4th National Symposium on
Complementary & Alternative Geriatric Health Care
and the 25th Annual Geriatric Research, Education & Clinical Center Symposium

Preventing Cognitive Decline in Older Adults



Logan College of Chiropractic
Thursday, October 28, 2010
1:00 – 5:15 p.m.

LOGAN
COLLEGE OF CHIROPRACTIC
UNIVERSITY PROGRAMS

WELCOME TO
LOGAN COLLEGE OF CHIROPRACTIC

4TH NATIONAL SYMPOSIUM ON COMPLEMENTARY AND ALTERNATIVE GERIATRIC HEALTH CARE PREVENTING COGNITIVE DECLINE IN OLDER ADULTS AND THE 25TH ANNUAL GERIATRIC RESEARCH, EDUCATION & CLINICAL CENTER SYMPOSIUM

October 28, 2010

Acknowledgements:

This educational activity is sponsored by the following:
Logan College of Chiropractic
Saint Louis University School of Medicine
Saint Louis University School of Nursing
Gateway Geriatric Education Center OF Missouri & Illinois
Veteran Integrated Service Network 15 GRECC

Conference Overview & Objectives:

The prevalence of Alzheimer's dementia (AD) is expected to increase dramatically over the upcoming decades due to the increase in the older population. Since treatments thus far are not curative, prevention will be important as a management strategy. Stimulating activities (cognitive, physical, and social), vascular risk factors, and diet may be important as prevention strategies. The role of complementary and alternative medicine techniques (CAM) in preventing neuro-degeneration will also be emphasized. This is a 4 hour course designed to highlight the basic science and clinical evidence underlying the techniques for the prevention of cognitive decline in older persons. Lectures will emphasize the etiology, risk factors and prevention strategies of neuro-degeneration. A discussion session following the lectures will allow for audience interaction and questions with the presenting faculty. This conference promises to be a clinical educational landmark, so mark your calendar and register with the Logan postgraduate division. The faculty will include **Norman W. Kettner DC, DACBR, DCBCN, FICC,** Professor and Chair of the Department of Radiology at Logan College of Chiropractic. Dr. Kettner is the conference organizer and will serve as facilitator. Dr. Kettner will discuss the recent advances and neuroimaging evidence for the structural and functional disconnections in brain networks of AD patients. These mechanisms are thought to represent biomarkers for the disruption of memory and cognitive function.

Planning Committee:

Norman W. Kettner, D.C., Chair, Department of Radiology, Logan College of Chiropractic
Nina Tumosa, Ph.D., GRECC Health Educational Specialist, St. Louis Veterans Affairs Medical Center
Kathy Leonard, Administrative Assistant, Saint Louis University School of Medicine
Elizabeth Goodman, D.C., Ph.D., Dean of University Programs, Logan College of Chiropractic
Carl Saubert, Ph.D., Associate Vice President, Logan College of Chiropractic
Glenn Bub, D.C., Chief of Staff, Logan College of Chiropractic
Fawn Knoll, Assistant to the Associate Vice President for Public Relations and Web-site Coordinator**,** Logan College of Chiropractic
Erica Collier, Administrative Assistant, Department of Radiology, Logan College of Chiropractic
John E. Morley, MB, BCh, St. Louis VAMC VISN 15 and Saint Louis University
Alicia Yochum, R.N., Student, Logan College of Chiropractic

Accreditation/Approval

American Nurses Credentialing Center (ANCC)

Saint Louis University School of Nursing is an approved provider of continuing nursing education by the Missouri Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. Missouri Nurses Association provider # 109-VII. California State Board Provider #13123.

American Medical Association (ACCME)

Saint Louis University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Saint Louis University maintains responsibility for the program. A certificate of attendance will be awarded to participants and accreditation records will be on file at the Saint Louis University CME office. In order to receive a certificate, participants must sign in at the beginning of this activity, complete an evaluation, attend 100% of the program, and pick up their own certificate at the conclusion of the program (certificates will not be mailed). Saint Louis University cannot issue certificates for less than 100% participation as required by accrediting body regulations.

Continuing Education Credits

Doctors of Chiropractic (DC)

Missouri is approved for 4 hours. Approval Number 2010000592. (2 hours differential diagnosis or physical diagnosis, .5 hours nutrition, .5 hours case studies, 1 hour general)

Illinois, Indiana, Nebraska, and Iowa require no prior approval.

Kentucky is approved for 4 hours.

Kansas: is approved for 4 hours.

American Nurses Credentialing Center (ANCC)

Saint Louis University School of Nursing designates this educational activity for 4 contact hours in continuing nursing education.

American Medical Association (ACCME)

Saint Louis University School of Medicine designates this activity for a maximum of 4 AMA PRA Category I Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity. Continuing Education Certificates will be mailed only to those participants who have requested and paid for them. The certificates will be mailed to the participants by December 15, 2010. Should you need verification of your attendance before this date, please see the attendant at the registration booth prior to your

Missouri Board of Nursing Home Administrators

The Division of Geriatrics at Saint Louis University is approved as a Training Agency (TA-064-408) by the Missouri Board of Nursing Home Administrators. This program is being reviewed for a maximum of 4 clock hours including a maximum of 4 hours that could be patient care hours. For your convenience, each presentation has been assigned the number of proposed patient care and/or administrative hours being reviewed by the Missouri Board of Nursing Home administrators. Continuing Education Certificates will be available at the registration booth prior to your departure from the conference. Copies of the sign-in/sign-out sheets will be forwarded to the Missouri Board of Nursing Home Administrators indicating those people who have paid for continuing education credits. This information will be sent within 30 days of the conclusion of the conference. In order to receive continuing education credit, participants must complete an evaluation for all sessions attended. Contact St. Louis University representative for NHA, Nina Tumosa at tumosan@slu.edu for questions related to NHA credit.

AMERICANS WITH DISABILITIES ACT POLICY:

In compliance with the Americans with Disabilities Act, if you need special assistance to participate in this meeting, please contact Erica Collier at (636) 227-2100 extension 1830. Notification 48 hours prior to the meeting will enable Logan to make reasonable arrangements to ensure accessibility to this meeting. {28 CFR 35.102-35.104 ADA Title II}

DISCLOSURE POLICIES:

It is the policy of Saint Louis University School of Medicine to insure balance, independence, objectivity, and scientific rigor in its continuing medical education program. Faculty and planning committee members participating in these activities are required to disclose to the audiences prior to the activity the following:

1. The existence of any significant financial or other relationship with the manufacturer of any commercial product or provider of any commercial service discussed.
2. Their intention to discuss a product that is not labeled for the use under discussion.
3. Their intention to discuss preliminary research data.

Saint Louis University School of Medicine will review this activity's disclosures and resolve all identified conflicts of interest, if applicable.

FACULTY DISCLOSURE POLICY

It is the policy of Saint Louis University School of Medicine to insure balance, independence, objectivity and scientific rigor in all its educational programs. All faculty participating in these activities are expected to disclose to the program audiences (1) any real or apparent conflicts of interest related to the content of their presentations, and (2) if their presentation will include any information regarding unapproved uses of pharmaceuticals or (3) ongoing research (preliminary data).

FACULTY DISCLOSURES

All faculty have indicated no disclosures.

SAINT LOUIS UNIVERSITY SCHOOL OF MEDICINE POLICY FOR RELATIONSHIPS WITH COMMERCIAL ENTITIES

The purpose of continuing medical education (CME) is to enhance the Physician's ability to care for patients. It is the responsibility of the accredited sponsor of a CME activity to assure that the activity is designed primarily for that purpose.

Accredited sponsors often receive financial and other support from non-accredited commercial organizations. Such support can contribute significantly to the quality of CME activities. The purpose of these guidelines is to describe appropriate behavior of accredited sponsors in planning, designing, implementing, and evaluating certified CME activities for which commercial support is received.

-Preamble: ACCME Standards for Commercial Support of CME

COMMERCIAL SUPPORT MAY BE ACCEPTED FOR AN EDUCATIONAL ACTIVITY UNDER THE FOLLOWING CONDITIONS

("Accredited sponsor" refers to Saint Louis University School of Medicine CME):

Statement of Purpose: The program must be for scientific and educational purposes only and will not promote the commercial entity's products, directly or indirectly.

Letter of Agreement: The accredited sponsor and the commercial entity must agree in writing (see Letter of Agreement) to abide by the ACCME Standards for Commercial Support of Continuing Medical Education and the FDA guidelines regarding same.

Design of Activity: In designing educational activities, the accredited sponsor (CME) must assure that the activities have the following characteristics: They must be free of commercial bias for or against any product; If the activities are concerned with commercial products, they must present objective information about those products, based on scientific methods generally accepted in the medical community. Full disclosure of potential conflicts of interest with industry must be made by all participating faculty members (see SLU Policy on Conflict of Interest and Disclosure form), and must be disclosed to the audience of the program through the publicity, in course syllabi, and/or in the introductions of presenters.

Independence of Accredited Sponsors: The design and production of educational activities shall be the ultimate responsibility of the accredited sponsor. Commercial supporters of such activities shall not control the planning, content or execution of the activity. To assure compliance with this standards, the following requirements must be adhered to.

Assistance with Preparation of Educational Materials: The content of slides and reference materials must remain the ultimate responsibility of the faculty selected by the accredited sponsor. A commercial supporter may be asked to help with the preparation of conference related educational materials, but these materials shall not, by their content or format, advance the specific proprietary interests of the commercial supporter.

Assistance with Educational Planning: An accredited sponsor may obtain information that will assist in planning and producing an educational activity from any outside source whether commercial or not. However, acceptance by an accredited sponsor of advice or services concerning speakers, invitees or other educational matters, including content, shall not be among the conditions of providing support by a commercial organization.

Marketing of CME Activities: Only the accredited sponsor may authorize a commercial supporter to disseminate information about a CME activity to the medical community. However, the content of such information is the responsibility of the accredited sponsor, and any such information must identify the educational activity as produced by the accredited sponsor.

Activities Repeated Many Times: If commercially supported educational activities are offered that repeat essentially the same information each time they are given, then it must be demonstrated that every iteration of that activity meets all of the Essentials and Standards of the ACCME.

Educational Activities or Materials Prepared by Proprietary Entities: When educational activities consisting of concepts or materials are prepared by proprietary entities, such activities must adhere to the Essentials and Standards in all respects, especially with regard to the provisions concerning the independence of the accredited sponsor in planning, designing, delivering and evaluating such activities.

Policy for Relationships With Commercial Entities

Enduring Materials: The accredited sponsor is responsible for the quality, content, and use of enduring materials for purposes of CME credit. (For the definition, see ACCME "Standards for Enduring Materials.")

Identifying Products, Reporting on Research, and Discussing Unlabeled Uses of Products

a. Generic and Trade Names: Presentations must give a balanced view of therapeutic options. Faculty use of generic names will contribute to this impartiality. If trade names are used, those of several companies should be used rather than only that of a single supporting company.

b. Reporting Scientific Research: Objective, rigorous, scientific research conducted by commercial companies is an essential part of the process of developing new pharmaceutical or other medical products or devices. It is desirable that direct reports of such research be communicated to the medical community. An offer by a commercial entity to provide a presentation reporting the results of scientific research shall be accompanied by a detailed outline of the presentation which shall be used by the accredited sponsor to confirm the scientific objectivity of the presentation. Such information must conform to the generally accepted standards of experimental design, data collection and analysis.

c. Unlabeled Uses of Products: When an unlabeled use of a commercial product, or an investigational use not yet approved for the purpose is discussed during an educational activity, the accredited sponsor shall require the speaker to disclose that the product is not labeled for the use under discussion or that the product is still investigational.

Exhibits and Other Commercial Activities:

Exhibits: When commercial exhibits are part of the overall program, arrangements for these should not influence planning nor interfere with the presentation of CME activities. Exhibit placement should not be a condition of support for a CME activity. If exhibits are included as a part of an activity, exhibitors should represent a diversity of companies/products rather than those of a single company.

Representatives from the exhibiting companies may not act in a manner which could be interpreted as interfering with the educational activity (e.g., actively pursing the participants for the purpose of promoting a product).

Continuing medical education activities are not trade shows and must not give the appearance that the primary intent is marketing of product.

Commercial Activities During Educational Activities: No commercial promotional materials shall be displayed or distributed in the same room immediately before, during, or immediately after an educational activity certified for credit.

Commercial Supporters at Educational Activities: Representatives of commercial supporters may attend an educational activity, but may not engage in sales activities while in the room where the activity takes place.

Management of Funds from Commercial Sources:

Independence of the Accredited Sponsor in the Use of Contributed Funds: The ultimate decision regarding funding arrangements for CME activities must be the responsibility of the accredited sponsor. Funds from a commercial source should be in the form of **an educational grant made payable to the accredited sponsor** for the support of programming (see also Saint Louis University School of Medicine Guidelines for Continuing Medical Education Activities). The terms, conditions and purposes of such grants must be documented by a signed agreement between the commercial supporter and the accredited sponsor. All support associated with a CME activity, whether in the form of an educational grant or not, must be given with the full knowledge and approval of the accredited sponsor. No other funds from a commercial source shall be paid to the director of the activity, faculty, or others involved with the supported activity.

Payments to Faculty: Payment of reasonable honoraria and reimbursement of out-of-pocket expenses for faculty is customary and proper. **Payments to the faculty must be from the accredited sponsor, NOT the commercial supporter. As outlined above, "funds from a commercial source should be in the form of an educational grant made payable to the accredited sponsor…" Under no circumstances should a commercial supporter pay a faculty member directly.**

Policy for Relationships With Commercial Entities

Acknowledgement of Commercial Support: Commercial support must be acknowledged in printed announcements and brochures, however, reference must not be made to specific products.

Accountability for Commercial Support: Following the CME activity, upon request, the accredited sponsor should be prepared to report to each commercial supporter and other relevant parties, and each commercial supporter to the accredited sponsor, information concerning the expenditures of funds each has provided. Likewise, each commercial supporter should report to the accredited sponsor information concerning their expenditures in support of the activity.

Commercially Supported Social Events: Commercially supported social events at CME activities should not compete with, nor take precedence over, the educational events.

Policy on Disclosure of Faculty and Sponsor Relationships:

a. Disclosure Policy for All CME Activities: An accredited sponsor shall have a policy requiring disclosure of the existence of any significant financial interest or other relationship a faculty member or the sponsor has with the manufacturer's) of any commercial product's) discussed in an educational presentation. All certified CME activities shall conform to this policy (see Saint Louis University Faculty Disclosure Policy).

b. Disclosure in Conference Materials: CME faculty or sponsor relationships with commercial supporters shall be disclosed to participants prior to educational activities in brief statements in conference materials such as brochures, syllabi, exhibits, poster sessions, and also in post-meeting publications.

c. Disclosure for Regularly Scheduled Activities: In the case of regularly scheduled events, such as grand rounds, disclosure shall be made by the moderator of the activity after consultation with the faculty member or a representative of the supporter. Written documentation that disclosure information was given to participants shall be entered in the file for that activity.

Financial Support for Participants in Educational Activities:

a. Use of funds: In connection with an educational activity offered by an accredited sponsor, the sponsor may not use funds originating from a commercial source to pay travel, lodging, registration fees, honoraria, or personal expenses for non-faculty attendees. Subsidies for hospitality should not be provided outside of modest meals or social events that are held as part of the activity.

b. Scholarships for Medical Students, Residents and Fellows: Scholarship or other special funding to permit medical students, residents, or fellows to attend selected educational conferences may be provided, as long as the selection of students, residents or fellows who will receive the funds is made either by the academic or training institution or by the accredited sponsor with the full concurrence of the academic or training institution.

   Funding for medical students, residents or fellows is acceptable, however, the selection of those individuals must be unrestricted and should be the choice of the accredited sponsor and not the commercial organization, with the full concurrence of the academic or training institution.

Program Schedule

12:30 PM Registration

12:55 PM Welcome/Introductions — George A. Goodman, DC, FICC

1:00 – 1:30 PM The Topology of Cognitive Networks or What's a Memory? — Norman W. Kettner, DC

The brain is a complex network performing both segregated and distributed information processing. To perform cognitive tasks such as memory and executive functions such as calculation, different areas of the brain must interact in a cooperative and coordinated function across relatively long distances. These complex networks of interactions are also known as brain functional networks.

Alzheimer's disease (AD) is a progressive, neurodegenerative disease that can be clinically characterized by impaired memory along with deficits in many other cognitive functions. Previous studies have demonstrated that the impairment is accompanied not only by regional brain abnormalities but also changes in the neuronal connectivity between anatomically distinct brain regions. The functional neuroimaging literature will be reviewed supporting the view that AD patients undergo integrative abnormalities in the distributed neuronal networks of the brain. The loss of network integration accompanies their cognitive decline but may offer therapeutic insights.

1:30 – 2:30 PM Dementia Risk Predictors: Are We There Yet? — Abhilash K. Desai, MD

From a clinical as well as public health perspective, it is important to be able to predict who is at highest risk of developing future dementia and when. A dementia risk predictor tool that is reminiscent of the coronary heart disease risk scales posted on the American Heart Association's website is urgently needed. The main value of such tools would be educational. Two risk assessment tools for predicting future dementia (one in middle-aged adults and one in older adults) will be discussed in terms of their clinical utility and limitations. More research needs to be done to improve these formulas and their ease of use (regarding complexity and cost) before they can be used in routine clinical practice.

2:30 – 3:00 PM Enhancing Cognitive & Brain Function of Older Adults — Arthur F. Kramer, PhD

Dr. Kramer will review research conducted in his laboratory, and the field in general, which has examined the extent to which cognitive and fitness training enhances cognition and brain structure and function of older adults. The presentation will cover both cross-sectional and intervention studies of fitness differences and fitness and cognitive training. Studies which assess cognition via both behavioral measures and non-invasive neuroimaging measures, such as magnetic resonance imaging, functional magnetic resonance imaging, event-related brain potentials, and the event-related optical signal, will be reviewed and discussed. Finally, he will explore the gaps in the human and animal literature on cognitive and brain health and the manner in which they can be addressed in future research.

3:00 – 3:15 PM Break

3:15 – 3:45 PM CAM Techniques for Preventing Cognitive Decline — Joseph H. Flaherty, MD

Alzheimer's dementia (AD) is expected to increase dramatically over the upcoming decades and its treatment is not curative. Therefore preventative strategies become the focus of clinical intervention. Complementary and alternative medicine techniques such as meditation, yoga, herbs and acupuncture may reduce stress related cortisol elevation, improve lipid profiles and lower oxidative stress. The combined action of these beneficial influences would provide enhanced neuronal function and neuroprotective effects, elevating cognitive reserve and lowering the risk of neurodegeneration associated with AD. Further clinical investigation, however, will be necessary in order to recommend routine incorporation of these techniques into an AD prevention program.

This lecture will review the basic and clinical evidence underlying the mechanisms for neuroprotection associated with the commonly employed CAM techniques and their efficacy in reducing the risk of AD.

3:45 – 4:15 PM Diet and Cognition: The Inflammatory Link — John E. Morley, MB, B.Ch.

The prevalence of dementia is expected to increase dramatically over the upcoming decades due to the increases in the aging population. Since treatment is not curative, preventative strategies are of the utmost importance. Stimulating activity (cognitive, physical, and social), vascular risk factors, and diet may be important in preventative strategies. In observational studies, vascular risk factors-including diabetes, hypertension, dyslipidemia, and obesity are fairly consistently associated with increased risk of dementia.

People who adhere to a Mediterranean diet or who have high intake of antioxidants and omega-3 fatty acids have reduced likelihood of dementia in observational studies supporting their anti-inflammatory action. However, supplementation in controlled trials has not generally been successful at improving cognitive outcomes. A single supplement may be insufficient to prevent dementia as the composition overall diet may be more important.

This lecture will review the evidence for neurocognitive improvement mediated by anti-inflammatory dietary interventions.

4:15 – 5:15 PM Panel Discussion — Drs. Kettner, Desai, Kramer, Flaherty and Morley

The objectives of the panel will include addressing audience questions from each speaker's talk, discussing current controversies in the prevention of cognitive decline, and outlining the future directions in research for preventing cognitive decline.

5:15 PM Evaluation — Staff

5:30 PM Adjournment

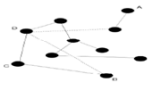
LECTURE NOTES

The Topology of Cognitive Networks or What's a Memory?

Norman W. Kettner, DC, DACBR

Norman W. Kettner, DC, DACBR
Department of Radiology
Logan College of Chiropractic
Chesterfield, MO

THE TOPOLOGY OF COGNITIVE NETWORKS OR WHAT'S A MEMORY?



OBJECTIVES

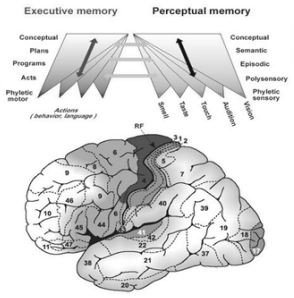
- Memory as a neural system
- Neuro-functional mechanisms of memory
- Functional connectivity of the brain
- Imaging neuro-functional resting networks
- Cognitive decline
- Future directions

Key Questions

- What are the neural substrates that interact to generate and retrieve memories?
- How can these neural interactions be measured and assessed using imaging techniques?
- Can imaging the topological neuro-dynamic framework be used to predict cognitive decline in dementia?

Memory

- In order to connect spatially (temporally) remote regions, the brain maintains a modular (specialized) and simultaneously integrative (distributive) functional architecture.
- Spatiotemporal dynamics operate from the scale of neurons (micro) to cortical columns (meso) and large-scale (macro) networks linking structure and function.



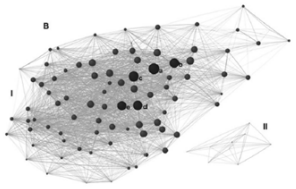
Joaquin M. Fuster (2007) Cortical memory. Scholarpedia, 2(4):1644

Memory

- Memory is a cognitive process arising from the acquisition, storage and retrieval of experience.
- Experience is encoded within the topology (interconnectivity) of cortical and sub-cortical large scale neuronal networks providing efficient specialized information flow across local and remote brain regions.

Memory

Large Scale Network



Buckner et al, 2009

Memory

- A recent neuro-dynamic framework proposes that multiband synchronous oscillatory electromagnetic activity enslaves (connects) (disconnects) local and remote brain regions thus unifying complex cognitive processes (Varela et al, 2001).

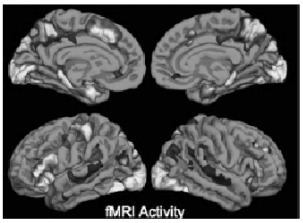
Memory

- Episodic (explicit) memory refers to conscious recollection such as facts, events, or autobiographical knowledge . Semantic (meaning) and episodic comprise declarative memory.
- Memory encoding, archiving and retrieval are likely associated with neural activity in the prefrontal and medial temporal lobe (Tulving et al, 1994).

Memory

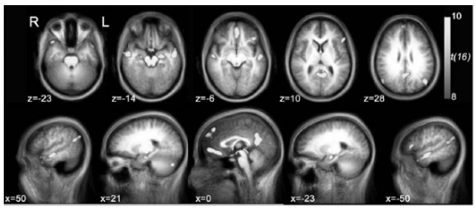
- Procedural memory (implicit) includes skills, habits, and conditioned responses.
- Amnestic patients can display intact or relatively preserved abilities in procedural learning, semantic memory or classical conditioning.

Memory Encoding



Sperling et al, 2009

Memory Retrieval

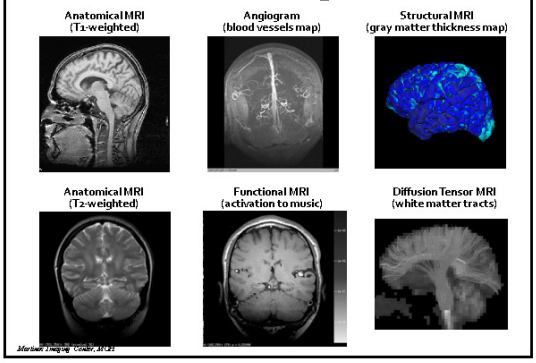


Mendelsohn et al, 2010

Functional Connectivity

- Functional connectivity defines linear (nonlinear) statistical interdependence between the time series of physiological signals recorded from different cortical columns or brain networks.
- Neuro-functional imaging techniques including MEG/EEG, DTI, VBM, and fMRI are utilized to study functional and structural (anatomic) and effective (causal) connectivity.

MRI Examples



Functional Connectivity

- Functional connectivity is assumed to reflect functional interactions between underlying brain networks occurring on variable spatiotemporal scales (neuron, column, network).

Functional Connectivity

- The imaging techniques for the study of functional connectivity have provided key insights into the functioning of brain systems including high level memory and cognition.

Functional Connectivity

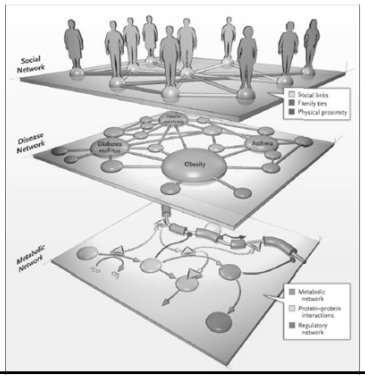
- It is now evident that the brain is capable of re-organizing its functional connectivity in networks with either beneficial or maladaptive outcomes (neuroplasticity) modified by phenotype and experience.

