score for each of the six different areas in the MTL was calculated by collapsing the bias scores for multiple ROI’s in the same area. Bias scores closer to zero connote separation while scores closer to one connote completion.

Fig. 1.
Sample stimuli sets showing version A and B of the same object.
Concluding remarks
The hippocampus is especially well-suited, by virtue of its anatomical wiring and neural firing properties, to perform pattern separation and pattern completion computations. In particular, an abundance of evidence indicates that the DG is necessary for pattern separation, whereas lesion and genetic knockout studies have strongly suggested a functional role for the CA3 in pattern completion.

Neurocognitive aging, both in rodents and humans, is a case where selective changes to the DG/CA3 network lead to pattern separation deficits that could underlie many of the episodic memory problems observed with older age. Although aging could negatively modulate pattern separation, evidence across several studies suggests that neurogenesis plays an important facilitative role in pattern separation, although the exact mechanisms are still unclear.
The CDR System picture recognition task:

*Fulfils requirement to be an Object Pattern Separation task*

20 pictures are presented to the subject at the rate of 1 every 3 seconds.
15 minutes later the 20 pictures are represented mixed with very similar ones. For each picture, the subject is required to press YES as quickly as possible if it was the original picture, or NO if it is a similar but different picture.
Key finding from fMRI work directly relevant to CDR System Object Pattern Separation Task

When humans are forced to make a decision whether a previously presented image as **the same** (pattern completion) *versus* rejecting it as a **closely similar** image (pattern separation) - the ability to accurately do the latter selectively reflects DG activity.

Originally Shown

Shown later each requiring a YES or NO response

- Yes reflects efficient pattern completion but not DG
- No reflects efficient pattern separation ie involves DG

---

15 mins
Neurogenesis declines with normal aging

The ageing systemic milieu negatively regulates neurogenesis and cognitive function

Saul A. Villeda, Jian Luo, Kira I. Mosher, Bende Zou, Markus Britschgi, Gregor Bieri, Trisha M. Stan, Nina Fainberg

In the central nervous system, ageing results in a precipitous decline in adult neural stem/progenitor cells and neurogenesis, with concomitant impairments in cognitive functions.

Testable Prediction

As neurogenesis declines with human ageing, older individuals should be more likely to exhibit dentate gyrus related difficulties in correctly identifying closely similar pictures.
Replication of Toner et al (n=40) with 3,067 healthy volunteers from the CDR System Database
Data are changes from 18-25 years
Selective decline to DG sensitive measure

Further replication of findings with 93,087 subjects aged 18-85 assessed via the internet

Selective decline to DG sensitive measure on accuracy as well as speed of recognition

Conclusions: These are, to our knowledge, the first human pattern separation data to suggest a possible genetic link to poor hippocampal neurogenesis in AD, as well as a relationship to Aβ42. Therapies which target neurogenesis may thus be useful in preventing the early stages of AD, notably in ApoE Ė4 homocytotes.
Figure 1 Comparison of the scores of the ApoE genotypes on the Pattern Separation Task. ApoE, apolipoprotein E; CDR, Clinical Dementia Rating; DG, dentate gyrus.
Conclusions: This is the first behavioural demonstration of compromised OPS in Parkinson’s patients, supporting work with rats and primates. This finding is consistent with impairment to DG function and thus potentially compromised neurogenesis. Implications for current and novel PD therapies will be discussed, in relation to compounds such as rasagiline which promote neurogenesis.
Low selenium levels associated with poor cognitive function

Review Article

Selenium and cognitive impairment:
A brief-review based on results from
the EVA study

Claudine Berr,1,2,3* Josiane Arnaud,4,5 and Tasnime N. Akbaraly4,2

Abstract.
Preventing cognitive impairment and dementia in the elderly is a major public health challenge for our century and all hypotheses should be explored. Selenium (Se) is one of the factors that may affect the risk of cognitive decline. Its importance in the health and aging process has been documented. Because of the potential of selenoproteins to protect against oxidative stress, Se raises significant expectations for the prevention of chronic diseases including cancer, cardiovascular disease, and type 2 diabetes conditions commonly associated with oxidative stress. Thus, the relationships between Se and cognitive impairment or dementia can be examined through vascular risk factors for dementia, with particular interest in diabetes and dyslipidemia. In addition, in cases of Se deficiency, the brain is the organ that remains Se replete the longest suggesting that Se plays an important role in brain functions. This article presents results obtained in the frame of a longitudinal study on Se and cognitive impairment. They are consistent with the hypothesis that low Se status is a risk factor for cognitive decline even after taking into account vascular risk factors. The concomitant evolution between plasma Se decrease over a 9-year period and cognitive decline suggested that optimal Se status is potentially important to maintain neuropsychological functions in aging people. However, as our understanding of Se biology is incomplete, epidemiological studies are needed to define the groups of population that could benefit from Se supplementation.

© 2012 International Union of Biochemistry and Molecular Biology, Inc.
Volume 38, Number 2, March/April 2012, Pages 139–144 ●
E-mail: claudine.berr@inserm.fr

Keywords: selenium, cognition, epidemiology, cohort
Selenium could promote human neurogenesis
PepsiCo acquires UK vitamin water brand - V Water

Deal highlights commitment to building a strong balanced beverage portfolio

PepsiCo today announced the acquisition of V Water, a leading vitamin water brand in the UK.