Functional Connectivity

- Functional connectivity is statistically challenging when applied to large scale complex brain networks.
- Recent breakthroughs in network theory have resulted in powerful new models, concepts and approaches for the connectivity analysis of systems with complex networks (Barabasi and Albert 1999).

Graph Theory Analysis

- Complexity arises in a network when the elements of a dynamical system combine statistical randomness with regularity. Networks from the scale of cell metabolism, neuronal connectivity in the brain or the World Wide Web are shaped by their constituent elements.
- Very different complex systems may share underlying principles of organization even though the macroscopic elements are different from those which are microscopic

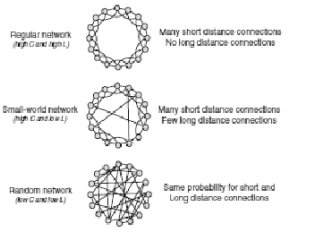


Christakis and Fowler 2007

Graph Theory Analysis

- One method for understanding complex network connectivity in the brain is graph theory analysis.
- Networks are graphically represented by a set of nodes (brain voxels) and edges representing connectivity (temporal correlation) of each node to every other and organized in a cross-correlation (connectivity) matrix.
- Networks can be analyzed by various metrics to characterize their properties. The number of edges connected to nodes is known as the degree (K). High degree defines a hub.

Graph Theory



Guye et al, 2009

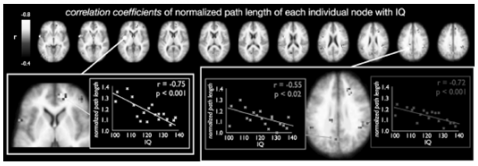
Graph Theory

- Watts and Strogatz (1998) introduced the concept of 'small-world' in the C. *elegans* neural network.
- Balanced between modules of local specialization and those of global integration, small-world networks optimize information processing.

Graph Theory

- Small-world networks are defined by a relatively high amount of local clustering i.e. nodes (hubs) have high connection frequency with their neighbors.
- Relatively short path lengths are seen with only a few connections necessary to reach any other node in the network.

Graph Theory

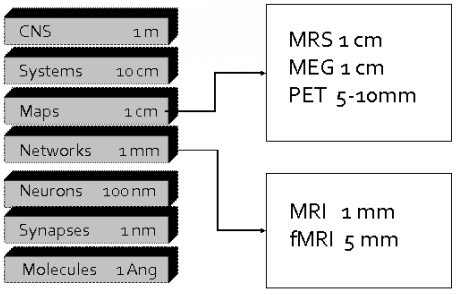


Van den Heuvel et al, 2009

Graph Theory

- Graph theory metrics can also model brain network organization i.e. attention, memory, reward clarifying the relation between network structure and activity in the networks.
- Graph theory analysis can also predict the optimal network (balanced separation and integration, performance and cost), as well as model vulnerability to pathological attack.

Imaging Spatial Resolution

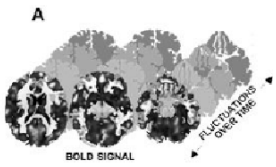


Toga and Mazziotta, 2002

Functional Imaging

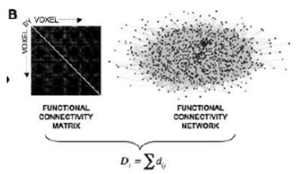
- One of the most productive neuro-imaging tools to study the topology of large scale neural networks has been resting-state fMRI.
- This technique measures intrinsic low frequency fluctuations in blood oxygen level dependent (BOLD) signals and can identify functionally (temporally) connected brain networks.

Functional Imaging



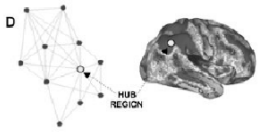
Buckner et al, 2009

Functional Imaging



Buckner et al, 2009

Functional Imaging



Buckner et al, 2009

Functional Imaging

- Functional neuro-imaging methods have identified the location of several major hubs of connectivity in the brain which serve to integrate inputs.
- These hubs include the heteromodal association areas of the parietal (precuneus/post cingulate), temporal and (medial) prefrontal cortex.

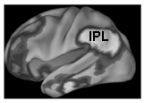
Resting State Network

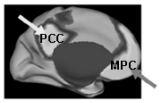
- The activation of brain networks is either evoked or intrinsic (spontaneous). A brain that is experiencing low demand will spontaneously activate numerous functionally connected regions, known as resting-state networks.

Default Mode Network and Resting BOLD Signal

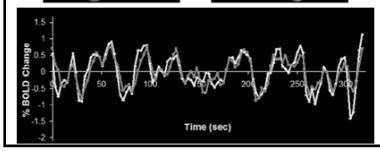
Anatomically defined brain regions which are more active at rest (internal focus) than during externally focused tasks (e.g. visual, motor, somatosensory, etc.)

Includes inferior parietal lobule (IPL), posterior cingulate cortex precuneus (PCC), medial prefrontal cortex (MPC)





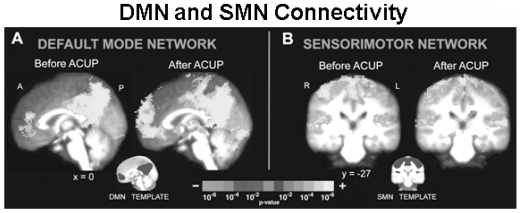
Shulman et al, 1997
Fox et al, 2005



Evaluating the Effects of Acupuncture on Resting State Connectivity

Dhond RP, Yeh C, Park K, Kettner N, Napadow V. Acupuncture Modulates Resting State Connectivity in Default and Sensorimotor Brain Networks. *Pain*. 2008, 136(3):407-18.

fMRI Results: Group Maps (n=15) for Resting DMN and SMN Connectivity



Good match between group maps and template

Can qualitatively see more extensive connectivity for DMN post- vs. pre-acupuncture.

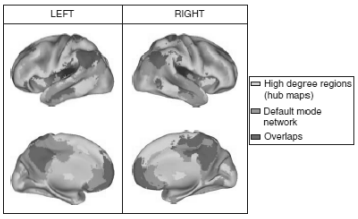
Resting State Network

- One interacting set of resting state brain regions is known as the default mode network (DMN). In contrast to unfocused activation, focused attention deactivates the DMN.
- The interplay between activation and de-activation of the DMN is necessary for the performance of autobiographical memory tasks.

Resting State Network

- The DMN overlaps with the brain's major hubs and consists of the posterior cingulate cortex/retrosplenial cortex, ventromedial prefrontal cortex, and inferior lateral parietal cortex.
- The DMN interacts with the medial temporal lobe memory system. (Gusnard et al, 2001; Raichle et al, 2001; Buckner et al., 2008).

Resting State Network

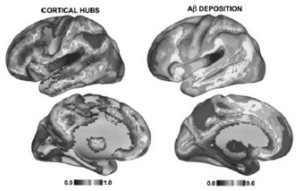


Guye et al, 2009

Resting State Network

- The hub areas display disproportionately high metabolism, aerobic glycolysis and are the earliest to undergo neuronal degeneration (Vlassenko et al, 2010).

Resting State Network

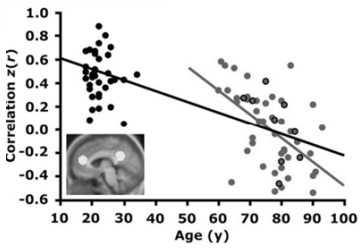


Sperling et al, 2009

Cognitive Decline

- Normal aging even in the absence of disease commonly results in cognitive decline.
- The "disconnection hypothesis" refers to loss of connectivity (white matter) and integration of brain systems (grey matter) (O'Sullivan et al, 2010)

Cognitive Decline



Andres-Hanna et al 2007

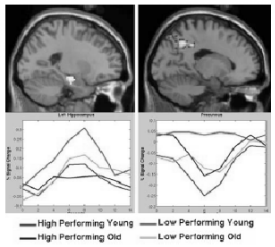
Cognitive Decline

- Alzheimer's disease is characterized by amyloid-β and hyperphosphorylated tau accumulation resulting in neuronal loss, white matter deterioration, loss of synaptic transmission and decreased neurotransmitter.
- This pathological complex disrupts the structural network connectivity and functional interactions across multiple cortical and sub-cortical regions.

Cognitive Decline

- One-third of individuals with moderate to high AD pathology at autopsy were not demented ante-mortem. Is compensatory activity in prefrontal neural networks counteracting AD neuropathology?
- Network compensations are also known to occur in chronic pain patients (Napadow et al, 2006).

Cognitive Decline



Sperling et al, 2009

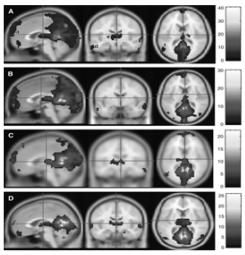
Cognitive Decline

- A few studies have shown that brain pathology may interfere with the normal small-world architecture. Resting-state fMRI in Alzheimer's disease revealed reduced DMN activity (Greicius et al, 2004).

Cognitive Decline

- Brain pathology likely triggers a deviation from the normal optimal small world organization of brain networks disrupting the coordination and topology of large-scale brain networks related to cognitive function.

Cognitive Decline



Zhang et al, 2010

Future Directions

- Imaging of disrupted functional connectivity in conjunction with other biomarkers, such as amyloid deposition (PiB) or CSF amyloid levels, may eventually allow for risk stratification and earlier diagnosis and treatment.

Future Directions

- Future work should determine whether the medial temporal lobe (hippocampus) is preferentially associated with connectivity disruption in the earliest pre-clinical stages of AD or whether the DMN is affected initially because of elevated metabolism (Buckner et al, 2005).

Future Directions

- Functional connectivity imaging may catalyze an increased understanding of the mechanisms underlying cognitive reserve and demonstrate evidence of enhancement following prevention techniques.

OBJECTIVES

- Memory as a neural system
- Neuro-functional mechanisms of memory
- Functional connectivity of the brain
- Imaging neuro-functional resting networks
- Cognitive decline
- Future directions

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Dementia Risk Predictors: Are We There Yet?

Abhilash K. Desai, MD

Dementia Risk Prediction

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Disclosures

- Abhilash Desai, MD declares:
  - Nothing to disclose.

Objectives

- Discuss research to date on tools to predict risk of future dementia.
- Describe potential clinical implications of such tools.
- Discuss limitations that future research needs to overcome before the tools can be used in clinical practice.

Clinical vignette

- Mrs. SM is a 77 years old married white female, a prominent internist, retired 4 years ago came for assessment of her memory. She reports memory complains and weight loss of 10 pounds in last 2 years. She has history of hypertension, CABG and sedentary lifestyle. No history of alcohol intake. Neuropsychological testing indicated mild executive dysfunction. MRI showed periventrucular hyperintensities. Mrs. SM is slow in her walking, has BMI of 20 and has significant carotid artery stenosis on ultrasound. APOE E4/3 genotype. Score 9. Risk of dementia in next 6 years is 56%!!!!

Clinical vignette

- FA is a 55 years old dentist, father of four children, husband of 27 years. He is worried about his own risk of AD. His both parents had dementia in their 80s and recently passed away. He was their primary caregiver. Patient has hypertension, hyperlipidemia and obesity. APOE e4 genotype is 4/3. Current blood pressure is 150/84. Current total cholesterol is 289. Body Mass Index is 31. Dementia Risk Score 12. Risk of dementia in next 20 years: 16.4% (1 in 6)!!!!
- 7 points can be lost with healthy lifestyle and control of VRFs!! Score: 5. Risk of dementia reduced to 1%!!

Prognostic Indices

- Fracture: The FRAX tool (available at www.NOF.org) can be used to integrate risk factors and bone mineral density (BMD) result to calculate absolute fracture risk over 10 years.
- Framingham Heart Index
- Breast Cancer Risk Assessment Tool
- Others: Diabetes, Mortality

Late-life dementia risk index

- 1. Older Age (75-79 [1]; 80-100 [2])
- 2. Worse Cognitive Test Performance ([2], [2])
- 3. Lower Body Mass Index (BMI less than 18.5 [2])
- 4. APOE e4 ([1])
- 5. MRI findings of white matter disease or ventricular enlargement ([1], [1])
- 6. Internal carotid artery thickening on ultrasound ([1])
- 7. History of bypass surgery ([1])
- 8. Slower physical performance ([1])
- 9. Lack of alcohol consumption ([1])
  - Barnes et al. Neurology 2009; 73:173-179.

Findings

- Dementia risk within 6 years was 4% in those with low scores (0-3); 23% in those with moderate scores (4-7); and 56% in those with high scores (8 or more)!!
- Authors suggest that such an index could be used to reassure those individuals whose risk is low or moderate and to provide those individuals whose risk is high with information that may help them better prepare and plan for their future.

Mid-life dementia risk tool

- 1. Older age (47-53 [3]; >53 [4])
- 2. Male sex (1)
- 3. Low educational level (7-9 [2]; 0-6[3])
- 4. Hypertension (Systolic >140 [2])
- 5. Obesity (BMI >30 [2])
- 6. Hypercholesterolemia (>200 [2])
- 7. Physical inactivity (1)
  - Kivipelto M et al. Lancet Neurol 2006; 5:735-741.

Risk over 20 years: Findings

- Score 0-5: 1.0%
- Score 6-7: 1.9%
- Score 8-9: 4.2%
- Score 10-11: 7.4%
- Score 12-15: 16.4%

Risk score for the prediction of AD

- Vascular risk score was assessed (age, sex, education, ethnicity, APOE e4 genotype, history of diabetes, hypertension, smoking, HDL levels, waist to hip ratio.
- Risk was 1.0 for a score of 0 to 14.
- Risk was 3.7 for score of 15 to 22.
- Risk was 12.6 fold for score of 23-28.
- Risk was 20.5 old for score of 29 and higher.
  - Reitz C et al. A summary risk score for the prediction of Alzheimer disease in Elderly Persons. Arch Neurol 2010;67(7):835-841.

Primary use of risk scores

- Target preventive measures to those most at risk of the disease.
- Risk scores can be used to distribute easily understandable information about risk factors to the general population.

Potential clinical implications

- Midlife risk score useful for primary, long-term prevention (reducing the lifetime dementia risk, preventing initiation of underlying pathologies).
- Late-life risk score is useful for secondary, short-term prevention (directed toward persons who already have such pathologies and signs of cognitive impairment, and may develop dementia within the next few years).

Potential implications

- Global risk assessment can provide quantitative overview of the patients' situation and help physicians and patients (on a clinical level) and general population (on a public health level) set goals and make decisions about necessary lifestyle – related changes or pharmacologic treatment, or both.

Stage based prevention

- Stage 1: Person at risk but without structural brain disease and without signs or symptoms. Identify and treat modifiable risk factors.
- Stage 2: Structural disease present but no clinical signs or symptoms. Identify and treat modifiable risk factors including secondary prevention of stroke, periodic cognitive screening. Clinical trials of disease-modifying drugs.
- Stage 3: Structural disease present with clinical signs and symptoms but no dementia. Management similar to Stage 2.
- Stage 4: Dementia. ChEIs, Memantine, Patient and family education and support, control CRFs.

New criteria for preclinical AD

- National Institute on Aging and Alzheimer's Association work group incorporated new knowledge of the AD process and defined 3 stages:
  - Preclinical
    - 3 criteria
      - Asymptomatic amyloidosis (CSF or brain scan)
      - Amyloidosis plus one other marker of the disease (atrophy, ABN PET scan, or ABN phosphorylated tau in CSF)
      - Amyloidosis plus a disease marker and "slight" cognitive symptoms
  - Mild Cognitive Impairment
  - Alzheimer's dementia

Limitations of current research

- They need to be validated in other populations.
- Late-life dementia index is impractical. Further studies are warranted to find simplified alternatives.
- Midlife dementia risk tool did not include other easily identifiable risk factors (e.g.diabetes).
- Lists of items in both tools need to be refined to improve accuracy.
- We need to study how these tools compare to new criteria proposed to diagnose asymptomatic AD.

Conclusion

- Research to date suggests the potential to develop a midlife and late-life dementia risk predictor in the near future.
- Such a tool can help at clinical level (reducing an individual patients risk of future dementia) as well as at public health level (reducing incidence and prevalence of dementia and thus public health costs).
- Future studies need to improve upon the accuracy of currently available tools before they can be applied in routine clinical practice.

Breath Awareness Exercises To Improve Memory and Promote Resilience

Find a quite spot. Sit on a flat but comfortable surface. Close your eyes and begin to pay attention to your breathing. Inhale through your nose. Slow down your breathing as you feel your breath enter and leave your body. Feel your lungs expand with the inhalation, retain the breath for a few seconds, and then exhale gently through your mouth. As you continue to breathe, try and keep your attention on all three aspects of breathing (inhalation, pause, exhalation). Slower the breathing, the greater are the benefits. Exhalation should be longer than inhalation. During exhalation, the heart slows down, the blood pressure drops and stress hormone levels also drop. By the end of the breathing exercise, stress hormone levels may be at their lowest. Also, try and do abdominal breathing / diaphragmatic breathing. Thus, during inhalation, your tummy should bulge outwards and during exhalation, your tummy should go towards the spine. Count your breaths. If you notice that you have lost count of your breaths, gently bring your attention to breathing and start counting again. Continue this for at least two minutes. Some of my patients do this for 20minutes twice a day (early morning and before sleep). Others do it for 2 minutes several times a day. Find your own rhythm, frequency and duration. If you are doing this for the first time, you may experience dizziness. Generally, it is mild and transient and passes quickly.

Modification: One could say positive affirmations in one's mind during this exercise. For example, one can say that "I am patient, kind and compassionate" or "I am a very forgiving person". Alternatively, one can send positive messages during this exercise to one's friends, family or the universe. For example, one can say "Let the pain of my loved one come to me (as you inhale) and let my love for them reach them (as you exhale). Another modification involves imagining all the positive energy from Earth entering you during inhalation and all your negative energy / feelings / thoughts leaving you when you exhale. Feel free to invent your own modification. This is your time with yourself. The goal is to become aware of one's own breathing, clear one's mind from thoughts, fantasies, and judgments and experience whatever happens. Often, the feelings that one has been running away for years return to be acknowledged, embraced and experienced. Research has shown remarkable healing effects of breathing exercises (breath awareness practices) and the benefits are thought to be due to improved balance between our emotional brain (limbic system) and rational brain (prefrontal cortex).

Benefits of Breathing exercises: Improved memory (through improved capacity to focus, pay attention, be aware), improved capacity to tolerate negative emotions (anxiety, anger, resentment, guilt, grief, sadness) and improved ability to manage stress and problem solve in creative and healthy ways.

Abhilash K. Desai MD

CHECKLIST TO PROMOTE HEALTHY BRAIN AGING:
A GUIDE FOR CLINICIANS*

1	Counseled regarding smoking cessation.	☐
	Comments:	
2	Advised to follow guidelines proposed jointly by the American Heart Association and the American College of Sports Medicine regarding daily physical activity.	☐
	Comments:	
3	Counseled regarding healthy nutrition (e.g., Mediterranean diet. "DASH" [Dietary Approaches to Stop Hypertension] diet).	☐
	Comments:	
4	Counseled regarding the importance of intellectually challenging and creative leisure time activities.	☐
	Comments:	
5	Counseled regarding strategies to promote emotional resilience and reduce psychological distress and depression (e.g., relaxation exercises, mindfulness-meditation practices).	☐
	Comments:	
6	Advised to maintain an active, socially integrated lifestyle.	
	Comments:	
7	Discussed strategies to achieve and maintain optimal daily sleep.	☐
	Comments:	
8	Provided education about strategies to reduce risk of serious head injury (e.g., wearing seat belts, wearing helmets during contact sports, bicycling, skiing, skateboarding).	☐
	Comments:	
9	Provided education about strategies to reduce exposure to hazardous substances (e.g., wearing protective clothing during the administration of pesticides, fumigants, fertilizers and defoliants).	☐
	Comments:	
10	Provided education and counseling provided regarding negative health effects of alcohol consumption more than recommended as safe by the National Institute of Alcoholism and Alcohol abuse.	☐
	Comments:	

11	Provided education about importance of achieving and maintaining healthy weight to promote overall health.	☐
	Comments:	
12	Discussed and implemented strategies to achieve optimal blood pressure control.	☐
	Comments:	
13	Discussed and implemented strategies to achieve optimal control of dyslipidemia (eg. High cholesterol)	☐
	Comments:	
14	Discussed and implemented strategies to achieve optimal control of blood sugar / diabetes.	☐
	Comments:	
15	Discussed risks and benefits of medications, supplements, herbal remedies and vitamins to promote brain health.	☐
	Comments:	
16	Discussed and implemented secondary prevention of stroke strategies (e.g., daily baby aspirin).	☐
	Comments:	

TO BE HAPPIER EVERY DAY, ALL YOU NEED IS "PSALMS"!

Abhilash K. Desai MD
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> It is not easy to find happiness in ourselves,
> and it is not possible to find it elsewhere.
> - Agnes Repplier

Happiness is one of several positive emotions (others for example are feeling relaxed, joyful, at peace with oneself, content, feeling connected with others and with the divine) that promote brain health. Feelings of happiness are associated with release of several brain chemicals that promote brain cell survival, strengthen brain cell connections and help create new brain cells. It is possible to be happier. Like patience, happiness is a skill that we need to cultivate with intention and persistence. Here are some simple strategies to cultivate happiness.

P: Engaging in activities that generate **Pleasure** on a regular basis is crucial to becoming happier. Our brains are hardwired to seek and have fun! Of course, if you seek too much pleasure the brain is as strongly hardwired to switch off! Just the right amount of pleasure is the key. Amazingly, even a small amount can have a dramatic effect! Make a list of activities that are pleasurable and include at least a few in your daily schedule.

S: Activities that exercise our **Strengths** (what we are good at) also generate feelings of happiness. Make a list of your strengths and gradually increase time spent engaging in these activities on a daily basis.

A: Appreciation of what we have, of all the little moments of pleasure and meaningful encounters that we have, improves the depth and duration of our happiness. Practice meditation and consider writing in a gratitude journal one or more times a week.

L: Cultivating our capacity to **Laugh** at our imperfections and not take life too seriously is important to being happier. So lighten up.

M: Engaging in activities that bring **Meaning** to our life (e.g., spending time with family and friends, helping others) is another necessary element to becoming happier. Start actively increasing engagement in the meaningful activities you identify.

S: Scheduling activities that are pleasurable and meaningful and that exercise our strengths on a daily basis is the most important goal. Otherwise life has a way of taking us away from what makes us genuinely happy. Write a daily schedule of happiness activities and happiness "boosters" and stick to the schedule.

Related references:

1. Penninx BWJH. A happy person, a healthy person? Journal of the American Geriatrics Society 2000; 48:473-8.
2. Book by Tal Ben-Shahar PhD. "Happier"

BRAIN HEALTHY NUTRITION

Abhilash K. Desai MD
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Nutrition*:

1. Fruits (4-6 servings daily recommended). Berries are best.
2. Vegetables and Legumes (4-6 servings daily recommended). Tomatoes, beet and green leafy vegetables are the best for brain health. Legumes include beans, lentils, peas.
3. Omega 3 food (one to two serving per day recommended of a variety of omega 3 rich food items). Best source of omega-3 is a variety of fatty fish (baked or broiled, NOT FRIED FISH). Other sources of omega – 3 foods include walnuts, Kiwi, flax seed, omega-3 enriched food items [e.g., eggs, milk, cereals]). Recommended fish: Pacific herring (sardine), sablefish (black cod), European anchovies, spanish Mackerel, wild sockeye salmon, farmed rainbow trout and albacore tuna. Avoid following fish due to high mercury content: King Mackerel, swordfish, tilefish.
4. Monounsaturated fatty acids (first cold-pressed extra-virgin olive oil, canola oil, avocados) (one to two servings per day recommended). It is high in calories and thus excess amount should be avoided.
5. Green tea (4-8 oz daily recommended).
6. Water (24-40oz daily recommended).
7. Whole grains (3-6 servings daily recommended). Includes wheat, barley, oats, maize, brown rice, whole wheat pasta, whole wheat bread, rolled oats.
8. Nuts (3-5 pieces) (tree nuts are the best: walnuts, almonds, pecans, hazel nuts, macadamia nuts). Avoid too many nuts as it contains high amount of fat and thus, high amount of calories.
9. Spices (e.g., turmeric, cinnamon, cloves, red pepper, black pepper, ginger, garlic). Turmeric is most beneficial of all spices.

Turmeric (present in some yellow mustard and some Asian curries) and dark chocolate (true dark chocolates are bitter) have been found to have beneficial effects on heart health and brain health. Exact amount is not clear; hence their use is recommended only in very modest amounts. E.g., a pinch of turmeric mixed in curries / sauce; an ounce of dark chocolate (at least 70% cocoa) per day.

* = Needs physician input and guidance.

What to avoid

Reduced intake of saturated fat (less than 5% of daily caloric needs), salt (less than 4 gm/d), refined sugar (consider anti-diabetic diet even if one does not have diabetes), red meat (once every two weeks or less) is as important as consuming brain healthy food. The American Heart Association recommends reduction in the intake of added sugars to reduce the risk of a variety of metabolic disorders (e.g., metabolic syndrome, diabetes, obesity). A prudent upper limit of intake for most American women is no more than 100

calories per day and for most American men is no more than 150 calories per day from added sugar. Try and completely avoid intake of trans-fatty acids, other partially hydrogenated fatty acids, high fructose corn syrup, fried foods, and food with long shelf life. Avoid refined grains such as white rice, white flour, white bread and pasta (non-whole wheat varieties).

Healthy Snacks. Examples: hummus with vegetables or whole grain crackers, small amount of nuts, organic low fat cottage cheese, fruits, fat free milk, plain oat meal with fruits, and some health bars.

Nutritional Supplements*: Omega – 3 pills (e.g., 500mg DHA/day), Vitamin D (e.g., 1,000IU/day), B12 (e.g., 500mcg/day).

Sweeteners: Splenda is recommended over other sweeteners. Recommend to use as less as possible as eating sweet food can train the tongue and brain to crave for sweet food.

Nutritional deficiencies need to be corrected. Common examples include vitamin deficiencies (D, B12, B1, Nicotinamide), protein energy malnutrition.

Celiac disease / Celiac Sprue / Gluten Sensitive Enteropathy: Associated with many nutritional deficiencies and impaired brain function (e.g., memory problems). Commonly manifests as bloating (especially after eating wheat products), abdominal discomfort, diarrhea and often misdiagnosed as Irritable Bowel Syndrome.

Note: It is very important the each person consumes calories that do not exceed calories needed to maintain healthy weight (Body Mass Index between 18 and 25).

Suggested Reading: Healthy Eating. A guide to the new nutrition. A special health report from Harvard Medical School. 2006 Harvard Health Publications, Boston, Massachusetts. www.health.harvard.edu

Website for healthy nutrition information

1. Pritikin Longevity Center: www.pritikin.com
2. www.dashdiet.org
3. American Heart Association website
4. Mayo Clinic

Enhancing Cognitive & Brain Function of Older Adults

Arthur F. Kramer, PhD

SCIENCE AND SOCIETY

Be smart, exercise your heart: exercise effects on brain and cognition

Charles H. Hillman, Kirk I. Erickson and Arthur F. Kramer

Abstract | An emerging body of multidisciplinary literature has documented the beneficial influence of physical activity engendered through aerobic exercise on selective aspects of brain function. Human and non-human animal studies have shown that aerobic exercise can improve a number of aspects of cognition and performance. Lack of physical activity, particularly among children in the developed world, is one of the major causes of obesity. Exercise might not only help to improve their physical health, but might also improve their academic performance. This article examines the positive effects of aerobic physical activity on cognition and brain function, at the molecular, cellular, systems and behavioural levels. A growing number of studies support the idea that physical exercise is a lifestyle factor that might lead to increased physical and mental health throughout life.

Participation in physical activity has been associated with the reduction of a number of physical (for example, cardiovascular disease, colon and breast cancer, and obesity) and mental (for example, depression and anxiety) disorders across the adult lifespan[1]. Despite mounting evidence for the importance of physical activity, 74% of adults in the United States do not meet the recommended guideline of at least 30 minutes of moderate-intensity physical activity on most days of the week[1,2]. Recent evidence further indicates that children are growing increasingly sedentary and unfit, and that these lifestyle factors are related to an earlier onset of several chronic diseases (such as type II diabetes and obesity), which typically do not emerge before adulthood[3]. As a result, recent estimates have indicated that younger generations, for the first time in United States history, might live less healthy lives than their parents[1–5]. The economic cost of this sedentary lifestyle is enormous in both developed and developing countries, with estimates indicating that inactivity was associated with 2.4% of healthcare expenditures in 1995 (REF. 6) and ~US$76 billion in medical costs in the year 2000 (REF. 7). Canadian estimates concur, as 2.5% (or $2.1 billion) of the total direct healthcare costs for the year 1999 were related to physical inactivity[8].

In addition to the physical and economic impact of physical inactivity, a growing body of literature has linked physical activity with improvements in brain function and cognition. Animal research has long shown that enriched environments, including access to exercise equipment (such as running wheels), has a positive effect on neuronal growth and on the neural systems that are involved in learning and memory, indicating that physically active behaviours influence cognitive function and the supporting brain structures[9]. A similar perspective has emerged in human research[10]; with recent advances in neuroimaging techniques showing that exercise leads to evident changes in brain structure and function. These findings allow for a better understanding of the implications of specific lifestyle factors for cognitive health.

Although the roots of a mind–body connection can be traced back to at least the ancient Greek civilization, the scientific investigation of the relation between physical activity and cognition began in the 1930s. Evidence for a relationship between physical conditioning and faster reaction time was observed during the next several decades[11–13] (although some studies indicated no such relationship[14]). The first systematic examination of this relationship began in the 1970s, with findings indicating that older adults who regularly participated in physical activity had faster psychomotor speed, relative to their sedentary counterparts, on simple and choice reaction-time tests. Interestingly, no such relationship was observed in comparable groups of younger adults[15–18], suggesting that the benefits of physical activity on cognition were specific to older adults (see REF. 19 for a review). With recent technical advancements, contemporary research has sought to understand the mechanisms that underlie the influence of exercise participation on cognition.

Here we describe the latest research, in both humans and non-human animals, on the relationship between physical activity (primarily aerobic exercise) and cognition. The research with humans has mostly focused on the effects of exercise on cognitive processes, as assessed with paper-and-pencil and computer-based tests. However, neuroimaging techniques, such as event-related brain potentials (ERP) and structural and functional MRI, are also being used to examine the link between exercise and cognition. Non-human animal research takes this investigation one step further, revealing some of the molecular and cellular changes that occur in the brain following exercise training. The findings we describe could have important implications for future healthcare and education policies.

Human research

Physical activity effects on cognition during childhood and young adulthood. Despite the fact that children in industrialized countries are growing increasingly unfit and unhealthy owing, in part, to the comforts of technological advancements, the investigation of the effects of physical activity on cognitive health during development has received surprisingly little attention. In

fact, only a handful of studies using true experimental designs exist in the literature and, arguably, these studies have done little to advance our understanding of the mechanisms by which exercise influences brain function and cognition. A recent meta-analysis determined a positive relation between physical activity and cognitive performance in school-age children (aged 4–18 years) in eight measurement categories (perceptual skills, intelligence quotient, achievement, verbal tests, mathematic tests, memory, developmental level/academic readiness and other). A beneficial relationship was found for all categories, with the exception of memory, which was unrelated to physical activity behaviour[20], and for all age groups (although it was stronger for children in the age ranges of 4–7 and 11–13 years, compared with the age ranges of 8–10 and 14–18 years)[20]. The effect size (ES) observed by Sibley and Etnier[20] in their meta-analysis was 0.32 (standard deviation = 0.27), which is similar to that which was observed in a meta-analysis of the effects of physical activity on cognition (ES = 0.25) across the lifespan (6–90 years)[21]. These findings suggest that although physical activity might be beneficial at all stages of life, early intervention might be important for the improvement and/or maintenance of cognitive health and function throughout the adult lifespan.

Recently, research efforts have focused on the relation between physical activity and the academic performance of school-age children (BOX 1). Several studies have suggested that participation in physical activity has either a positive relation or is unrelated to academic performance, with differences across studies probably reflecting the techniques that were used to assess behaviour and/or the aspects of scholastic aptitude that were measured (achievement testing, grade-point average and academic records, for example)[22–24]. Regardless of the measure, these studies indicated that an increase in the amount of time dedicated towards physical health-based activities (such as physical education) is not accompanied by a decline in academic performance. The implications of these findings are important for promoting better physical health, without the loss of other educational benefits, in school-age children.

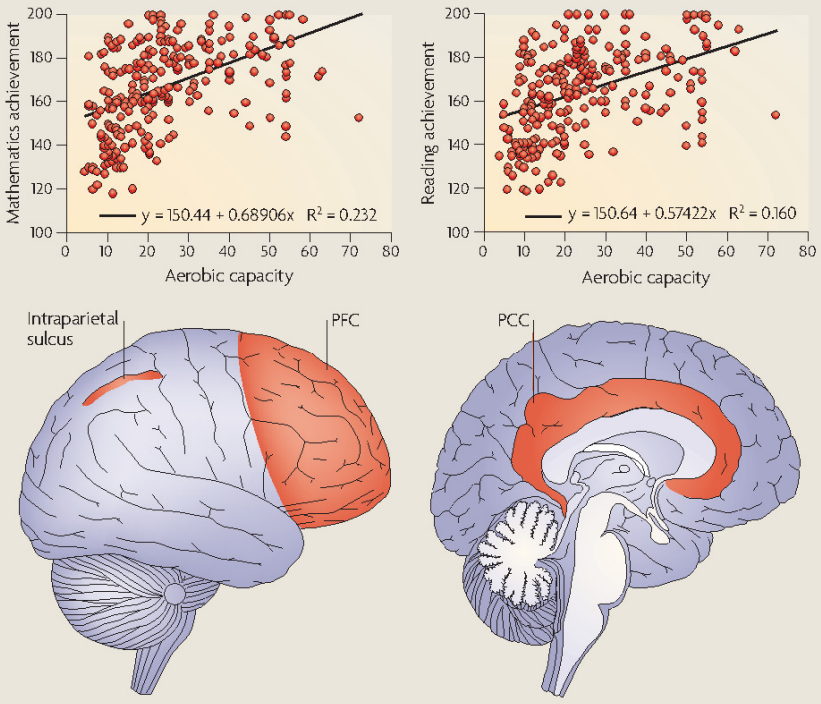
Similar to the situation with children, there is a dearth of research on exercise–cognition effects in young adults. Although exceptions exist, especially with regards to acute exercise effects on cognition[25–26] (see REF. 27 for a review), most research has used

Box 1 | **Physical activity and academic performance in school-age children**

Recently, owing to the increasing importance placed on standardized testing, many schools in the United States have reduced or eliminated physical education (PE) requirements, in an effort to increase students' academic performance. However, no empirical evidence exists to suggest that the elimination of non-academic programmes (such as PE) is related to higher academic achievement. In fact, empirical evidence suggests otherwise. Aerobic fitness has a small but positive relation to academic achievement, whereas body mass index (BMI) has a negative relation[23]. Recent studies have indicated that achievement in standardized tests of mathematics (the left-hand graph in the figure) and reading (the right-hand graph in the figure) was positively related to physical fitness scores, measured using the progressive aerobic cardiovascular endurance run (PACER) test (a 20 metre shuttle run that increases in difficulty and is considered a field test of aerobic capacity), in school-age children[88]. This relationship was selective to aerobic fitness, as muscle strength and flexibility fitness were unrelated to academic achievement[23]. Similarly, beneficial relationships have been observed between physical activity and other measures of academic performance, such as academic grades in the classroom[24,89–90].

Relevant neural networks have been identified for component processes that might be involved in mathematics and reading performance (see the lower two panels of the figure). Research that examined the functional neuroanatomy of reading comprehension revealed an activation of the prefrontal cortex (PFC) and parietal/posterior cingulate cortex (PCC)[91]. Likewise, mathematical calculations and numerical magnitude processing have been linked to bilateral regions of the intraparietal sulcus in children and adults[92–94]. However, children also recruit the right dorsolateral prefrontal cortex[92,94]. Given that both mathematics and reading elicit activation in the frontoparietal network, there is a sound basis for examining these structures in relation to academic performance. As fitness has also been related to the frontoparietal network[48,53,55], it would follow that children might derive benefits in school performance from increased participation in physical activity.

Finally, a few studies have indicated that physical activity is unrelated to academic performance. For example, a study that relied on the self-reported teacher perception of students' physical activity did not find a relation with academic performance[22]. However, another study[95] reported that pupils who engaged in vigorous physical activity performed better in school than those that performed moderate or no physical activity. Sallis *et al.*[96] observed a trend for improved achievement test scores following physical activity, but the relationship might have been blunted because the school district examined was one with historically high test scores. Collectively these data indicate that, at the very least, time spent in physical activity programmes does not hinder academic performance, and it might indeed improve performance. Given the positive health benefits that are derived from physical activity, these studies support PE as an important component of children's health and wellbeing. Bottom panels adapted from REF. 97 © (1996) Appleton & Lange.



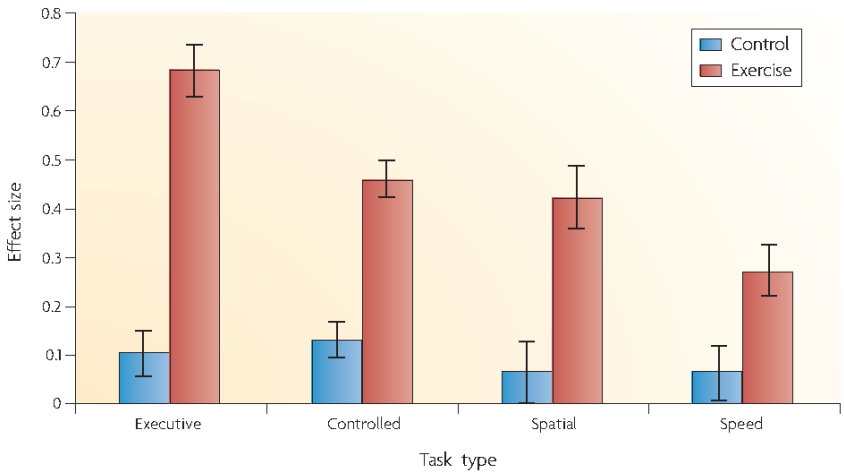


Figure 1 | **Meta-analytic findings of exercise-training effects on cognition in older adults.** The results of a meta-analysis of the effects of fitness training on cognition showed that the benefits of fitness training on four different cognitive tasks were significant. As illustrated in the figure, fitness training has both broad and specific effects. The effects are broad in the sense that individuals in aerobic fitness training groups (represented by the red bars) showed larger fitness training effects across the different categories of cognitive processes illustrated on the x-axis. They are specific in the sense that fitness training effects were larger for some cognitive processes, in particular executive control processes, than for other cognitive processes. Figure reproduced, with permission, from REF. 32 © (2003) Blackwell Publishers.

younger adults merely for the purpose of comparison with older adults, to provide a basis for age-related deficits in cognitive function and to better understand the prophylactic or ameliorative effects of chronic physical activity participation on cognitive ageing. One obvious reason for this paucity of literature is that cognitive health peaks during young adulthood[28], suggesting that there is little room for exercise-related improvement to cognitive function during this period of the lifespan. However, recent trends indicating a declining health status among children[3] suggests that future research should extend to periods of the lifespan that are characterized by peak cognitive health.

There is a small body of literature that examines neurophysiological indices of the benefits of chronic physical activity participation on cognitive function in young adults; however, the vast majority of this research is focused on cognitive ageing (see below). Future research in this area needs to continue to build the physical activity–cognition literature base, similar to that for older adults and, if it is to have societal implications, it should also focus on bridging the gap between the basic mechanisms that underlie the effects of exercise on the brain and applied aspects of cognition related to classroom and job performance.

Physical-activity effects on cognition during older adulthood. The study of exercise and cognition with older adults dates back several decades. Recently the exercise–cognition relation in older adults has been strengthened by the observation, in prospective epidemiological studies, that there are a number of lifestyle factors — including intellectual engagement, social interaction, diet and physical activity — that are associated with the maintenance of cognitive function and a reduction in risk for age-associated neurodegenerative disorders, such as Alzheimer's disease and vascular dementia[9,29–30].

A small but growing number of randomized intervention studies have examined whether fitness training has a positive effect on different aspects of perception and cognition in older adults. These studies generally enrol healthy but sedentary adults between the ages of 60 and 85 years and ask them to participate in an exercise regime several times per week over the course of several months to several years. Cognition and fitness is assessed before and after the intervention. The central question is whether individuals who participate in an aerobic training regime show larger gains in cognition than wait-list control subjects or control subjects who participate in non-aerobic regimes, such as toning and stretching. In one example[31], older adults were randomized into a pool-based aerobic exercise group or a wait-list control. All participants were tested with a series of single and dual auditory and visual discrimination tasks both before and after the 10-week intervention. Participants in the aerobic training programme, but not those in the control group, showed significant improvement in dual-task performance over the 10-week period. Improvements in single-task performance were equivalent for the two groups.

Although a number of intervention studies have found improvements in performance on cognitive tasks for aerobically trained but not control subjects, other studies have found equivalent performance improvements for both aerobic and control subjects across cognitive tests. Given that the number of randomized intervention trials that have examined fitness training effects on cognition is relatively small, and that the particulars of these studies were varied, there are a number of factors that might be responsible for the mixed pattern of results. Some of these factors include: the cognitive processes examined; the length, intensity and type of exercise programme; the age range, health and education of participants; and the manner in which fitness improvements were measured. Fortunately, a few meta-analyses have been conducted in recent years to determine first whether the fitness–cognition effect is robust across the literature and second which factors might moderate this relation[32–34]. Several important results have been obtained from these meta-analyses, which examined partially overlapping sets of studies. First, and perhaps most importantly, the effect size in each meta-analysis was significant. That is, in all studies, physical activity had a positive effect on cognition. Second, a significant relationship between physical activity training and improved cognition was obtained for both normal adults and patients with early signs of Alzheimer's disease, in which memory or cognitive ability was mildly impaired[32–34]. Thus, it appears that physical activity can have a positive effect on a wide range of cognitive functions. Several other moderator variables were also revealed[32]. As indicated in FIG. 1, physical-activity training appears to have both broad and specific cognitive effects: broad in the sense that various different cognitive processes benefit from exercise participation, and specific in the sense that the effects on some cognitive processes, especially executive control processes (which include scheduling, planning, working memory, multi-tasking and dealing with ambiguity), are disproportionately

larger. This is particularly interesting as executive control processes, and the brain regions that support them (chiefly the prefrontal cortex), show substantial age-related deterioration — the findings suggest that even processes that display substantial age-related change are amenable to intervention. Additionally, the relationship between physical activity training and cognition was also influenced by programme duration, age, gender[35] and type[32].

In summary, although there are a multitude of unanswered questions regarding physical activity and cognition in older adults, there is evidence of a relationship between fitness training and improvements in various aspects of cognition across a broad range of ages. Collectively, the findings suggest that physical activity is beneficial across the human lifespan. However, the mechanisms that underlie this relationship are unclear and might differ during development and ageing, as the brains of children are still developing and undergoing organization whereas the brains of adults are not. Physical activity during childhood might encourage optimal cortical development, promoting lasting changes in brain structure and function. Future research should address whether the mechanisms that support the physical activity–cognition relationship are different in children and adults.

Neuroimaging studies of physical activity in humans. Neurophysiological studies have revealed differences in cognitive function that are related to physical activity behaviour. Examination of baseline spectral frequency distributions of electroencephalograms (EEGs) has revealed increased activation in the theta (4–8 Hz), alpha (8–13 Hz) and beta (13–20 Hz) spectral bands, and higher mean frequency in the delta (0.25–4 Hz), theta and beta bands in more active or aerobically fit individuals[36–39]. These findings suggest that physical activity influences baseline electrocortical function and, thus, that it might affect cognitive operations. Support for this influence is garnered from the finding that inter-individual variability in spectral frequency activation is related to individual variations in the P3 component of the ERP[40–41], which has been found to be especially sensitive to changes in physical activity participation and aerobic fitness.

Research conducted over the past two decades has described both aerobic fitness- and physical activity-related differences in the amplitude and latency of the P3 component in pre-adolescent children[42], young adults[43–44] and older adults[37,45–46]. This component appears to be generated by a network of neural structures, including the frontal lobe, the anterior cingulate cortex (ACC), the infero-temporal lobe and the parietal cortex, that are involved in cognitive operations, including stimulus processing and memory updating[47]. Consistent and robust findings have emerged: larger amplitude and shorter latency P3s are observed across a variety of cognitive tasks in individuals with high aerobic fitness compared with unfit individuals. These results indicate that greater amounts of physical activity or aerobic fitness are generally beneficial to cognitive processes that are related to the allocation of attentional resources and faster cognitive processing during stimulus encoding. In agreement with these findings, functional MRI (fMRI)[48] and behavioural[49–50] data show a physical activity-related modulation that is disproportionately larger for task components that necessitate greater amounts of executive control[19].

More recently, neurophysiological research has focused on response-monitoring processes elicited by the evaluation of conflict during instances of erroneous action. Specifically, smaller error-related negativity (ERN) amplitude following error commission has been observed in more active older adults[51] and fit young adults than in unfit individuals of similar age[26]. Given that source-localization techniques, such as dipole modelling[52], have localized the generation of the ERN to the caudal portion of the ACC, these findings corroborate previous fMRI research that showed reduced activation of the ACC in fit older adults during participation in tasks that required variable amounts of executive control relative to unfit individuals[18] (BOX 2). The implication of these findings is that greater amounts of physical activity and/or fitness might be associated with a reduction in task-related response conflict owing to increased top-down control during task execution. Physical activity-related influences on task performance are further observed through the regulation of top-down control, as more active and fit individuals exhibit longer reaction times on trials following erroneous action[26,51].

MRI has also been used to examine the effects of fitness on cognition. For example, in cross-sectional comparisons between individuals with high and low levels of fitness and aerobic fitness training studies, Colcombe and colleagues[18,53] found that higher levels of fitness and fitness improvements were related to larger volumes of prefrontal and temporal grey matter, as well as anterior white matter (see also REFS 54,55). Such increases in brain volume have previously been shown to be predictive of performance in older adults[35,55].

Aerobic fitness training has also been found to induce changes in patterns of functional activation using fMRI. For example, older adults who participated in a walking intervention over a 6-month period showed increases in activation in the middle frontal gyrus and superior parietal cortex and decreases in activation in the ACC, relative to a non-aerobic toning and stretching control group[18]. These changes in patterns of fMRI activation were related to significant and substantial improvements in the performance of a selective-attention task. More recently, increases in measures

Glossary

Aerobic fitness
The maximal capacity of the cardiorespiratory system to take up and use oxygen.

Behavioural conflict
The indecision that arises when multiple conflicting responses can be elicited in response to a stimulus.

Dipole modelling
A method to determine the location of the sources that underlie the responses measured in an electroencephalographic experiment. It provides an estimate of the location, orientation and strength of the source as a function of time after the stimulus was presented.

Error-related negativity
(ERN). A negative deflection in a response-locked ERP that reflects neural correlates of action monitoring that is associated with the evaluation of conflict.

Event-related brain potential
(ERP). A time-locked index of neuroelectrical activation that is associated with specific cognitive processes.

Executive control
Computational processes involved in the selection, scheduling and coordination of complex cognitive functions.

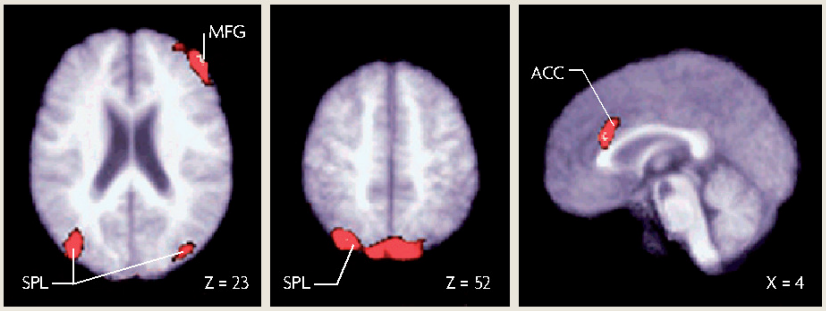
Exercise
Repetitive and planned physical activity with the goal of maintaining or improving physical fitness.

P3
A positive deflection in a stimulus-locked ERP that reflects changes in the neural representation of the stimulus environment and is proportional to the amount of attention that is required to encode a given stimulus (amplitude) as well as the speed of stimulus evaluation (latency).

Physical activity
Bodily movement produced by skeletal muscles with the expenditure of energy.

Top-down control
Refers to an individual's ability to selectively process information in the environment. Top-down control relies on an observer's expectancies about events in the environment, knowledge of and experience with similar environments, and the ability to develop and maintain an attentional set for particular kinds of environmental events.

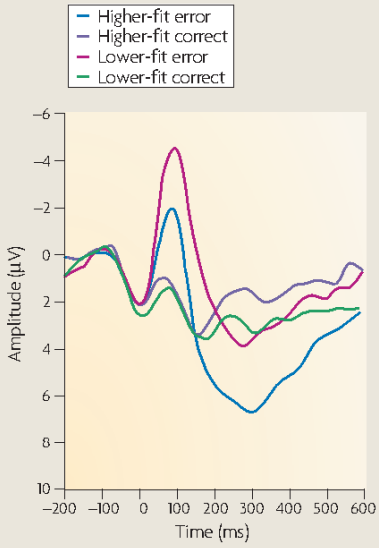
Box 2 | **Physical activity and the anterior cingulate cortex**



Physical activity has been found to enhance cognition, with a selectively larger effect on executive control functions compared with other cognitive processes[32,50,98]. Accordingly, brain structures that mediate executive functions would be expected to show disproportionate changes as a result of participation in physical activity. One such structure is the anterior cingulate cortex (ACC), which is part of the brain's limbic system and has connections with multiple brain structures that process sensory, motor, emotional and cognitive information[99]. Two convergent lines of research indicate that physical activity exerts a substantial influence on the ACC and the concomitant executive processes that it mediates.