V Water is a leading brand in a dynamic and growing category. The brand was launched in 2005, and now has a range of six flavours. All products are made with spring water, and have no artificial flavours, sweeteners, colours or preservatives. The V Water range contains a number of added vitamins, minerals and herbal extracts including Vitamin C, Zinc, Selenium and Ginseng.
Table 1
Nutritional composition of Fortasyn™ Connect, the nutrient combination in Souvenaid

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount per daily dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eicosapentaenoic acid, mg</td>
<td>300</td>
</tr>
<tr>
<td>Docosahexaenoic acid, mg</td>
<td>1200</td>
</tr>
<tr>
<td>Phospholipids, mg</td>
<td>106</td>
</tr>
<tr>
<td>Choline, mg</td>
<td>400</td>
</tr>
<tr>
<td>Uridine monophosphate, mg</td>
<td>625</td>
</tr>
<tr>
<td>Vitamin E (alpha-tocopherol equivalents), mg</td>
<td>40</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>80</td>
</tr>
<tr>
<td>Selenium, µg</td>
<td>60</td>
</tr>
<tr>
<td>Vitamin B12, µg</td>
<td>3</td>
</tr>
<tr>
<td>Vitamin B6, mg</td>
<td>1</td>
</tr>
<tr>
<td>Folic acid, µg</td>
<td>400</td>
</tr>
</tbody>
</table>

*Souvenaid (125 mL [125 kcal] daily dose) contains Fortasyn Connect. Souvenaid is a registered trademark of Nutricia N.V. Fortasyn is a trademark of Nutricia N.V.
Alzheimer’s disease is not the only motivating factor for the increased focus on cognitive health. The terms neuroplasticity and neurogenesis have caught the eye of many different people from medical professionals to athletes to top executives.

The terms refer to the ability of the brain to recover from damage, regrow neuronal connections, and even function at a higher level.

The mechanism of neuroplasticity and neurogenesis is being applied to accident victims, concussed athletes and those with neurodegenerative diseases.

The concepts are very promising and more research is now finding that natural substances have powerful properties to not only stop damaging processes in the brain but also to promote recovery.
The way forward – huge increasing opportunities for nutritional products
AD precipitated by impaired microvascular function

Perspective

The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer’s disease

David A. Drachman*

UMass Medical School, Worcester, MA, USA

Abstract

The “amyloid hypothesis” has dominated Alzheimer research for more than 20 years, and proposes that amyloid is the toxic cause of neural/synaptic damage and dementia. If correct, decreasing the formation or removing amyloid should be therapeutic. Despite discrepancies in the proposed mechanism, and failed clinical trials, amyloid continues to be considered the cause of a degenerative cascade. Alternative hypotheses must explain three features: (i) why amyloid toxicity is not the etiology of Alzheimer’s disease (AD), (ii) what alternative mechanisms cause the degeneration and dementia of AD, and (iii) why increased amyloid accumulates in the brain in AD. We propose that AD, which occurs in elderly, already vulnerable brains, with multiple age-related changes, is precipitated by impaired microvascular function, resulting primarily from decreased Notch-related angiogenesis. With impaired microvasculature, a lack of vascular endothelial-derived trophic factors and decreased cerebral blood flow cause the atrophy of neural structures. Therapeutic strategies should focus on supporting normal angiogenesis.

© 2014 The Alzheimer’s Association. All rights reserved.
Age-associated cognitive decline

Ian J. Deary†++, Janie Corley†, Alan J. Gow†++, Sarah E. Harris†++§, Lorna M. Houlihan†++, Riccardo E. Marioni†, Lars Penke†++, Snorri B. Rafnsson†, and John M. Starr†#

†Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK;

Emerging areas for developing research: Genome-wide scans are a likely source to establish genetic contributions. The role of vascular factors in cognitive ageing is increasingly studied and understood. The same applies to diet, biomarkers such as inflammation and lifestyle factors such as exercise. There are marked advances in brain imaging, affording better in vivo studies of brain correlates of cognitive changes. There is growing appreciation that factors affecting general bodily ageing also influence cognitive functions in old age.
Leading Alzheimer’s Researcher feels there is no magic bullet for dementia but a lifestyle change is the best protection.
He founded the International Working Group for the Harmonization of Dementia Drug Guidelines and co-founded or has leadership roles in other national and international groups focusing on the consequences of aging on the world.

He is the author (with Danny George) of a provocative book entitled *The Myth of Alzheimer’s: What You Aren’t Being Told About Today’s Most Dreaded Diagnosis*. Through this book and related projects he hopes to transform our thinking about brain aging and contribute to his own successful cognitive aging.
Conclusions

• Helping to prevent the cognitive declines which accompany normal and pathological ageing is of paramount importance.

• While the pharmaceutical industry have made little progress, clear opportunities exist for nutrition products.

• Trials in normal aging including the new diagnosis of Preclinical AD require longitudinal cognitive testing.

• To be fit for purpose such tests must be valid, repeatable and sensitive to change.

• Testing cognitive function remotely via the internet has huge potential in this area.

• It is becoming widely accepted that lifestyle changes are the best protection, creating a massive opportunity for nutritional products.