Neuroimaging research that examined the effects of changes in fitness on the ACC found that aerobically trained older adults exhibited a reduction in activation (see figure, top panels), with a concomitant decrease in behavioural conflict, during a task that required variable amounts of executive control, relative to untrained individuals[48]. Furthermore, increased activation of the dorsal prefrontal and parietal brain regions involved with task-related inhibitory functioning was observed[48], suggesting an increased ability of the frontal attentional network to bias task-relevant activation in the posterior cortex[48].

These findings are supported by neurophysiological and task-performance data[26,51], which demonstrated a reduction in error-related negativity (ERN) amplitude[52]; an event-related brain potential (ERP) component with its primary neural generator in the caudal ACC (see figure, bottom panel). This reduction in the ERN amplitude was associated with greater regulation of behavioural responses for physically active younger and older adults compared with inactive individuals. These findings suggest an improvement in task performance in aerobically active individuals through a reduction in conflict-related activation of action monitoring processes, resulting in a more efficient neurophysiological profile. Collectively, convergent evidence supports the view that higher levels of physical activity correlate with increased top-down control, which could be mediated through more efficient activation of the ACC, resulting in better performance during tasks requiring executive control. MFG, middle frontal gyrus; SPL, superior parietal lobule. Coordinates for the locations of the clusters are given in Montreal Neurological Institute space. Top panel reproduced, with permission, from REF. 48 © (2004) National Academy of Sciences. Bottom panel reproduced, with permission, from REF. 26 © (2006) Elsevier Science.



of cerebral blood volume (CBV) in the dentate gyrus of the hippocampus were observed in a small group of middle aged participants in a 3-month fitness training study[56]. The increases in CBV were associated with improvements in verbal learning and memory and cardiorespiratory fitness. The regional specificity of the CBV changes are particularly interesting, given previous demonstrations of neurogenesis in the dentate gyrus[57–59] as well as the association between increased CBV and neurogenesis in mice[56]. CBV changes in the hippocampus might serve as a biomarker for neurogenesis in humans.

Non-human animal research

Research on humans has demonstrated improved cognitive performance as a result of physical activity in both children and older adults. However, there are clearly limitations on the extent to which the human brain can be examined with neuroimaging techniques. Non-human animal research can directly examine the cellular and molecular cascades that are triggered by exercise, which in humans can only be indirectly examined and inferred. Additionally, investigating the effect of exercise in non-human animal populations has the benefit of markedly reducing some of the inherent confounding variables that are often present in human studies (for example, lack of adherence to treatment protocols, and covariation with other lifestyle factors, such as social interaction and diet with an exercise intervention) while also providing a translational and cross-species approach to studying exercise-induced neural and cognitive plasticity.

An increase in cell proliferation and cell survival in the dentate gyrus of the hippocampus is one of the most consistently observed effects of exercise treatment[57–61]. Exercise-induced hippocampal cell proliferation and cell survival can occur at many stages of development, including young adulthood[58], and in old age[62]. Even newborn pups with mothers that had carried out aerobic exercise during the gestational period of the pregnancy exhibited a greater number of surviving cells in the hippocampus than pups born from sedentary mothers[63–64]. The functional significance of hippocampal neurogenesis and the survival of the new neurons is a source of great controversy, but the behavioural performance improvements that are associated with exercise treatments suggest that these newborn cells might facilitate learning and memory. Furthermore, dementias such as Alzheimer's disease are characterized by a marked reduction in the number of neurons in the hippocampus, which might be alleviated, in part, by increased neurogenesis resulting from aerobic activity.

The proliferation of new cells in the brain is accompanied by an increased need for nutrients. This demand is met by the stimulation of new blood vessel growth in the cortex[65], the cerebellum[66], the striatum[67] and the hippocampus[68]. The growth of new vasculature might be

dependent on the presence of molecules such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF1). For example, systemic injection of IGF1 effectively stimulates angiogenesis in the brain, and inhibiting IGF1 reduces angiogenesis. IGF1 might induce new blood vessel formation through the regulation of VEGF[68], a growth factor that is prominently involved in blood vessel formation and development. Aerobic exercise increases the production and release of both IGF1 and VEGF in young rodents, leading to the formation of new blood vessels. It is likely that angiogenic processes resulting from aerobic activity occur both in childhood and in old adulthood[67] (however, see REF. 62 for an exception).

Besides IGF1 and VEGF, brain-derived neurotrophic factor (BDNF) is another molecule that is consistently demonstrated to be upregulated with exercise treatments[69]. BDNF has been shown to be necessary for long-term potentiation (LTP), a neural analogue of long-term memory formation, and for the growth and survival of new neurons. Blocking the binding of BDNF to its tyrosine kinase receptor (TRKB) abolishes LTP and neurogenesis. Additionally, BDNF levels in the hippocampus have been directly related to the enhanced learning and memory processes that are observed with exercise treatments in rodents[70]. Even in humans, serum concentrations of BDNF are increased after acute exercise regimens[71] in both young adults and patients with multiple sclerosis[72]. Increases in BDNF levels in response to an exercise treatment could be an important finding, as serum and cortical concentrations of BDNF are reduced in Alzheimer's disease, Parkinson's disease, depression, anorexia and many other diseases. Aerobic activity might be neuroprotective, preventing the development of certain cognitive and neural symptoms that are associated with these diseases, through the regulation of BDNF secretion[73].

In summary, non-human research strongly supports the positive effects of exercise on cognition: aerobic activity improves learning and task acquisition, increases the secretion of key neurochemicals associated with synaptic plasticity and promotes the development of new neuronal architecture. In addition, non-human animal research is not only consistent with human literature on aerobic activity, but also provides some important mechanistic claims for how exercise exerts its effects on the nervous system in humans (see REF. 74 for an in-depth review of the cellular and molecular effects of exercise in non-human animals). Despite having gained some mechanistic insights, a large number of questions regarding the generality of the effects of exercise on learning, the molecular and genetic transcription cascades that result from exercise and the durability of the effects, remain unresolved. Although there are many missing links between the human neuroimaging results and non-human molecular and cellular work, both bodies of research suggest that aerobic exercise is an important lifestyle factor that influences cognitive function throughout the lifespan.

Conclusions and future directions

The human and non-human animal research discussed above suggests that physical activity, and aerobic fitness training in particular, can have a positive effect on multiple aspects of brain function and cognition. Although the number of studies on physical activity is certainly larger for older adults than for other age groups, the data suggest that physical activity can have beneficial effects throughout the lifespan, even for individuals with neurodegenerative diseases[31,75]. Studies with non-human animals have begun to shed light on the molecular and cellular changes that are engendered by exercise and that appear to underlie the effects of fitness on cognition and performance. Fitness training has been observed to selectively enhance angiogenesis, synaptogenesis and neurogenesis (in the dentate gyrus of the hippocampus), as well as to upregulate a number of neurotrophic factors in the mouse brain[9,74].

Despite the wealth of knowledge that has been obtained concerning the effects of exercise and physical activity on brain and cognition, there are a multitude of important questions that remain to be answered. From a practical perspective, at present we know little about how to design exercise interventions that optimize the effects on cognition and brain health. Future research might be able to answer questions such as: when is it best to begin? What are the best varieties, intensities, frequencies and durations of exercise? Is it ever too late to start an exercise programme? Can exercise be used to reduce the deleterious effects of neurodegenerative diseases[32,77]?

Some intriguing research has begun the important task of exploring how exercise interacts with other lifestyle factors in influencing cognition and brain health. For example, Molteni and colleagues[78] investigated the interaction of diet and exercise at the behavioural and molecular levels through their effects on learning and BDNF. Exercise served to reverse the negative effects of high-fat diets on BDNF levels and learning. In another recent study, the effects of exercise on hippocampal neurogenesis were substantially delayed and reduced for a group of socially isolated rodents compared with animals that were housed in a group setting[79]. Such results suggest the need to further study the potential relationship between social interaction (and social isolation) and exercise on brain function and cognition in humans. Finally, several recent studies have described the benefits of exercise training for the treatment of depression[79–80].

Although the prospective epidemiological literature has examined the influence of various lifestyle factors on cognition and neurodegenerative disease, few studies have explored the separate and interactive effects of lifestyle factors. Karp *et al.*[29] recently reported that cognitive, physical and social engagement had served to decrease the risk of dementia in a group of 778 adults over a period of three years, with those adults with high scores in all three factors showing the greatest benefit. The results of these studies are both intriguing and provocative; however, they only scratch the surface in terms of explaining the manner in which different lifestyle factors interact to promote healthy brains and minds. Clearly, additional observational and experimental studies are needed to further explain the effects of these interactions with regards to cognition.

In recent years there has also been increased acknowledgment of the role of genetic polymorphisms on the heterogeneity of treatment effects in drug trials, especially with regards to the speed with which individuals metabolize different agents[81]. The study of the potential moderating effect of genetic variability has also begun to have a role in the study of exercise effects on cognition. More specifically, a number of observational studies have examined whether the presence of the e4 allele on the *APOE* gene (which encodes apolipoprotein E) influences the relationship between fitness and cognition in older adults[82–85]. The answer to this question is, at present, unclear. However, given that single nucleotide polymorphisms exist on a number of genes that influence proteins implicated in fitness-training effects[86–87] (like BDNF and IGF1, for example) future studies will certainly benefit from the examination of the moderating influence of genetic variability on relevant target systems.

In conclusion, there is converging evidence at the molecular, cellular, behavioural and systems levels that physical activity participation is beneficial to cognition. Such evidence highlights the importance of promoting physical activity across the lifespan to reverse recent obesity and disease trends, as well as to prevent or reverse cognitive and neural decline. Accordingly, physical activity can serve to promote health and function in individuals, while also lessening the health and economic burden placed on society.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
APOE | BDNF | IGF1 | TRKB| VEGF
OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Alzheimer's disease | Parkinson's disease

FURTHER INFORMATION

Charles H. Hillman's homepage: http://www.kch.uiuc.edu/labs/neurocognitive%2Dkinesiology/default.htm

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

CAM Techniques for Preventing Cognitive Decline

Joseph H. Flaherty, MD

Complementary and Alternative Therapies to Promote Brain Health

Tai Chi
Yoga
Meditation
Gingko and Ginseng

Joseph H. Flaherty
Saint Louis University
& St. Louis VA GRECC

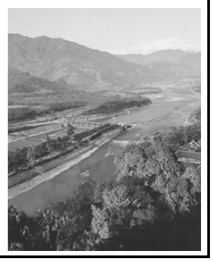
Disclosures/Disclaimers

1. No financial or other support from any of the products or techniques discussed

Longevity Population of Dujiangyan

Longevity Population of Dujiangyan

- Home of Daoism
- Longevity Food



Objectives

At the end of this lecture, the attendees will

1. Have knowledge about one perspective of what "promoting brain health" means
2. Understand what Western-style studies have to offer in the form of evidence for use of four specific types of Complementary and Alternative Therapies to promote brain health
3. The role of stress in aging (if we have time)

Objectives

At the end of this lecture, the attendees will

2. Understand what Western-style studies have to offer in the form of evidence for use of four specific types of Complementary and Alternative Therapies to promote brain health

   a. Should we recommend for our patients?

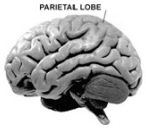
   b. Should we recommend for ourselves?

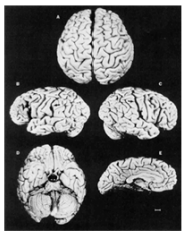
Promoting Brain Health

- What is it?
- When does it start?
- Is it ever too late?
- What is the goal?

Promoting Brain Health

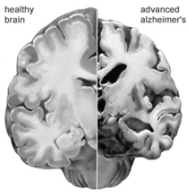
- What is it?
  - Ability to use your brain to its full capacity





Promoting Brain Health

- What is it?
  - Ability to use your brain to its full capacity
  - Keeping that ability throughout life



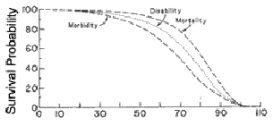
Promoting Brain Health

- What is it?
- When does it start?
- Is it ever too late?
- What is the goal?

Aging

- "the random systemic loss of molecular fidelity, that… accumulates to levels that eventually exceed repair, turnover, or maintenance capacity"
- "the progressive loss of molecular fidelity increases vulnerability to age-associated diseases"

The mortality (observed), morbidity (hypothetical), and disability (hypothetical) survival curves for US females in 1980. (Source: World Health Organization 1984).



Promoting Brain Health

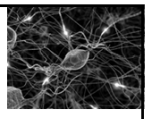
- What is it?
- When does it start?
- Is it ever too late?
- What is the goal?

Aging

- "There's no need to keep those molecules in a perfect state after reproductive maturity, because the animal possessing those molecules has already done what nature intends for it to do, and that is to reproduce."

-Leonard Hayflick

Plasticity of the Brain



- The relative strengthening of certain connections in the brain (synapses), or an increase or decrease in the number of synaptic connections.
- When new information is learned, it causes brain plasticity since connections are added or strengthened.

Plasticity of the Brain

- **Researchers amputated the nerve on an adult monkey's middle finger to see what effect it would have on the corresponding brain maps of the monkey.**
- **After a couple of months, there was no longer a map for the middle finger in the monkey's brain.**
- **The maps of the adjacent fingers had grown into the place where the middle finger's map used to be.**

M.M. Merzenich, R. J. Nelson, M. P. Stryker, M.S. Cynaderm, Schoppmann, and J.M. Zook. 1984. "Somatosensory cortical map changes following digit amputation in adult monkeys." *Journal of Comparative Neurology*, 224 (4): 591-605.

Plasticity of the Brain

- **When a monkey's fingers were sewn together, the maps for the two fingers merged into one map.**
- **Even in adults, your brain physically changes its maps based on what you are using and paying attention to.**

M.M. Merzenich, R. J. Nelson, M. P. Stryker, M.S. Cynaderm, Schoppmann, and J.M. Zook. 1984. "Somatosensory cortical map changes following digit amputation in adult monkeys." *Journal of Comparative Neurology*, 224 (4): 591-605.

Promoting Brain Health

- What is it?
- When does it start?
- Is it ever too late?
- What is the goal?

Promoting Brain Health

- What is the goal?
  - Survival (evolution?)*
  - QOL
  - Prevention of decline/impairment
    - Dementia
    - MCI
    - Depression
    - Delirium

"Aging is something that was never intended for us to see in the first place. It is an artifact of civilization." (Hayflick)

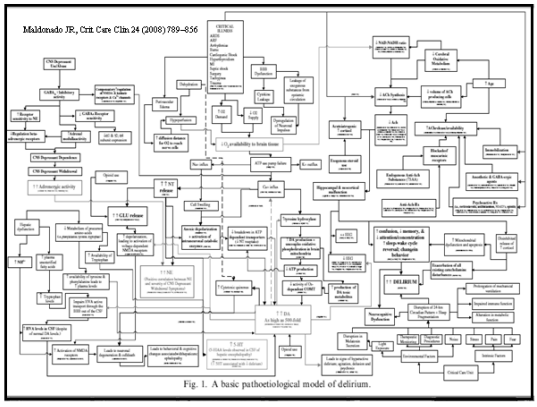
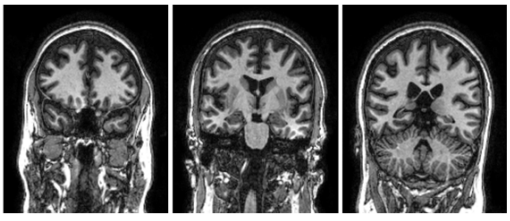
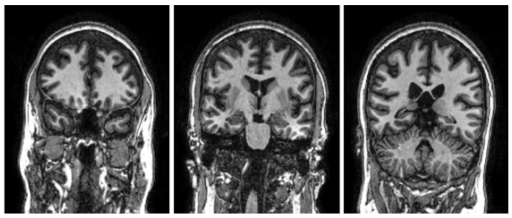


Fig. 1. A basic pathoetiological model of delirium.



Loss of Brain on MRI:
49 y/o Patient 2 years after ICU stay for Sepsis
(had been normal at ICU discharge)



Patient's pre-illness IQ was 140; following her sepsis and delirium, her IQ was 110 at 6 months and 118 at 2 years

Objectives

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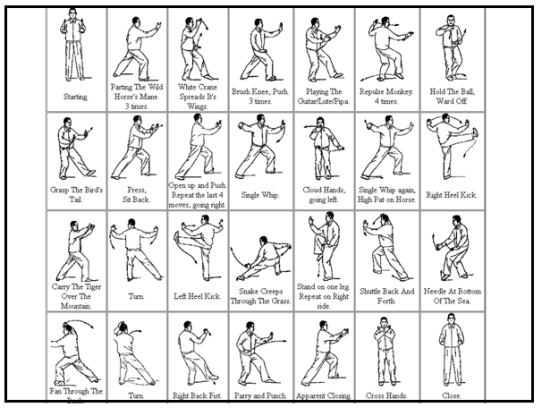
1. Have knowledge about one perspective of what "promoting brain health" means
2. Understand what Western-style studies have to offer in the form of evidence for use of four specific types of Complementary and Alternative Therapies to promote brain health

THE COCHRANE COLLABORATION®

Cochrane Central Register of Controlled Trials

The Cochrane Collaboration is named after Archie Cochrane (1909-1988), a British epidemiologist, who advocated the use of randomised controlled trials as a means of reliably informing healthcare practice.

Tai Chi (Chuan) 太极拳



Tai Chi and traumatic brain injury

- N=18 participants, with TBI
- Control (waiting list) group (n = 9) or Tai Chi group (n = 9)
- 6-week course

Gemmell C, Leathem JM. Brain injury : [BI]. 20(2):151-6, 2006 Feb

Tai Chi and traumatic brain injury

- Significant improvement on all Visual Analogue Mood Scales scores (except fatigue) with decreases in sadness, confusion, anger, tension, fear and increases in energy and happiness.
- No significant between-group differences on the SF-36 or Rosenberg Self-Esteem Scale.

Gemmell C, Leathem JM. Brain injury : [BI]. 20(2):151-6, 2006 Feb

Tai Chi training on physical function among the elderly

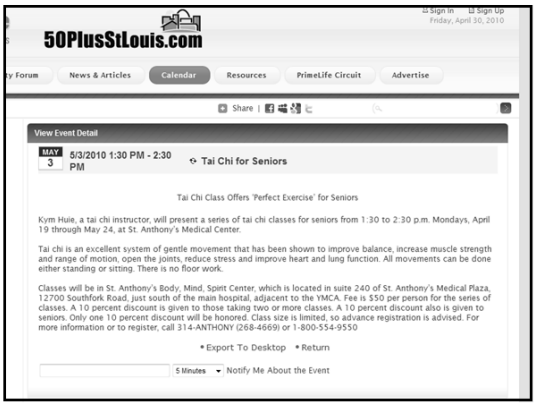
- Physically inactive participants aged > or =65 years were randomly assigned to one of two groups: Tai Chi (n=49) and a wait-list control (n=45).
- 6-month, twice a week
- Significant improvements in *perceived* physical function compared to those in the control group.

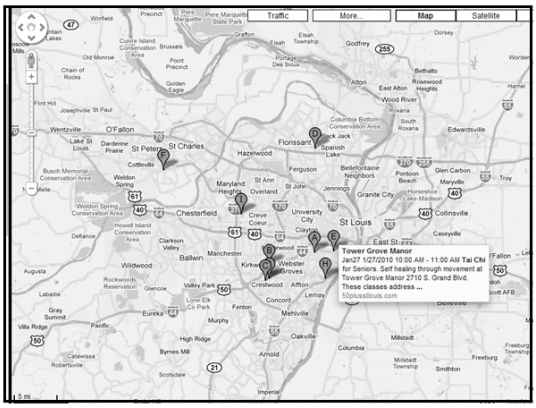
Li F, et al. American journal of preventive medicine. 23(2 Suppl):92-7, 2002 Aug.

Tai Chi training on physical function among the elderly

- Significant interindividual variability in response to Tai Chi.
- Lower levels of physical function at baseline benefited more from the Tai Chi training program than those with higher physical function scores.
- Class attendance also explained some differences in treatment responses.

Li F, et al. American journal of preventive medicine. 23(2 Suppl):92-7, 2002 Aug.





Tai chi and CHF

- N=30, chronic stable heart failure (LVEF $\leq$40%)
- Age, 64$\pm$13 years;
- Baseline EF 23% $\pm$ 7%; median New York Heart Association class, 2 [range, 1 to 4])

Yeh GY, et al. The American journal of medicine. 117(8):541-8, 2004 Oct

Tai chi and CHF

- Pharmacologic therapy and dietary and exercise counseling, or 12 weeks of tai chi training in addition to usual care. (1-hour class, twice weekly)

Yeh GY, et al. The American journal of medicine. 117(8):541-8, 2004 Oct

Tai chi and CHF

- At 12 weeks, tai chi group showed
  - improved quality-of-life scores (mean between-group difference in change, -25 points, P = 0.001),
  - increased distance walked in 6 minutes (135 meters, P = 0.001),
  - decreased serum B-type natriuretic peptide levels (-138 pg/mL, P = 0.03)
  - trend towards improvement was seen in peak oxygen uptake.

Yeh GY, et al. The American journal of medicine. 117(8):541-8, 2004 Oct

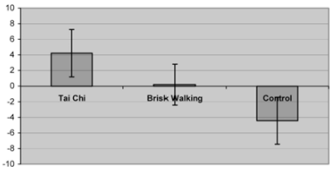
Tai Chi vs brisk walking in elderly women

- N=19 community-dwelling, sedentary women (aged 71.4±4.5 years)
- Randomly assigned (Tai Chi n = 11) or brisk walking group (BWG; n = 8) or sedentary comparison group (SCG; n = 8).

Audette JF, et al. Age and ageing. 35(4):388-93, 2006 Jul

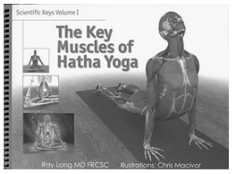
Tai Chi vs brisk walking in elderly women

- Tai Chi 1 h, three days per week for 12 weeks.



Audette JF, et al. Age and ageing. 35(4):388-93, 2006 Jul

Hatha-Yoga



Yoga breathing and spatial memory scores

- School children (N = 108; ages 10 to 17 years); four groups.
- Yoga breathing technique: (i) right nostril breathing, (ii) left nostril breathing, (iii) alternate nostril breathing, or (iv) breath awareness without manipulation of nostrils. Practiced for 10 days.
- Verbal and spatial memory was assessed initially and after 10 days.
- Age-matched control group (n=27).

Naveen KV, et al. Psychological reports. 81(2):555-61, 1997 Oct

Yoga breathing and spatial memory scores

- All 4 trained groups showed a significant increase in spatial test scores at retest, but not verbal. Control group showed no change.

Naveen KV, et al. Psychological reports. 81(2):555-61, 1997 Oct

Physiological and psychological effects of Hatha-Yoga

- Yoga practicing group and a control group of young female volunteers reading in a comfortable position during the experimental period.
- No substantial differences between the groups in endocrine parameters (cortisol, prolactin and growth hormone) or BP.

Schell FJ International journal of psychosomatics. 41(1-4):46-52, 1994

Physiological and psychological effects of Hatha-Yoga

- HR significantly decrease during the yoga
- Significant differences in psychological parameters.
  - Yoga: personality inventory showed markedly higher scores in life satisfaction and lower scores in excitability, aggressiveness, openness, emotionality and somatic complaints.
  - Yoga: Significant differences in coping with stress and the mood at the end of the experiment.
  - Yoga: significant higher scores in high spirits and extravertedness.

Schell FJ International journal of psychosomatics. 41(1-4):46-52, 1994

Yoga or Brief Supportive Therapy in Breast Cancer Outpatients

- N=88, stage II and III breast cancer outpatients
- Randomly assigned: yoga (n = 44) or brief supportive therapy (n = 44) prior to radiotherapy treatment.
- Diurnal salivary cortisol levels 3 days before and after radiotherapy
- Self-ratings of anxiety, depression, and stress collected before and after 6 weeks of radiotherapy.

Vadiraja HS, et al. Integrative cancer therapies. 8(1):37-46, 2009 Mar

Yoga or Brief Supportive Therapy in Breast Cancer Outpatients

- Significant decreases in anxiety ($P < .001$), depression ($P = .002$), perceived stress ($P < .001$), 6 a.m. salivary cortisol ($P = .009$), and pooled mean cortisol ($P = .03$) in the yoga group compared with controls. (ANCOVA)

Vadiraja HS, et al. Integrative cancer therapies. 8(1):37-46, 2009 Mar

Visuospatial processing and Buddhist Deity meditation

- Two groups: Deity Yoga (focused attention on an internal visual image) or Open Presence (evenly distributed attention, not directed to any particular object).
- Both groups of meditators completed computerized mental-imagery tasks before and after meditation.
- Control groups, (either rested or performed other visuospatial tasks between testing sessions).

Kozhevnikov M, et al. Psychological science. 20(5):645-53, 2009 May

Visuospatial processing and Buddhist Deity meditation

- All the groups performed at the same baseline level, but after meditation, Deity Yoga practitioners demonstrated a dramatic increase in performance on imagery tasks compared with the other groups.
- The results suggest that Deity meditation specifically trains one's capacity to access heightened visuospatial processing resources, rather than generally improving visuospatial imagery abilities.

Kozhevnikov M, et al. Psychological science. 20(5):645-53, 2009 May


中药房

Gingko Biloba

- A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract EGb 761 [120-mg dose (40 mg t.i.d.)] in dementia.
- Mildly to severely impaired and diagnosed with uncomplicated Alzheimer's disease or multi-infarct dementia according to ICD-10 and DSM-III-R criteria

Le Bars PL et al. Dementia and geriatric cognitive disorders. 11(4):230-7, 2000 Jul-Aug
Memory Centers of America Inc., New York, NY, USA

Gingko Biloba

- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Geriatric Evaluation by Relative's Rating Instrument (GERRI).
- 244/309 patients (76% for placebo and 73% for EGb) reached the 26th week visit.

Le Bars PL et al. Dementia and geriatric cognitive disorders. 11(4):230-7, 2000 Jul-Aug
Memory Centers of America Inc., New York, NY, USA

Gingko Biloba

- In comparison to the baseline values, the placebo group showed a statistically significant worsening in all domains of assessment
- Mean treatment differences favored EGb with 1.3 and 0.12 points, respectively, on the ADAS-Cog ($p = 0.04$) and the GERRI ($p = 0.007$).

Le Bars PL et al. Dementia and geriatric cognitive disorders. 11(4):230-7, 2000 Jul-Aug
Memory Centers of America Inc., New York, NY, USA

Gingko Biloba

- In the group receiving EGb, 26% of the patients achieved at least a 4-point improvement on the ADAS-Cog, compared to 17% with placebo ($p = 0.04$).
- On the GERRI, 30% of the EGb group improved and 17% worsened, while the placebo group showed an opposite trend with 37% of patients worsening for 25% improved ($p = 0.006$).

Le Bars PL et al. Dementia and geriatric cognitive disorders. 11(4):230-7, 2000 Jul-Aug
Memory Centers of America Inc., New York, NY, USA

Gingko Biloba

- 12-week, double-blind, placebo-controlled
- Healthy young (n=104) (18-43 years)
- Older adults (n=93) (55-79 years).
- Wide range of cognitive abilities, executive function, attention and mood

Burns NR, et al. Human psychopharmacology. 21(1):27-37, 2006 Jan. Department of Psychology, University of Adelaide, South Australia,

Gingko Biloba

- For the older adult sample, longer-term memory assessed by associational learning tasks showed improvement with ginkgo ($d = 0.52$, $p = 0.04$).
- No statistically significant difference on any other measure.
- For the young adult group no measure showed statistically significant effects of ginkgo enhancement.

Burns NR, et al. Human psychopharmacology. 21(1):27-37, 2006 Jan. Department of Psychology, University of Adelaide, South Australia,

Objectives

At the end of this lecture, the attendees will

1. Have knowledge about one perspective of what "promoting brain health" means

   The brain is plastic, i.e., can change

   It's never too late

   Choose your own goal (evolution or QOL or prevention)

Objectives

At the end of this lecture, the attendees will

2. Understand what Western-style studies have to offer in the form of evidence for use of four specific types of Complementary and Alternative Therapies to promote brain health

   Tai Chi Yoga Meditation Gingko

Objectives

At the end of this lecture, the attendees will

2. Understand what Western-style studies have to offer in the form of evidence for use of four specific types of Complementary and Alternative Therapies to promote brain health

   a. Should we recommend for our patients?

   b. Should we recommend for ourselves?

Objectives

a. Should we recommend for our patients?

Yes

-individualize

-even the weakest can benefit

-consider cost (not just financial)

-don't get carried away (ie. don't miss the western diagnosis)

Objectives

b. Should we recommend for ourselves?

-when it's time

-when it's time for a "change of brain"

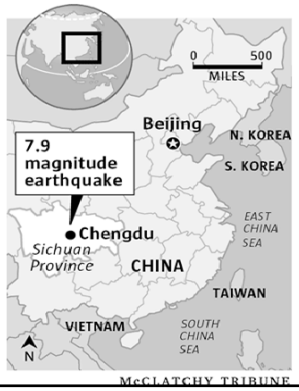
The Role of Stress in Aging

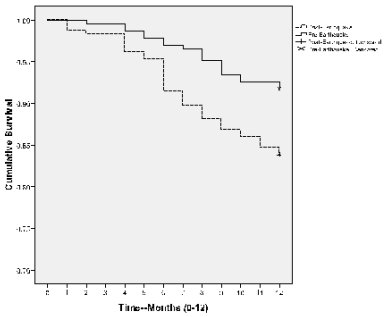
- Death of a spouse
- Caregiver burden (e.g. Alzheimer's Disease)
- Loss of independence

Longevity Population of Dujiangyan

- July 2005 "The PLAD Study"
  - Project of Longevity and Aging in Dujiangyan
- Geriatrics Dept of Sichuan University+
  Government of Dujiangyan +
  Dujiangyan Hospital +
  Directors of each township (n=20 townships)
- N=870, ages 90-108
- 62.1% (870/1401) of the population 90+

Mean age = 94±4 years, 68% women





Predictors of Mortality

- Being in the post-earthquake group continued to be the strongest risk factor associated with mortality (HR 2.46,95% CI, 1.38-4.39,P<.002).
- Other:
  - Impaired cognition (HR 1.96,95% CI, 1.09-3.54,P<.024)
  - Decreased albumin (HR 0.90,95% CI, 0.82-0.98,P<.015)

The

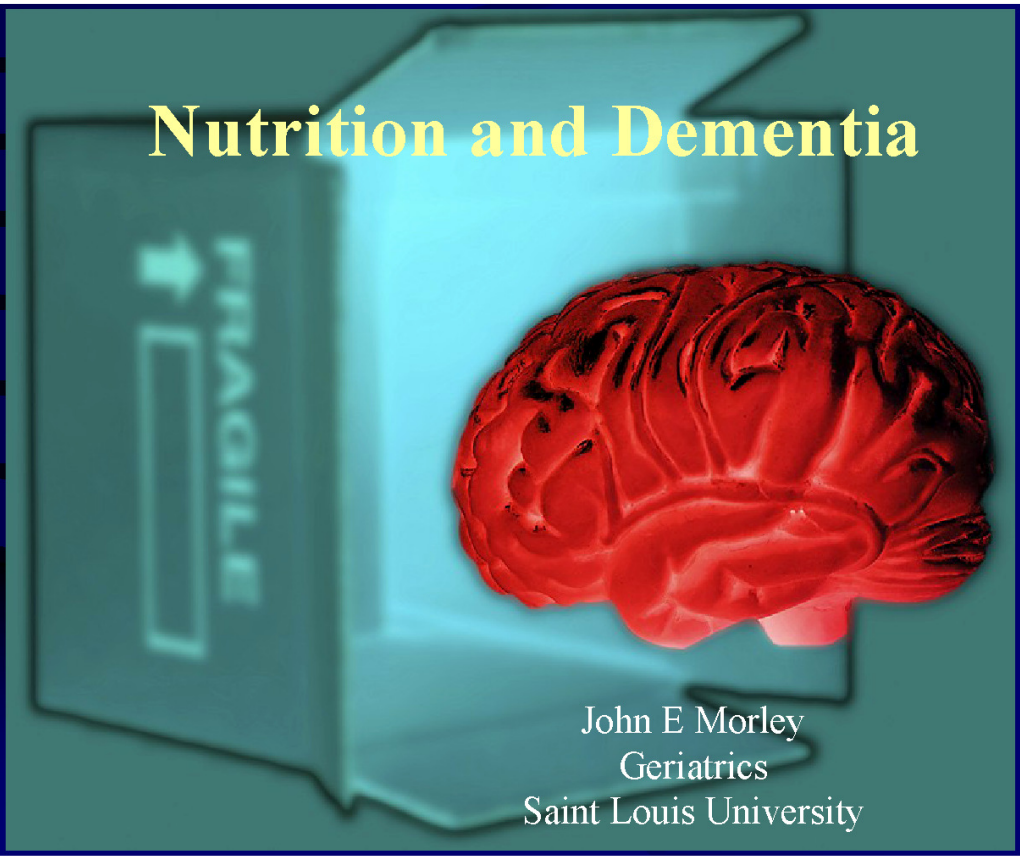
End

Thank you

Diet and Cognition: The Inflammatory Link

John E. Morley, MB, B. Ch.

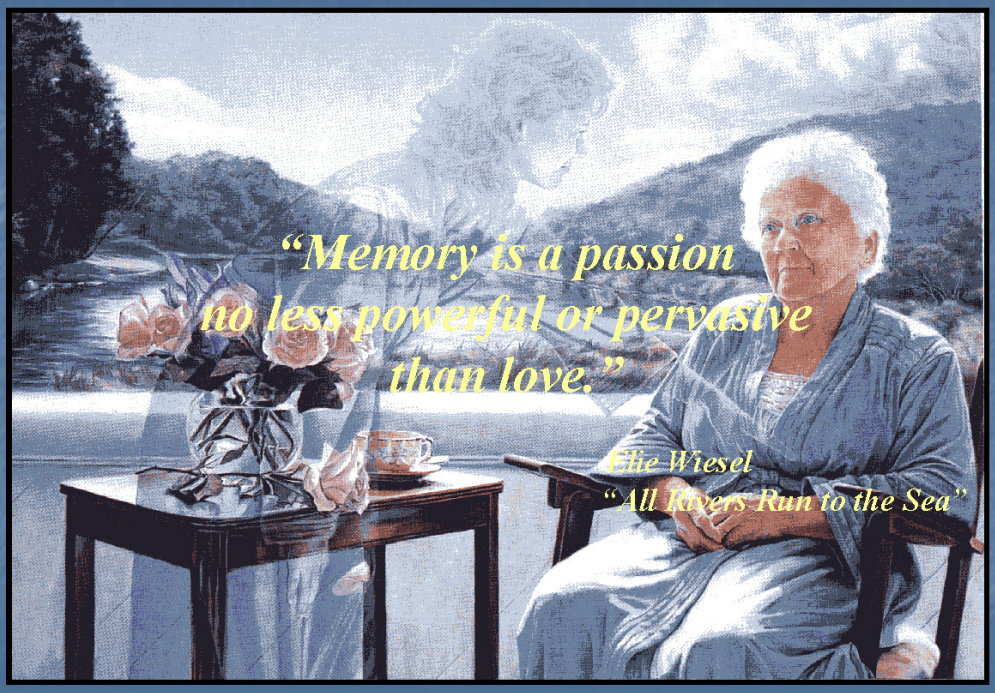
Nutrition and Dementia



John E Morley
Geriatrics
Saint Louis University

Potential Conflicts

- Edunn Biopharm
- Nutrica
- Healthspan

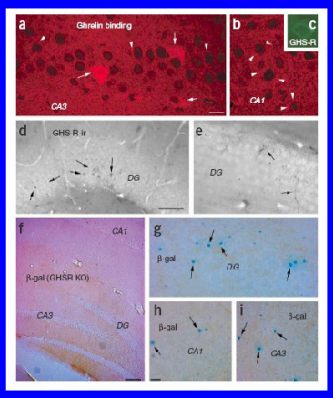


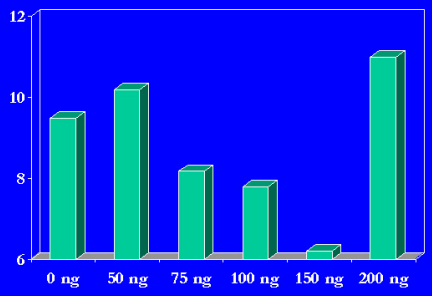
The Gut-Brain Axis

- Acquisition and retention of memories are enhanced by feeding immediately after learning
- Cholecystokinin enhances acquisition and memory by activating the ascending fibers of the vagus.The pathway is Duodenum-vagus-NTS-amygdala-hippocampus
- Blocking the effect of cholecystokinin blocks the effect of feeding on memory

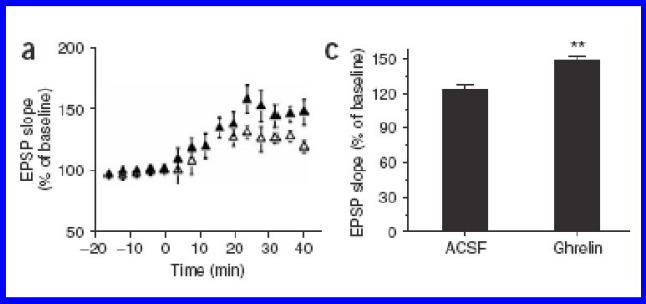
Science 15:832,1987
Neurobiol Learn Mem 64:13
Brain Res 10:585,1992

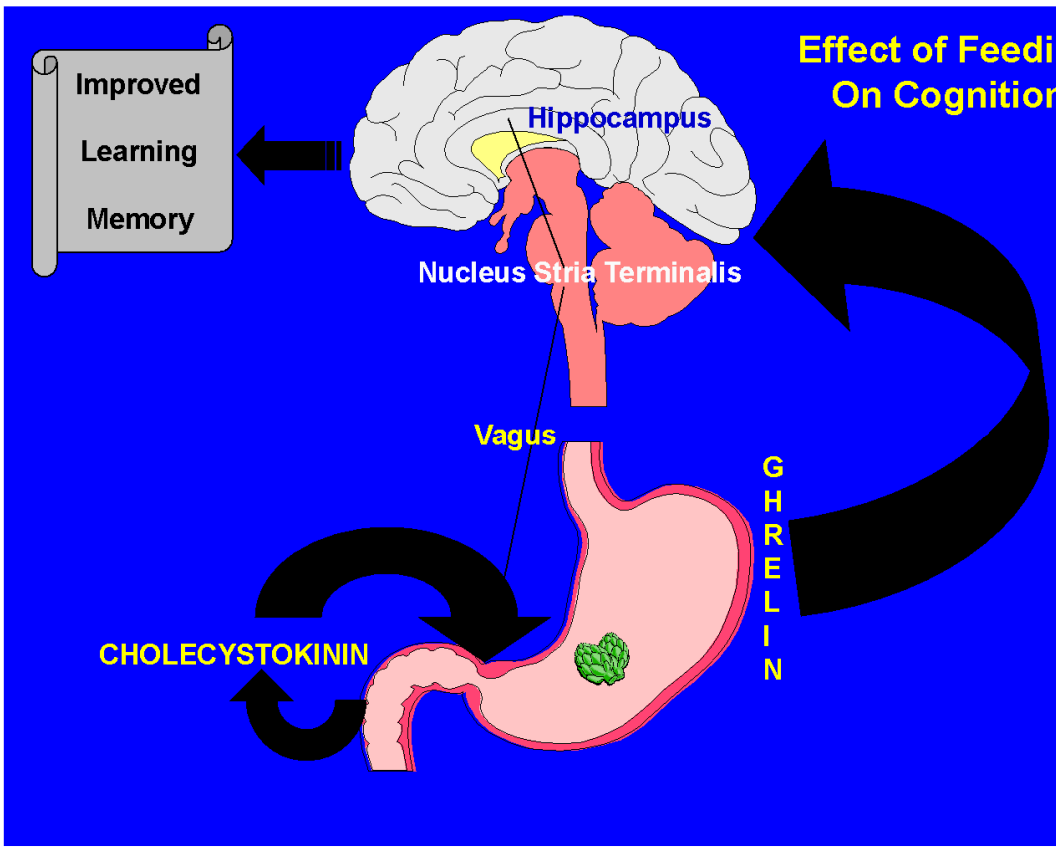
Ghrelin Enhances Memory



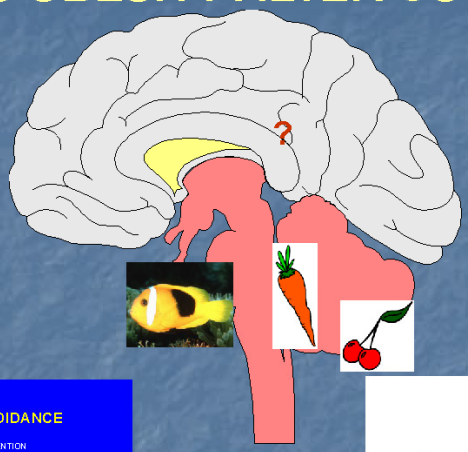


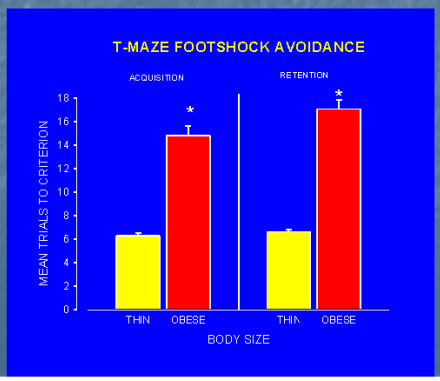
Nature Neuroscience 2006

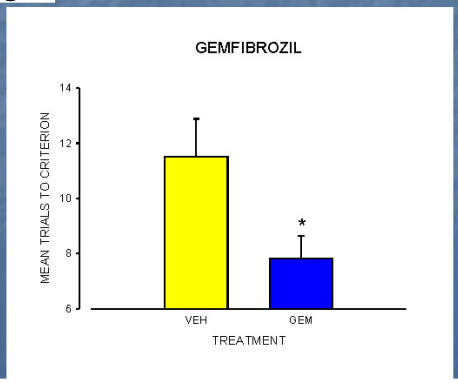




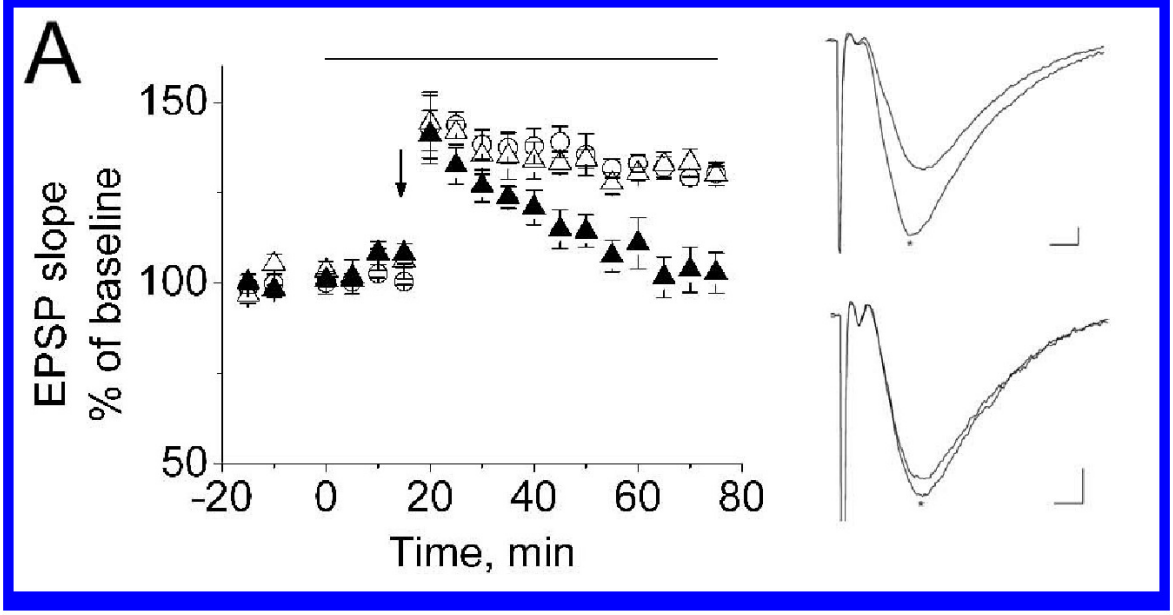
DOES OBESITY ALTER COGNITION?

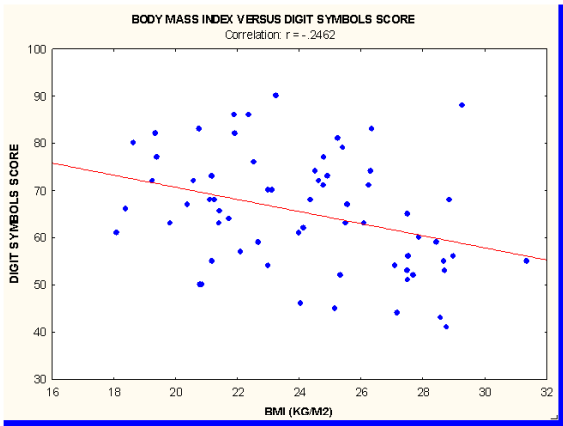






Triglycerides impair long term potentiation

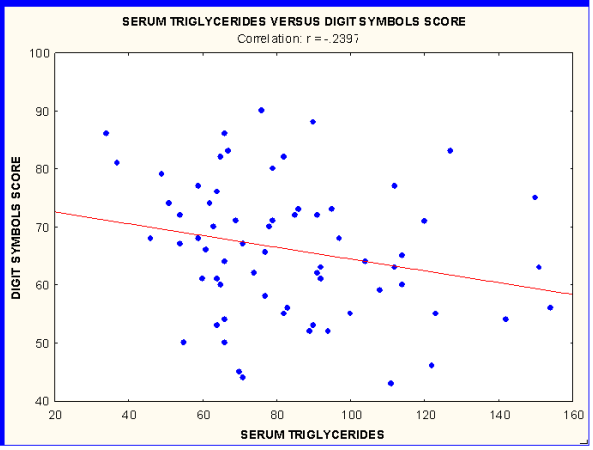




Obesity is associated with poor digit symbol score

Postmenopausal women (n=68, aged 48 – 60 years)

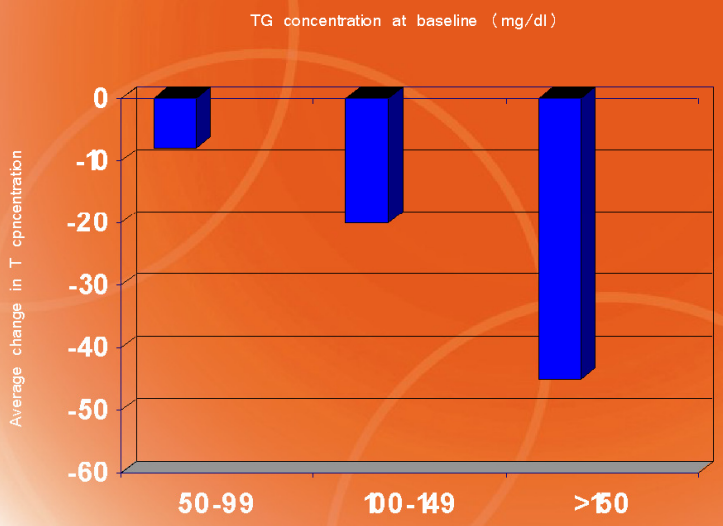
Hypertriglyceridemia is associated with poor digit symbols score



TRIGLYCERIDES AND COGNITION

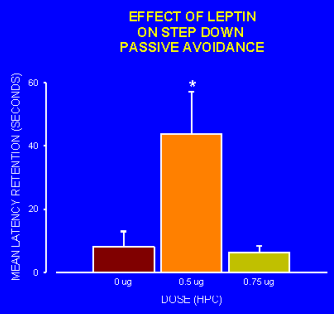
- In Type II diabetes elevated triglycerides are associated with poor performance on the digit symbol substitution test,digit span backward test and reaction time…J Diabet Complic 2:210,1988
- Elevated triglycerides are associated with poor retrieval from semantic memory in Type II DM…Diabetes Care 18:681,1995
- Reducing hypertriglyceridemia with gemfibrozil improved cerebral blood flow and function on the cognitive capacity screening examination…….Angiology 40:260,1989

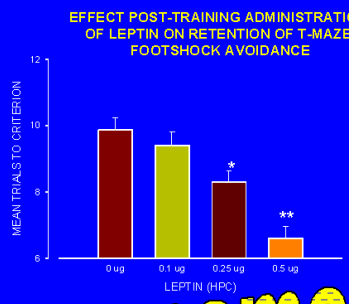
Effects of EAAs on Plasma Trilycerides in Elderly



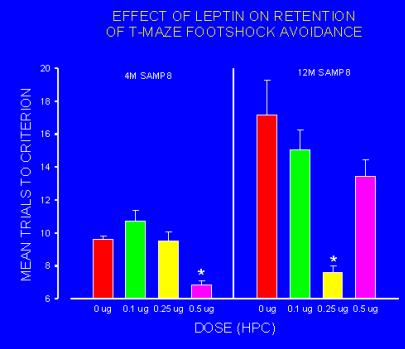
Borsheim, et al., Nutrition 25: 281-288, 2009

BeneVia

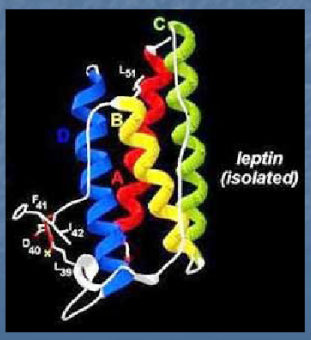




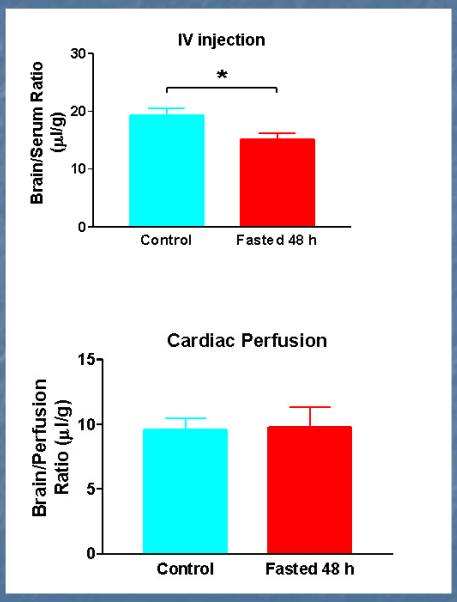
Leptin improves memory

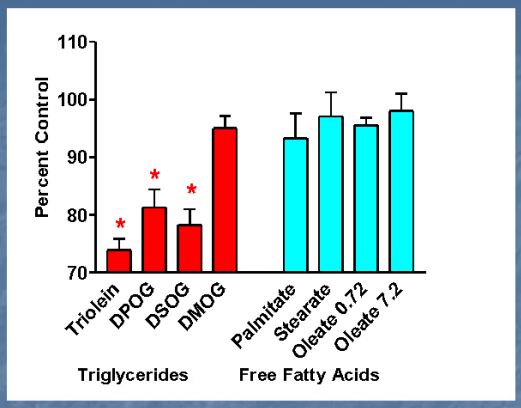


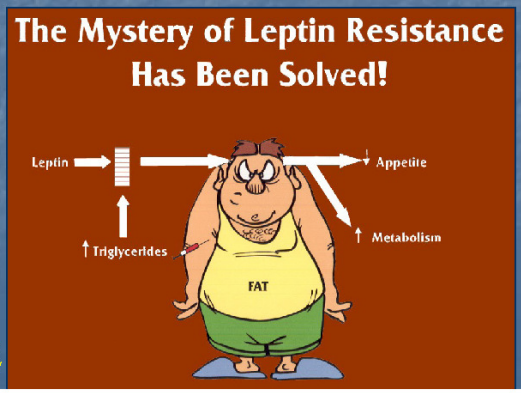
OBESITY IS ASSOCIATED WITH LEPTIN RESISTANCE



LEPTIN AND THE BLOOD BRAIN BARRIER

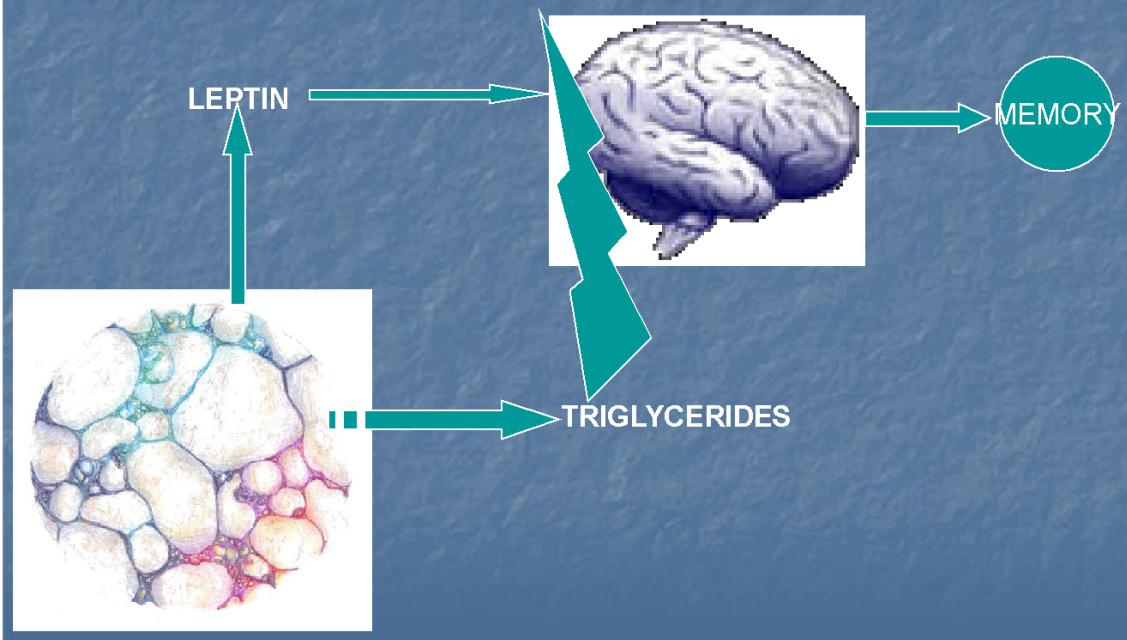






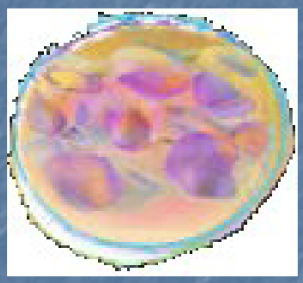
SERUM FACTOR PRODUCES LEPTIN RESISTANCE

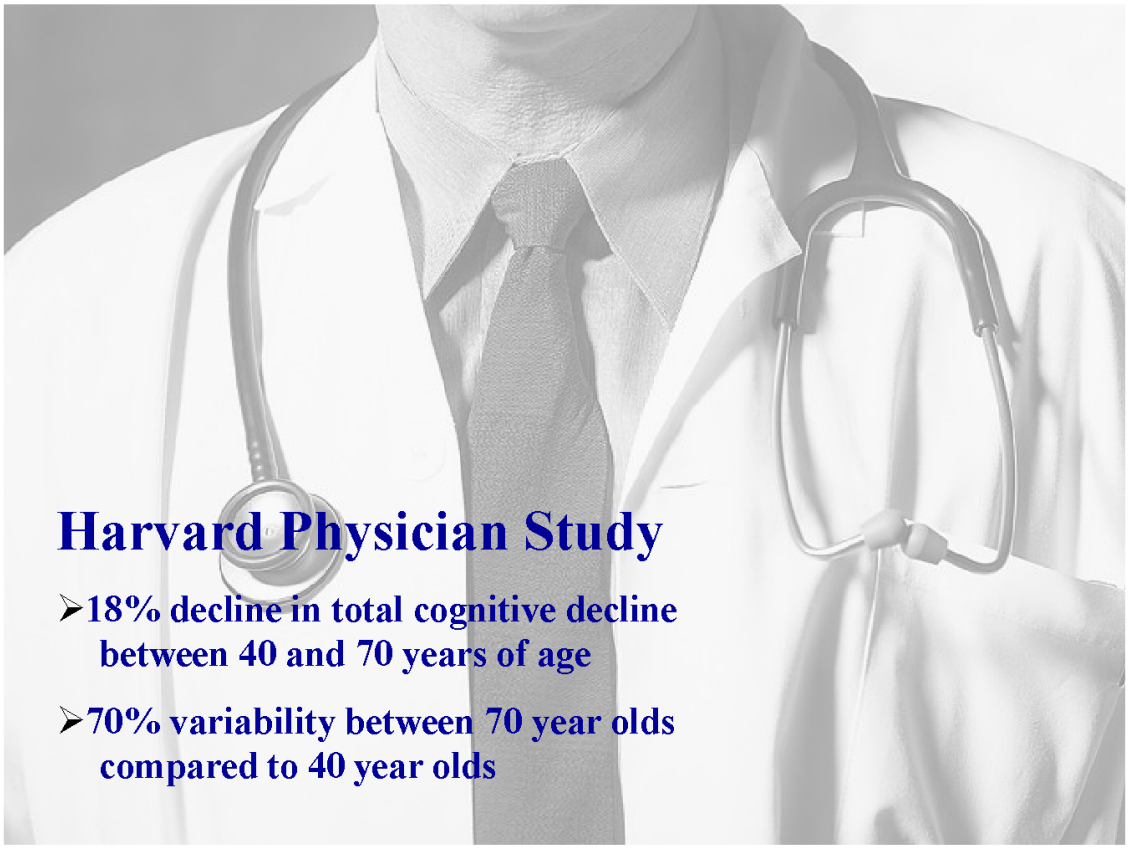
The Fat-Brain Axis



FAT PRODUCES CYTOKINES

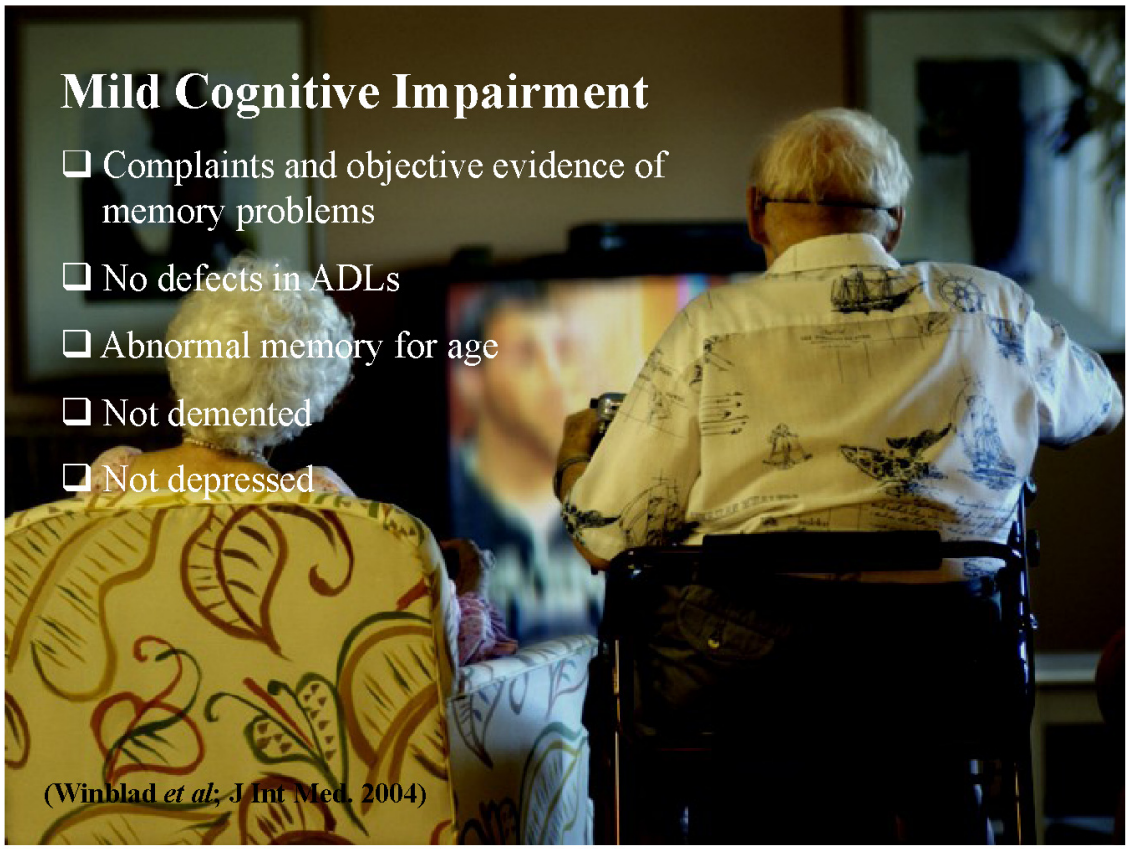
Do cytokines alter memory?





Harvard Physician Study

- 18% decline in total cognitive decline between 40 and 70 years of age
- 70% variability between 70 year olds compared to 40 year olds



Mild Cognitive Impairment

- ❑ Complaints and objective evidence of memory problems
- ❑ No defects in ADLs
- ❑ Abnormal memory for age
- ❑ Not demented
- ❑ Not depressed

(Winblad *et al*; J Int Med. 2004)

Mild Cognitive Impairment

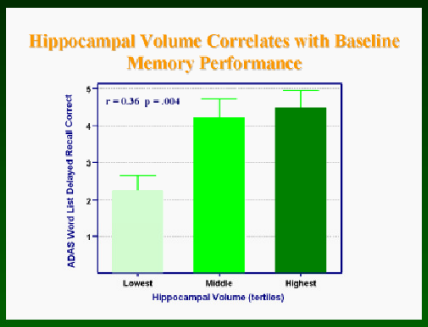
OUTCOMES

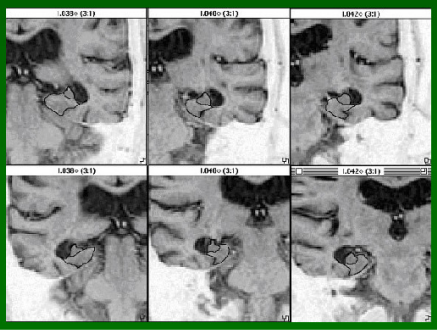
- Poor functional recovery from major event
- 30% dead within 5 years
- 30% develop Alzheimer's disease within 5 years

Mild Cognitive Impairment is NOT BENIGN

Mild Cognitive Impairment
WHO PROGRESSES?

- Small hippocampal volumes
- Decreased blood flow to posterior cingulate gyrus
- Increased CSF tau protein and decreased beta-amyloid (1-42)

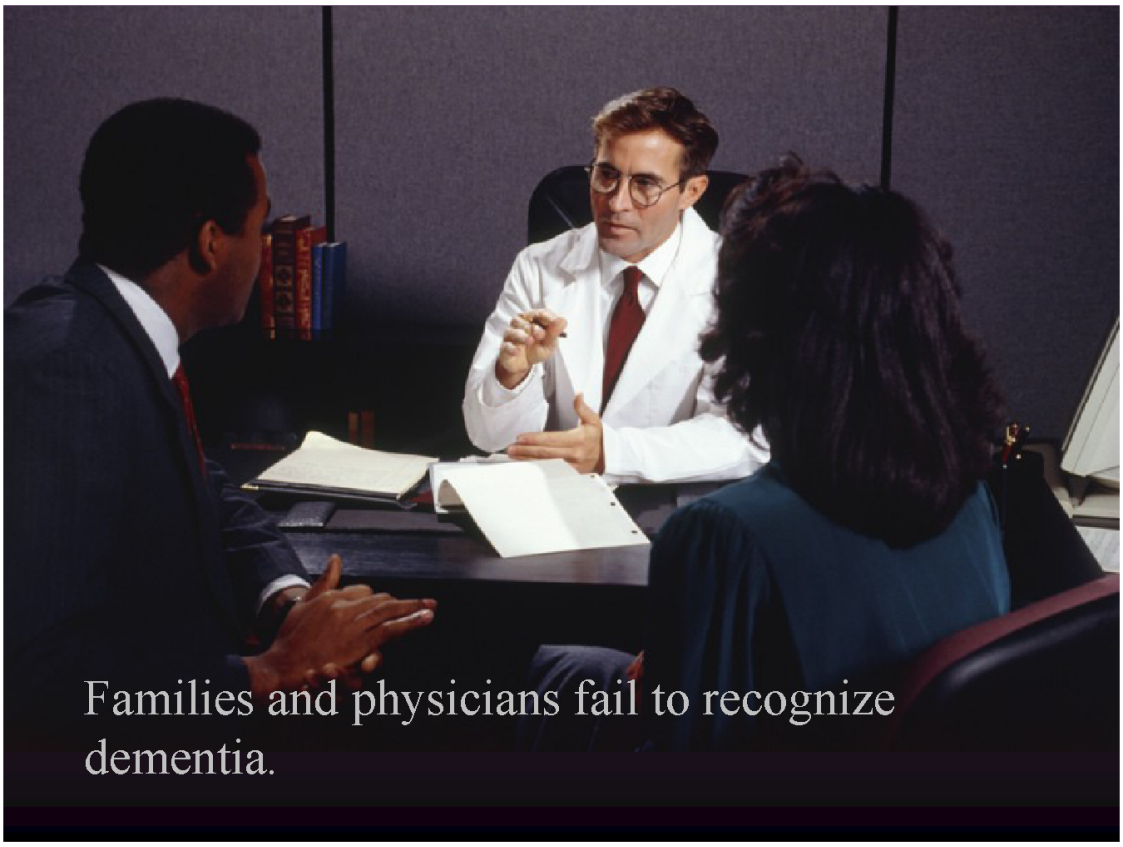




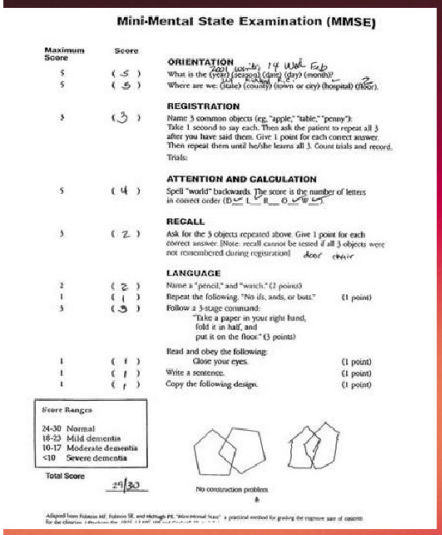
Dementia Prevalence

8% over 65 years
+ 8% MCI

47% at 85 years



Families and physicians fail to recognize dementia.



Mini-Mental State Examination (MMSE)

Maximum Score	Score	
		ORIENTATION
5	(5)	What is the (year) (season) (date) (day) (month)?
5	(5)	Where are we: (state) (county) (town or city) (hospital) (floor).
		REGISTRATION
3	(3)	Name 3 common objects (eg, "apple," "table," "penny"). Take 1 second to say each. Then ask the patient to repeat all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials:
		ATTENTION AND CALCULATION
5	(4)	Spell "world" backwards. The score is the number of letters in correct order (D-L-R-O-W).
		RECALL
3	(2)	Ask for the 3 objects repeated above. Give 1 point for each correct answer. [Note: recall cannot be tested if all 3 objects were not remembered during registration] door chair
		LANGUAGE
2	(2)	Name a "pencil," and "watch." (2 points)
1	(1)	Repeat the following, "No ifs, ands, or buts." (1 point)
3	(3)	Follow a 3-stage command: "Take a paper in your right hand, fold it in half, and put it on the floor." (3 points)
1	(1)	Read and obey the following: Close your eyes. (1 point)
1	(1)	Write a sentence. (1 point)
1	(1)	Copy the following design. (1 point)

Score Ranges

24-30 Normal
18-23 Mild dementia
10-17 Moderate dementia
<10 Severe dementia

Total Score 29/30

No construction problem

Adapted from Folstein MF, Folstein SE, and McHugh PR. "Mini-mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198.

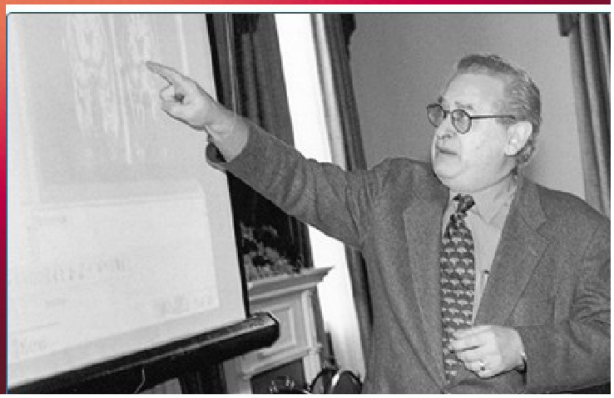
Mini-Mental Status Examination

Folstein *et al.* 1975

Educationally dependent

Both false positives and false negatives

Minimal testing of visuospatial system



SLUMS

Saint Louis University

Mental Status (SLUMS) Examination

Name _____ Age _____
Is patient alert? _____ Level of education _____

1. What day of the week is it?
2. What is the year?
3. What state are we in?
4. Please remember these five objects. I will ask you what they are later.
   Apple Pen Tie House Car
5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.
   How much did you spend?
   How much do you have left?
6. Please name as many animals as you can in one minute.
   0 0-4 animals 1 5-9 animals 2 10-14 animals 3 15+ animals
7. What were the 5 objects I asked you to remember? 1 point for each one correct.
8. I am going to give you a series of numbers and I would like you to give them to me backwards. For example, if I say 42, you would say 24.
   0 87 1 649 1 8537
9. This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o'clock.
   2 Hour markers okay
   2 Time correct
10. Please place an X in the triangle.
    Which of the above figures is largest?
11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.

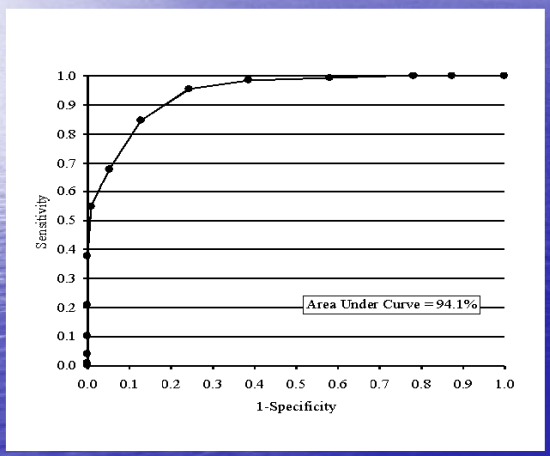
    Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.

    2 What was the female's name?
    2 When did she go back to work?
    2 What work did she do?
    2 What state did she live in?

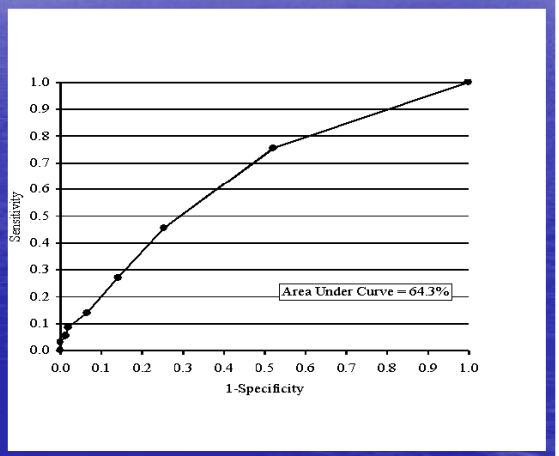
Scoring

High School Education		Less than High School Education
27-30	Normal	20-30
20-26	MCI	15-19
1-19	Dementia	1-14

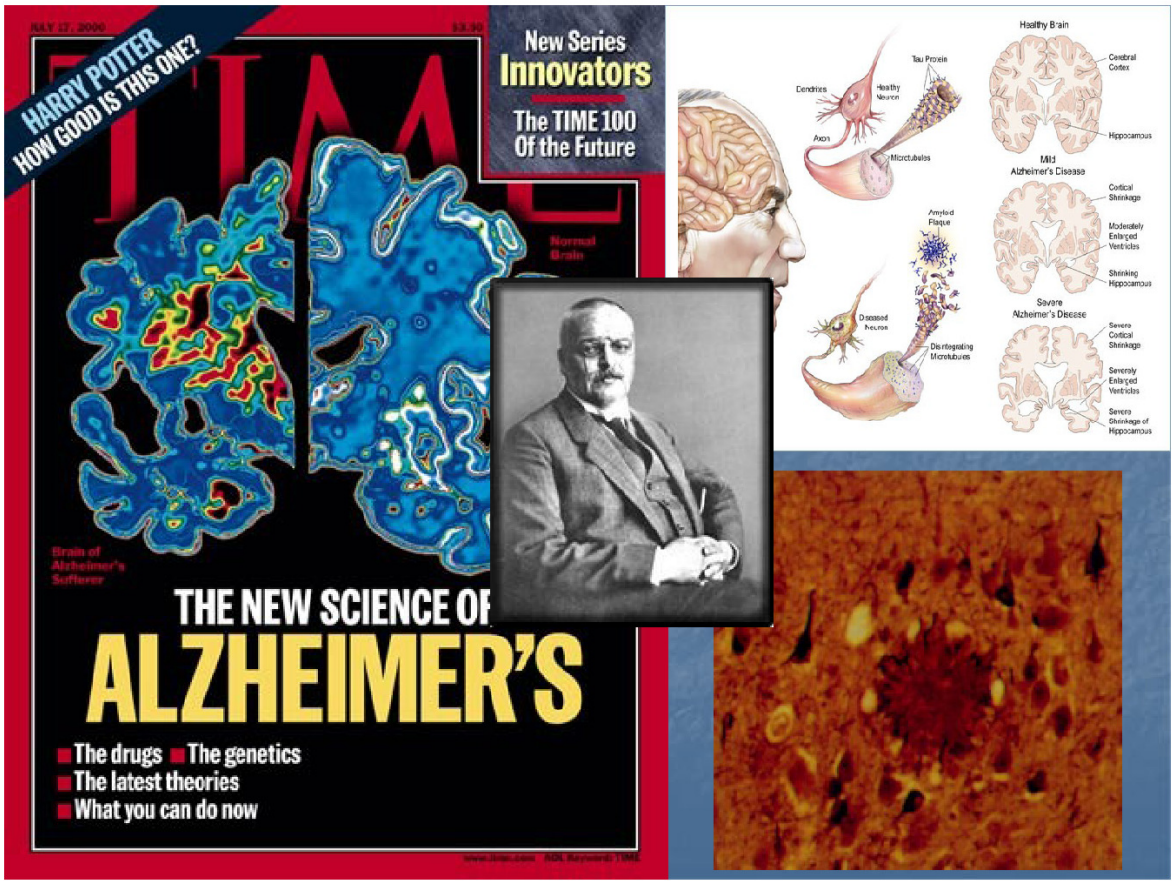
ROCs For SLUMS &MMSE for MCI ≥ HS Education



SLUMS



MMSE



How clouds are transformed into fried eggs

Maurer K, Froehlich L. How clouds are transformed into fried eggs. Alzheimer Insights, 2000, 6: 4-7

Carolus Horn

Approach to Diagnosis of Dementia

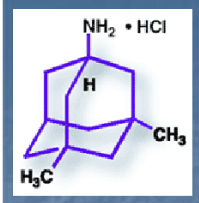
- SAD = Depression
- Exclude other reversible dementias
- No loss of function = MCI
- Abrupt onset,stepwise progression,other vascular disease = Vascular Dementia
- Behavioral Disturbance early,Parkinsonism =Frontotemporal or Lewy Body
- All others = Alzheimer disease

Meta-analysis : Cholinesterase Inhibitors

- 9% more global responders to ChEI than placebo; 8% higher adverse events….less with donapezil

Lanctot et al CMAJ 169:557,2003

" Flawed methods and small clinical benefits…make recommendations for treatment questionable "



Memantine : Meta-analysis Cochrane Database

- Improved behavior (2.76/144)
- Improved ADLs (1.27/54)
- Decreased Agitation (8% vs 12%)

? DUE TO DECREASED NMDA ACTIVITY DECREASING PAIN

Effectiveness of Cholinesterase Inhibitors and Memantine for Treating Dementia : Evidence Review for a Clinical Guideline

- Treatment of dementia with cholinesterase inhibitors and memantine can result in statistically significant (cognition and global assessment) but CLINICALLY MARGINAL IMPROVEMENT

Raina et al, Annals Int Med 148:379, 2008

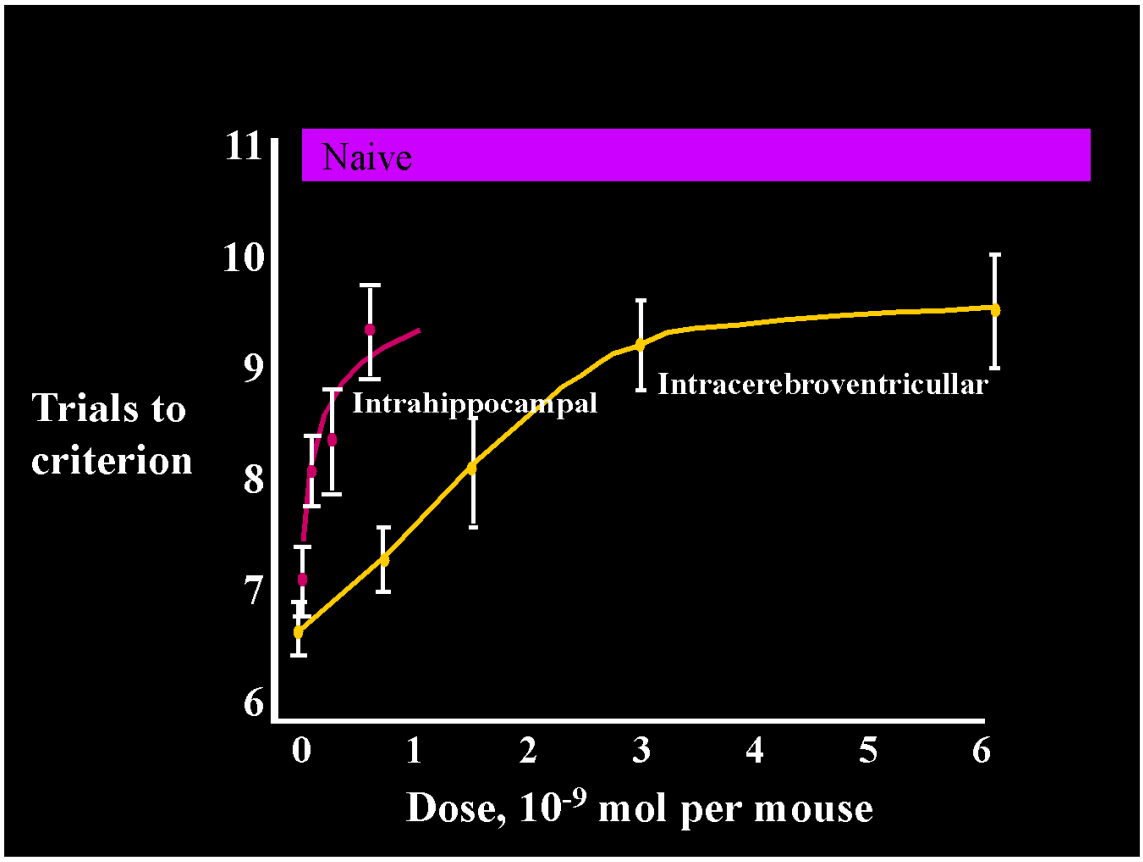
NONAChE INHIBITORS

- GINGKO EXTRACTS

- NOOTROPICS

Amyloid Beta Protein:

Learning and Memory



What is the physiological role of amyloid beta protein?

Low doses of Amyloid Beta Protein Enhance Memory

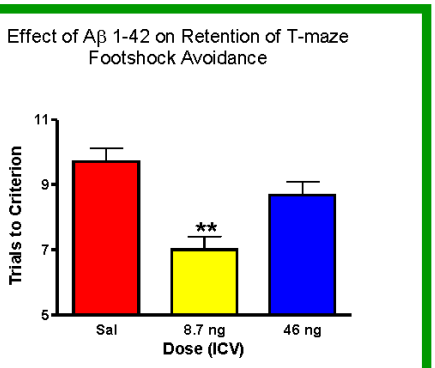


Figure 5. Low doses of Aβ 1-42 administered ICV immediately after training improves retention in T-maze footshock avoidance. The ** indicates P<0.01.

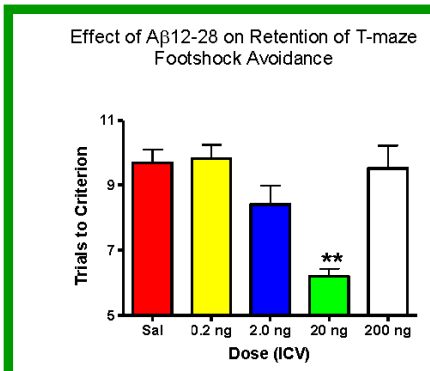


Figure 4. Low doses of Aβ 12-28 administered ICV immediately after training improves retention in T-maze footshock avoidance. The ** indicates P<0.01.

Inhibition of Amyloid Beta Protein inhibits learning in young animals

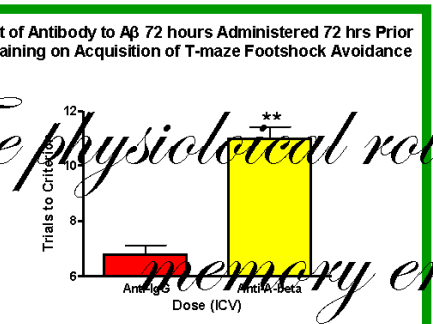


Figure 1: Antibody to Aβ administered 72 hours prior to training in CD-1 mice impaired acquisition of T-maze footshock avoidance. The ** indicates P<0.01.

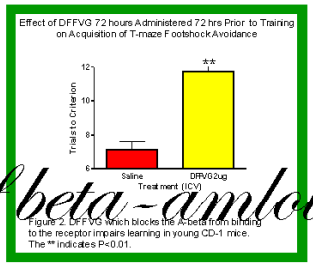


Figure 2. DFFVG which blocks the A-beta from binding to the receptor impairs learning in young CD-1 mice. The ** indicates P<0.01.

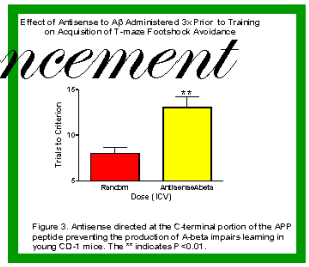
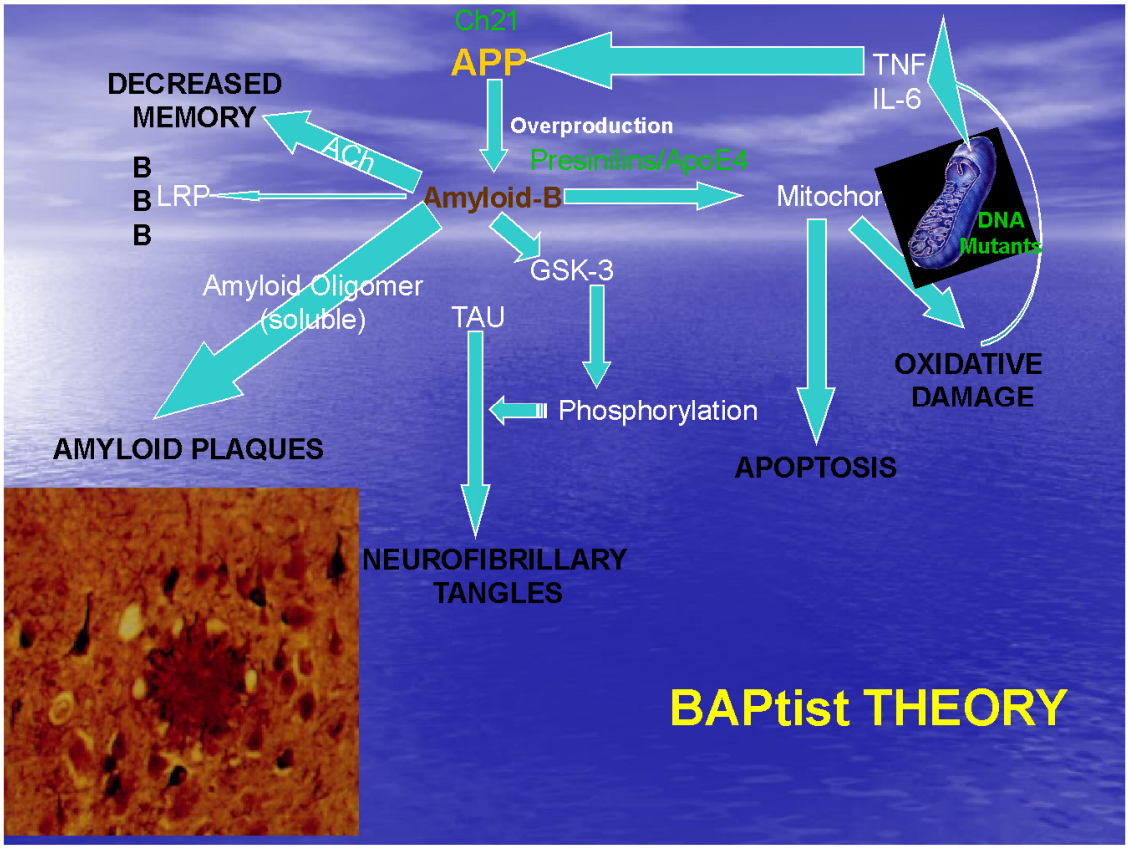
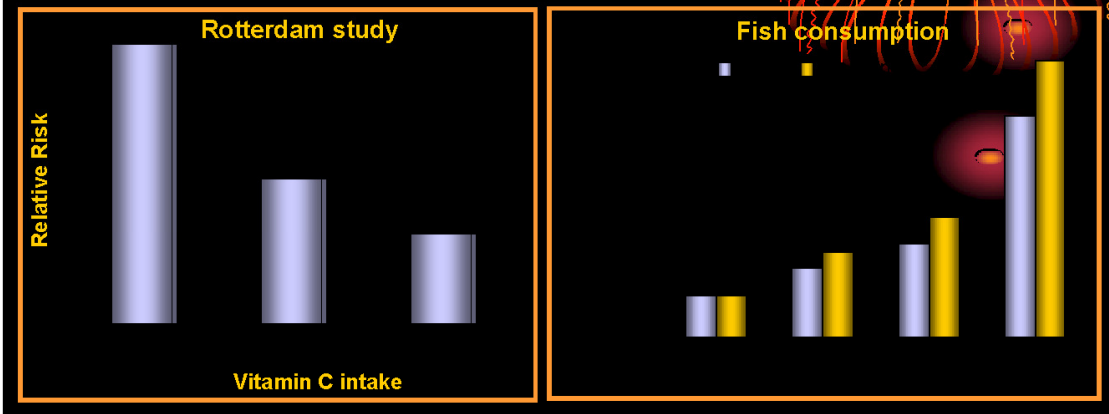


Figure 3. Antisense directed at the C-terminal portion of the APP peptide preventing the production of A-beta impairs learning in young CD-1 mice. The ** indicates P <0.01.

The physiological role of beta-amloid is memory enhancement



Nutrients are implicated as a risk factor for AD

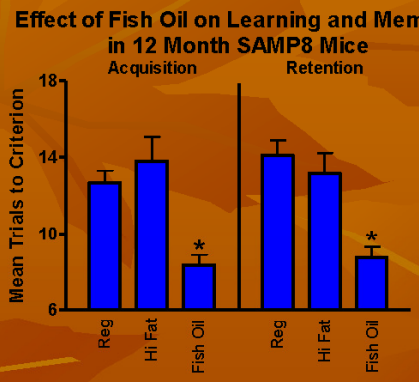


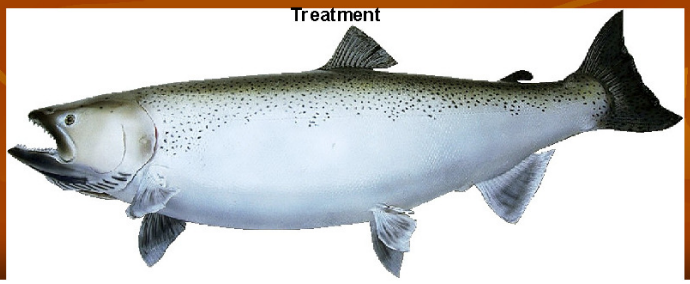
Adapted from Engelhart et al., JAMA 2002

Adapted from Barberger-Gateau et al., BMJ, 2002

- **Several prospective studies showed that low intake of PUFAs and specific vitamins is a risk factor for cognitive decline and dementia**

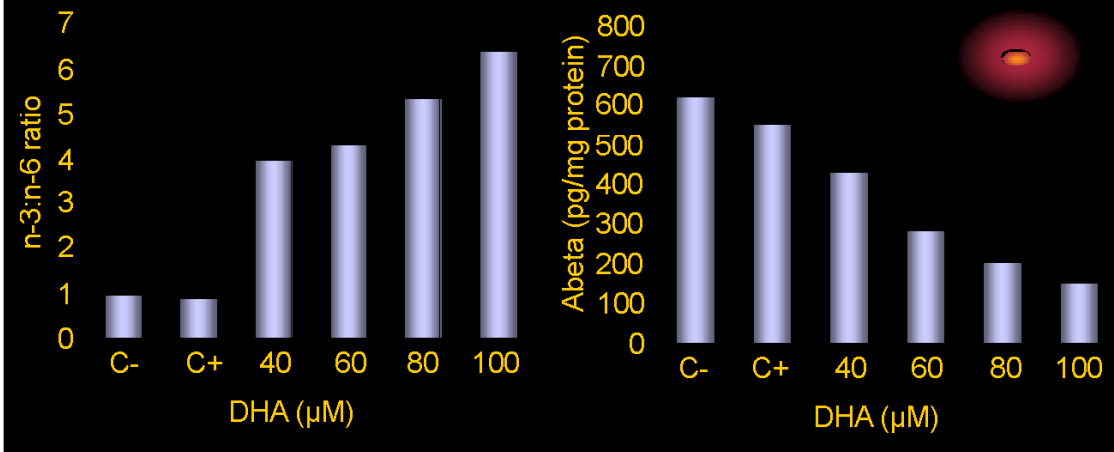
DHA/EPA and Memory





DHA inhibits β-amyloid formation *in vitro*

APP transfected cells



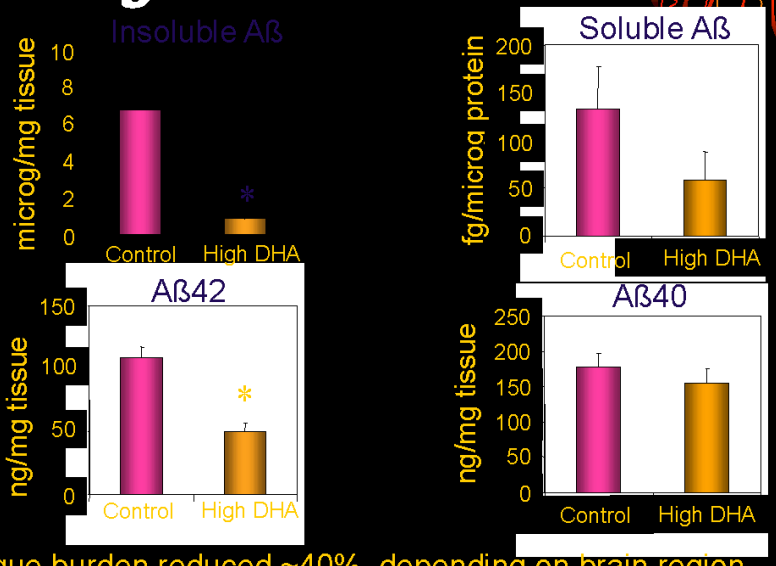
Increase membrane n-3/n-6 ratio

Inhibition formation of $Abeta_{1-42}$

De Wilde et al., Soc Neurosc, abstract, 2003

DHA inhibit β-amyloid formation

AD transgenic mouse model



- Plaque burden reduced ~40%, depending on brain region

Adapted from Lim et al., J Neuroscience, 2005

Lessons learned DHA trial

ORIGINAL CONTRIBUTION

ω-3 Fatty Acid Treatment in 174 Patients With Mild to Moderate Alzheimer Disease: OmegAD Study

A Randomized Double-blind Trial

Yvonne Freund-Levi, MD; Maria Eriksdotter-Jönhagen, MD, PhD; Tommy Cederholm, MD, PhD; Hans Basun, MD, PhD; Gerd Faxen-Irving, PhD; Anita Garlind, MD, PhD; Inger Vedin, MSci; Bengt Vessby, MD, PhD; Lars-Olof Wahlund, MD, PhD; Jan Palmblad, MD, PhD

Background: Epidemiologic and animal studies have suggested that dietary fish or fish oil rich in ω-3 fatty acids, for example, docosahexaenoic acid and eicosapentaenoic acid, may prevent Alzheimer disease (AD).

Objective: To determine effects of dietary ω-3 fatty acid supplementation on cognitive functions in patients with mild to moderate AD.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Participants: Two hundred four patients with AD (age range [mean±SD], 74±9 years) whose conditions were stable while receiving acetylcholine esterase inhibitor treatment and who had a Mini-Mental State Examination (MMSE) score of 15 points or more were randomized to daily intake of 1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid (ω-3 fatty acid–treated group) or placebo for 6 months, after which all received ω-3 fatty acid supplementation for 6 months more.

Main Outcome Measures: The primary outcome was cognition measured with the MMSE and the cognitive portion of the Alzheimer Disease Assessment Scale. The secondary outcome was global function as assessed with the Clinical Dementia Rating Scale; safety and tolerability of ω-3 fatty acid supplementation; and blood pressure determinations.

Results: One hundred seventy-four patients fulfilled the trial. At baseline, mean values for the Clinical Dementia Rating Scale, MMSE, and cognitive portion of the Alzheimer Disease Assessment Scale in the 2 randomized groups were similar. At 6 months, the decline in cognitive functions as assessed by the latter 2 scales did not differ between the groups. However, in a subgroup (n=32) with very mild cognitive dysfunction (MMSE >27 points), a significant (P<.05) reduction in MMSE decline rate was observed in the ω-3 fatty acid–treated group compared with the placebo group. A similar arrest in decline rate was observed between 6 and 12 months in this placebo subgroup when receiving ω-3 fatty acid supplementation. The ω-3 fatty acid treatment was safe and well tolerated.

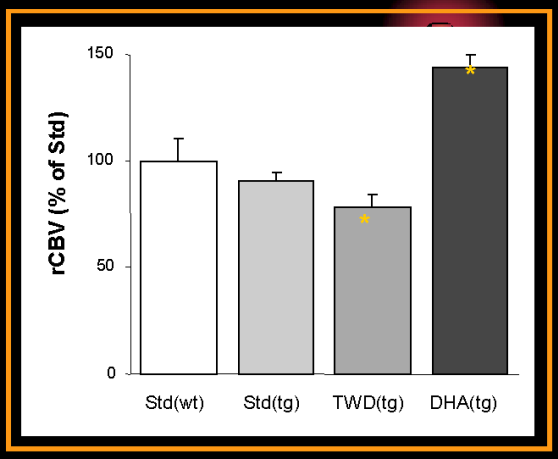
Conclusions: Administration of ω-3 fatty acid in patients with mild to moderate AD did not delay the rate of cognitive decline according to the MMSE or the cognitive portion of the Alzheimer Disease Assessment Scale. However, positive effects were observed in a small group of patients with very mild AD (MMSE >27 points).

Trial Registration: clinicaltrials.gov Identifier: NCT00211159

Arch Neurol. 2006;63:1402-1408

Nutrients are implicated as a risk factor for AD

- **DHA diet increased relative Cerebral Blood Volume (rCBV) in APP/PS1mice**
- **rCBV was measured using contrast enhanced MRI**



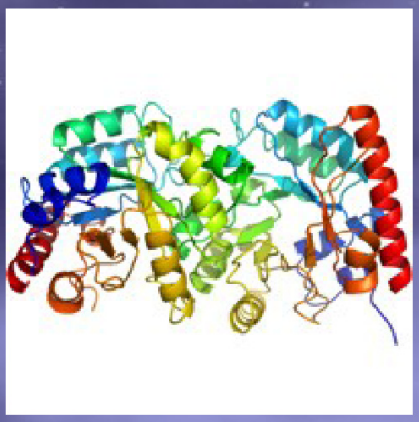
De Wilde et al (2003) Brain Res; Farkas et al (2002) Ann NY Acad Sci; Hooijmans et al (in press) Neurobiol Dis

Omega-3 Polyunsaturated Fatty Acids

- In mice docosahexanoic acid decreases amyloid burden
- Epidemiological studies show higher fish intake less cognitive impairment especially in persons with APOE-4
- 1.7g DHA and 0.8g EPA slowed deficits in MMSE > 27 but no effects in others…Arch Neurol 2006; 63:1402

Novel Nutriceutical approach

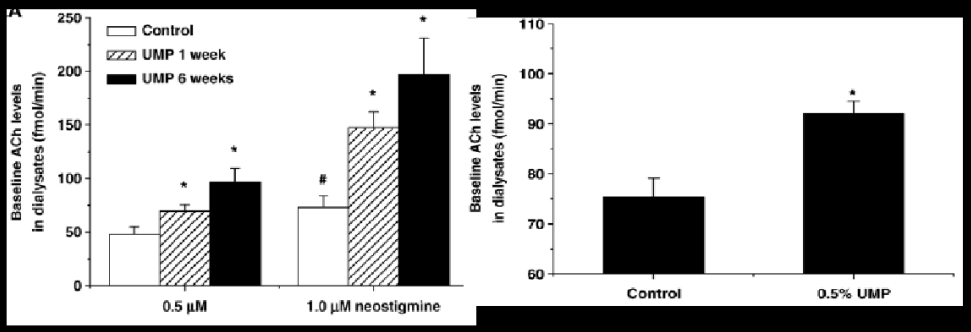
- Uridine-monophospate
- Choline
- N-3 fatty acids (DHA and EPA)



- RATIONALE: choline and UMP interact to form phosphatidylcholine that is incorporated into the membranes. In animal studies this increases neuritic outgrowth, acetylcholine production and cognition

UMP and ACh Level and Release

- **In animal studies, UMP has been shown to increase acetylcholine level and release**

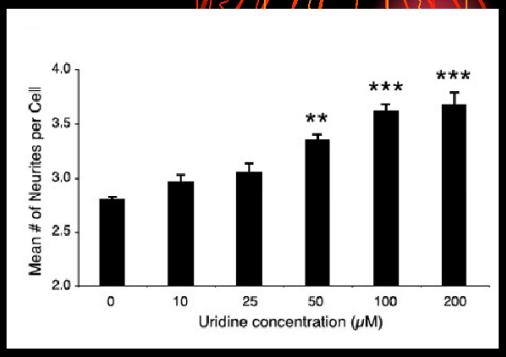


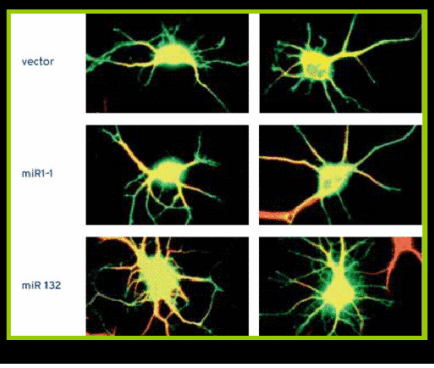
Wang et al, 2007

Uridine increases Neurite Outgrowth

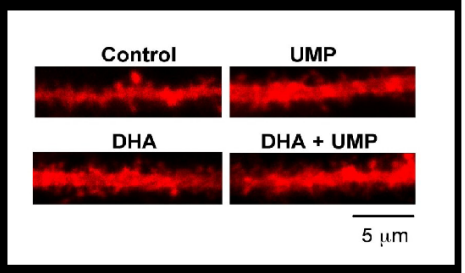
- **Preclinical studies suggest that the nucleotide uridine can stimulate neurite outgrowth by stimulating PC synthesis**

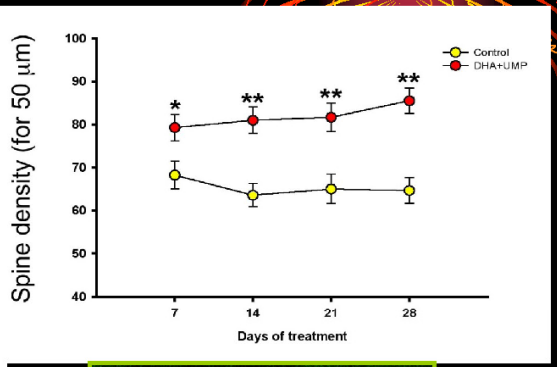
Pooler et al, Neuroscience, 2005

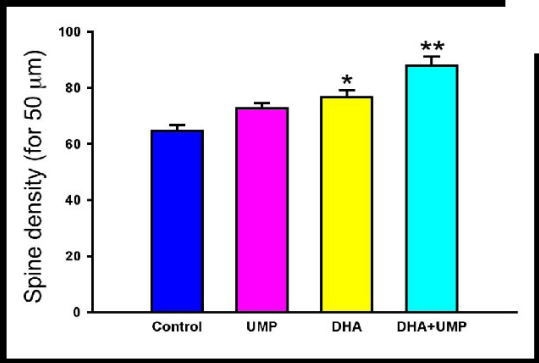


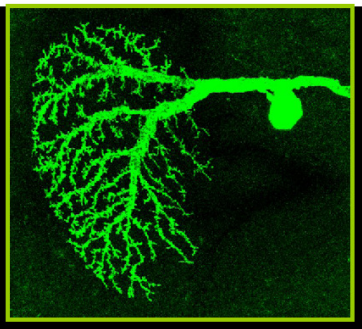


Effects of oral DHA alone or in Combination with a Uridine-Supplemented Diet on Dendritic Spine Density

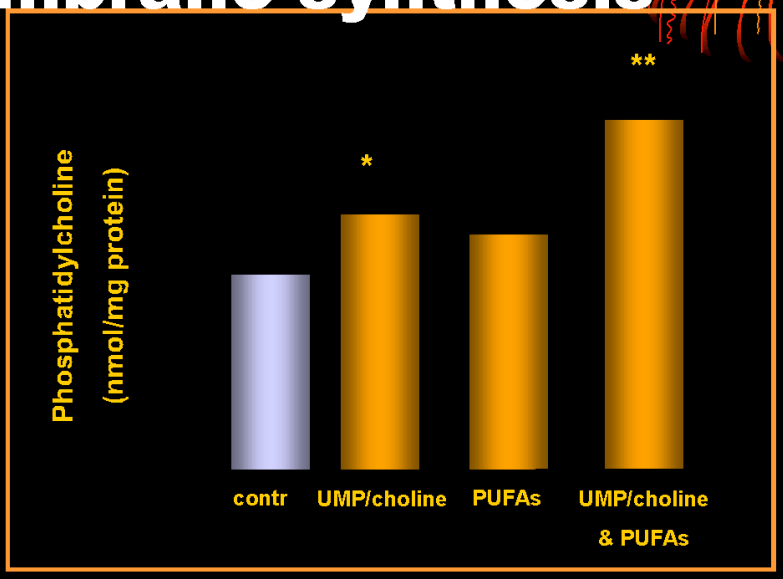








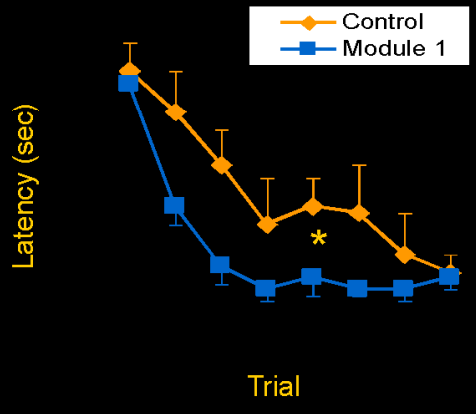
Nutrients regulate neuronal membrane synthesis



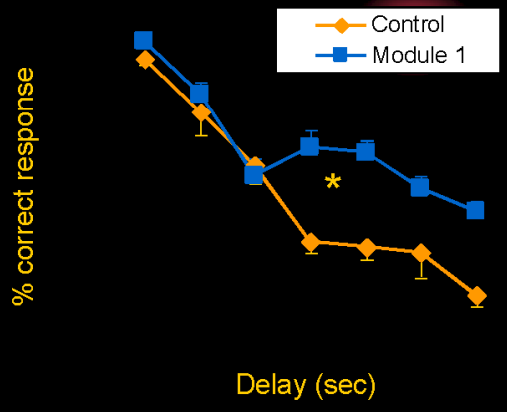
Wurtman et al (2006) Brain Res; Ulus et al (2006) Cell Mol Neurobiol

UMP/choline improved learning and memory hypertensive rats

Morris water maze



Visual attention task



De Bruin et al (2003) J Learn & Memory

Active Nutrients

Supported by 8 years of pre-clinical research

Active nutrients
(Fortasyn™ Connect)

UMP
DHA, EPA
Choline
Phospholipids
B vitamins
Antioxidants

Aid in the formation of synapses
- Stimulate neurite outgrowth
- Increase synaptic protein
- Increase dendritic spine density

Neuroprotective to brain cells

Form Cell Membranes
- Precursors phosphatide synthesis

Clinical trial

Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial

Philip Scheltens , Patrick J.G.H. Kamphuis, Frans R.J. Verhey,.

Alzheimer's & Dementia
Volume 6, Issue 1, January 2010, pages 1-10.

Baseline Characteristics

No significant differences between Souvenaid™ and Control

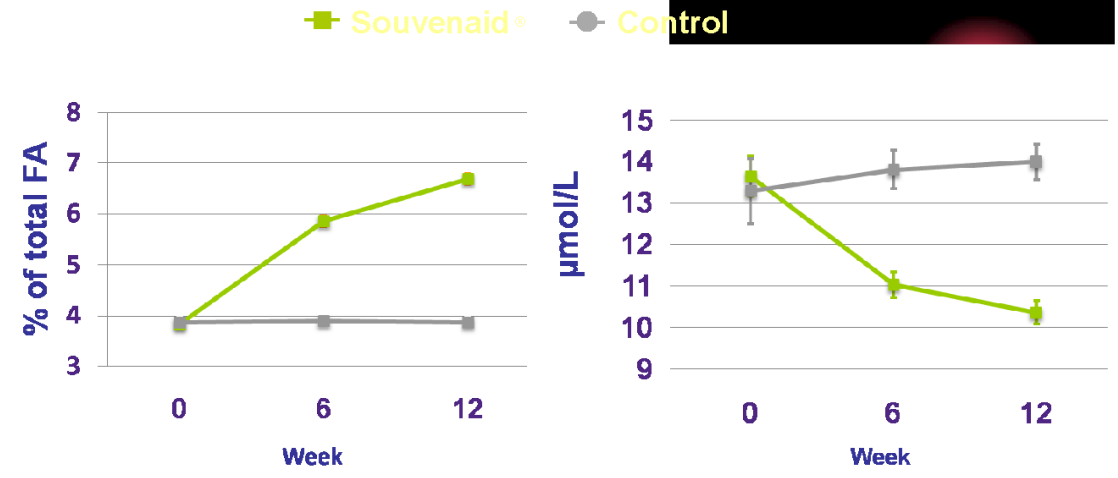
	Souvenaid™	Control	p-value
Sex (male/female; counts)	54 / 52	52 / 54	p=0.891
Age (yrs)	74.1 ± 7.2	73.3 ± 7.8	p=0.482
BMI (kg/m²)	26.2 ± 4.8	26.2 ± 3.5	p=0.938
Level of Education (yrs)	5.5 ± 3.9	6.0 ± 4.0	p=0.332
Days since AD diagnosis (median)	30.0 (0 – 1932)	31.5 (0 – 1036)	p=0.643
MMSE	23.8 ± 2.7	24.0 ± 2.5	p=0.631
WMS-r delayed (0-25; median)	1.0 (0 – 15)	2.0 (0 – 19)	p=0.299
Modified ADAS-cog (0-85)	25.9 ± 7.6	25.5 ± 8.8	p=0.702

Values are Mean ± SD, unless stated otherwise

Souvenaid® increases DHA levels & reduces homocysteine levels

Increased (p<0.001) % DHA in plasma erythrocyte membrane

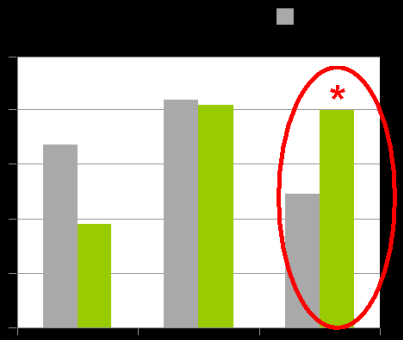
Reduced (p<0.001) plasma homocysteine



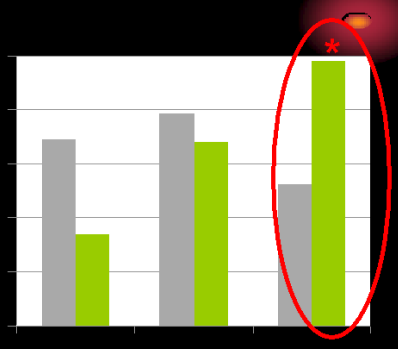
Souvenaid™ improves memory in mild Alzheimer's

delayed verbal memory WMS-r

Significantly* (p=0.021) more responders in Mild (ITT) AD after 12 weeks



Significantly* (p=0.019) more responders in very Mild (MMSE>23) AD after 12 weeks



* Chi-square

No Differences in Adverse Events

	Souvenaid™	Control	Examples	p-value
Gastrointestinal system	17.7%	17.9%	Diarrhea, constipation, nausea	p=1.000
Infections	9.7%	4.5%	Nasopharyngitis, influenza	p=0.193
Musculo-skeletal	8%	3.6%	Osteoarthritis, stiffness	p=0.253
Neurological	8%	8%	Dizziness, headache	p=1.000
Procedures, investigations, administrations	11.5%	7.1%	Abnormal hematology, Abnormal liver function Abnormal renal function	p=0.360
Psychiatric	6.2%	9.8%	Depression, insomnia	p=0.338
Skin	2.7%	6.3%	Prutitus, eczema	p=0.215
General	5.3%	4.5%	Malaise, tiredness	p=1.000

Less than 5%: Blood; coronary artery disease; eye; female reproductive system; metabolic and endocrine; injury; oncology; respiratory; ears nose throat; urogenital system; vascular system

Lutein

- Lutein is one of over 600 known naturally occuring plant pigments, known as carotenoids
- Rich dietary sources of lutein include green leafy vegetables such as spinach and kale
- Lutein selectively accumulates in human brain
- Lutein status is related to cognition

Dietary Recommendations for Lutein

While no recommended daily allowance currently exists for lutein, positive effects on eye disease prevention have been seen at dietary intake levels of ~6 mg/day

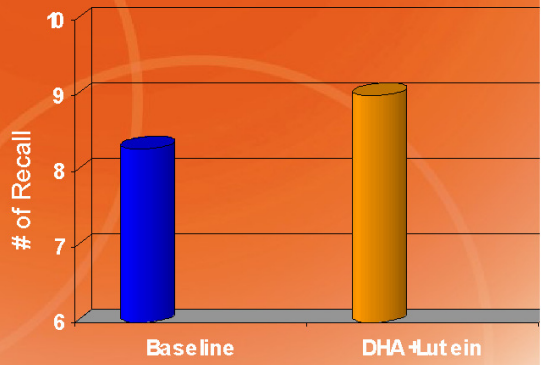
Source: Seddon et al, JAMA 1994

Green Leafy Vegetable Consumption (Lutein)

Older adults consuming the most green leafy vegetables experienced slower cognitive decline than those consuming the least amount

Source: Kang et al. Ann Neural, 2005

Combination of DHA and Lutein improves memory

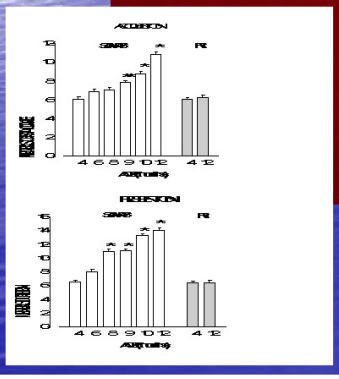


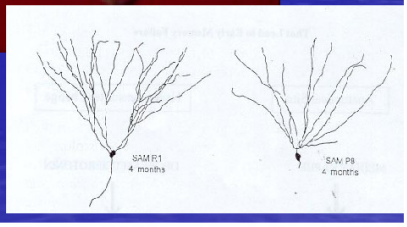
Effect of lutein and Omega-3 DHA supplementation on cognition

	Placebo	Lutein	DHA	Lutein + DHA
Verbal fluency		**Improve**	**Improve**	**Improve**
Shopping list Memory Test				**Improve**
Word List Memory Test				**Improve**
Apartment Memory Test				**Improve**

Johnson et al, 2008

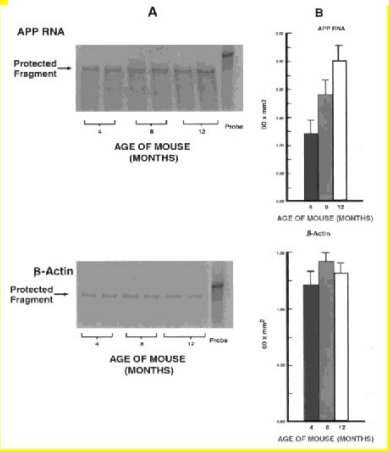
SAMP8 MOUSE



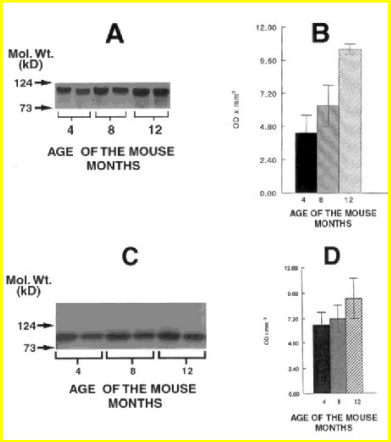


Increased Beta-amyloid in SAMP8 Mice

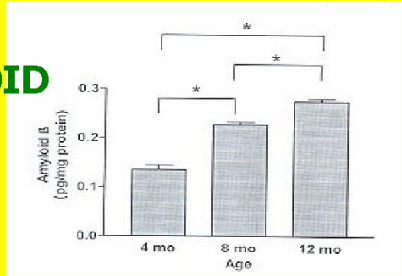
mRNA

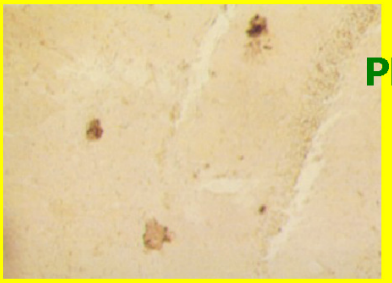


APP



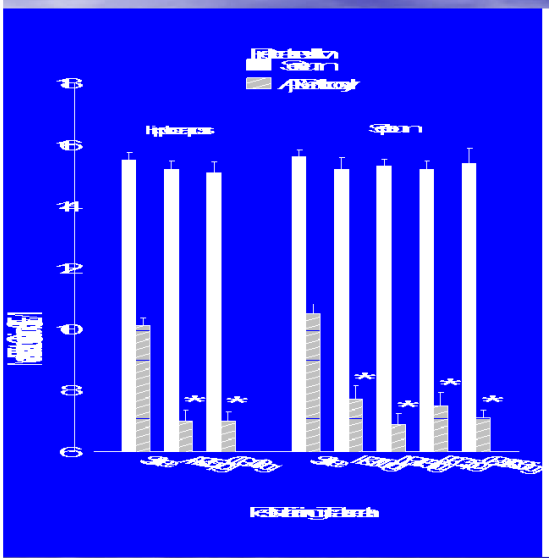
AMYLOID β

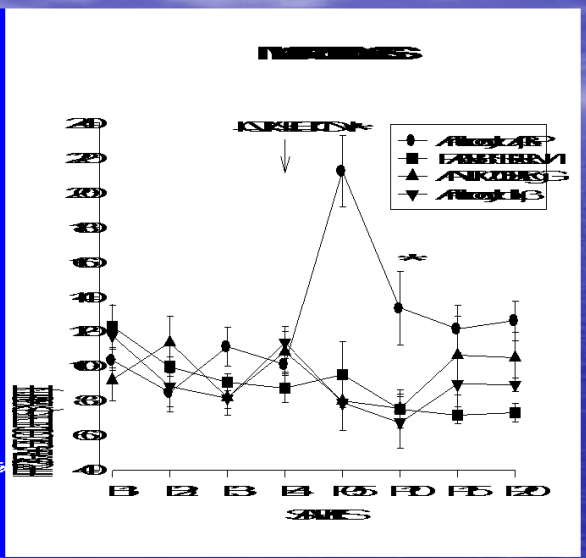




PLAQUE

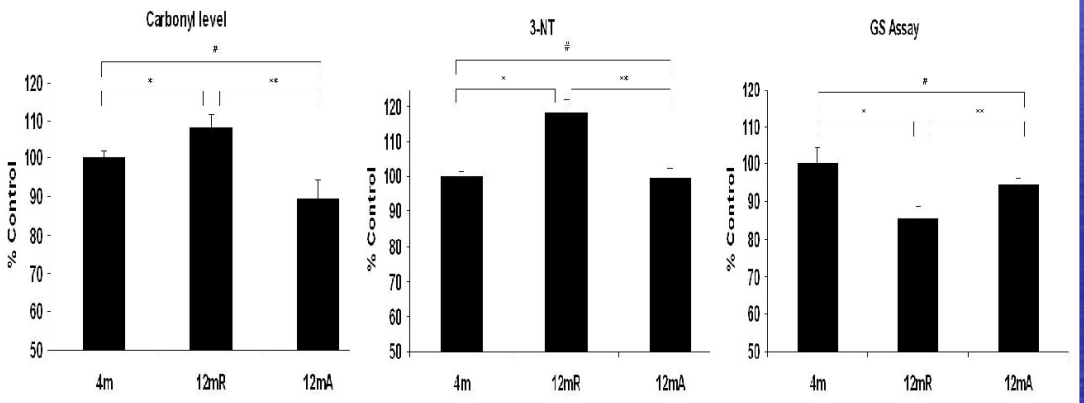
Antibodies to β-Amyloid reverse memory deficit and increase acetylcholine





SAMP8 MICE

AO Treatment Decreases Protein Oxidation in Aged SAMP8 Mice Brain

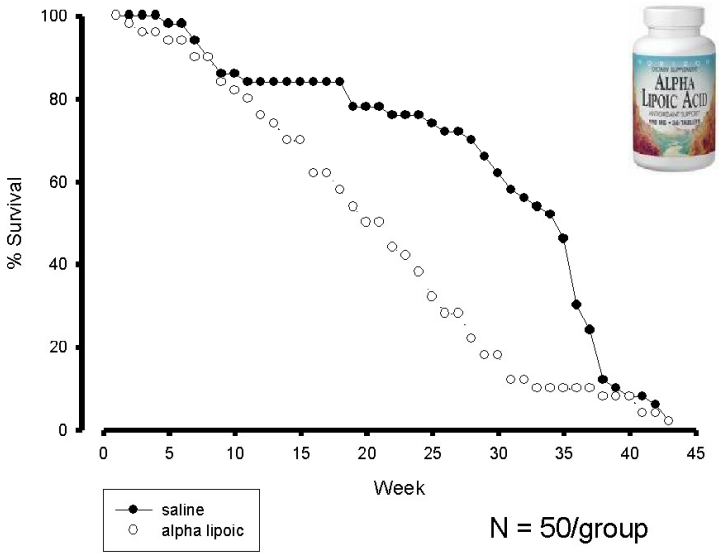


* $p < 0.05$, ** $p < 0.05$

Poon et al., 2004, Brain Res

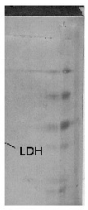
ALPHA-LIPOIC ACID, SAMP8 AND PROTEIN OXIDATION

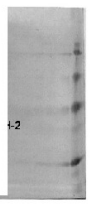
Survival % of mice on alpha lipoic from 12M



N = 50/group

Trials to First Avoidance
18
16
14
12
10
8
6
4
2
0



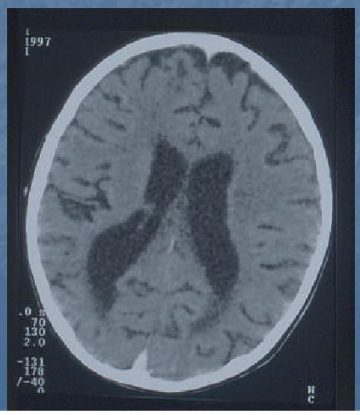


Exercise and the Brain

- Aerobic exercise for 6 months decreased brain atrophy…..

Colcombe et al

J Gerontol A 2006; 61:1166



Increased cognition

Decreased dysphoria

Exercise and incident dementia in persons 65 years and older

Larson et al, Ann Int Med 2008;144:73

- 1740 older persons who scored above 25th percentile cognitively
- Follow-up 6.2 years
- Exercise 3 times/week: 13.0 per 1000
- Exercise less: 19.7 per 1000
- OR 0.62 (0.44 – 0.86, p = 0.004)

Exercise Program for Nursing Home Residents with Alzheimers

Rolland et al, JAGS 55:158, 2007

- Objective: Would exercise reduce ADL decline in AD residents in nursing homes
- Design: 12 month multicenter, randomized, single-blind study
- 134 patients with AD from 5 nursing homes, I hour exercise twice weekly for one year , 88 sessions
- Exercises were walking, strength (squats/leg raises), flexibility and balance (one or two leg with foam-rubber)
- At end of study 11 (7 dead) in exercise and 13 (8 dead) in control discontinued

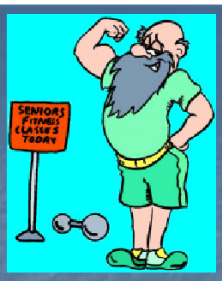
Exercise and AD

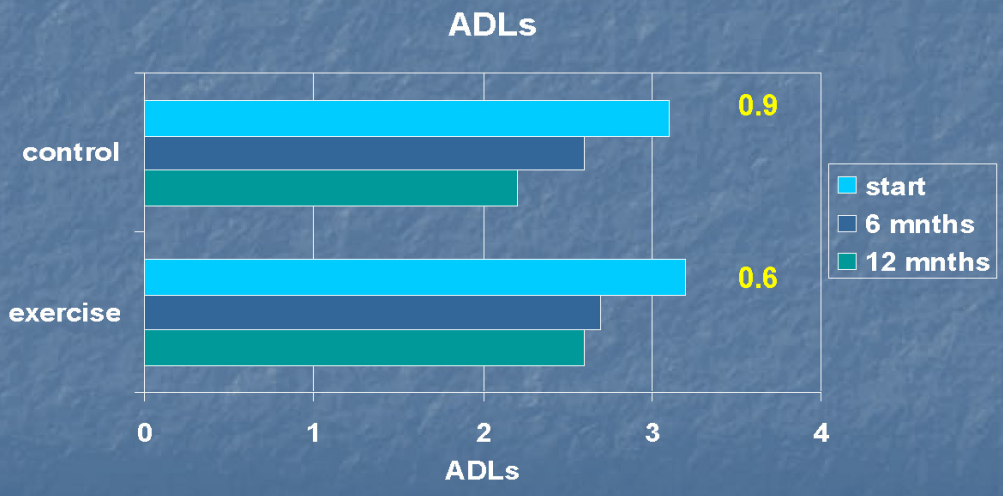
Rolland et al

- Age 83 years (62 – 103)
- MMSE 8.8
- ADL 3.1 (6 included walking and transfer)
- No difference between groups
- ADHERENCE : 19.4% > 60 sessions, 41.8% < 30 sessions.

Exercise and AD

Rolland et al, 2007



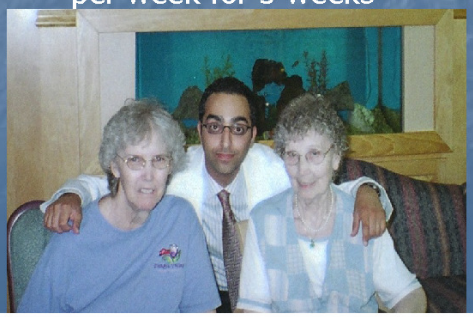


Less ADL reduction at 12 months in exercise group (P<0.02)

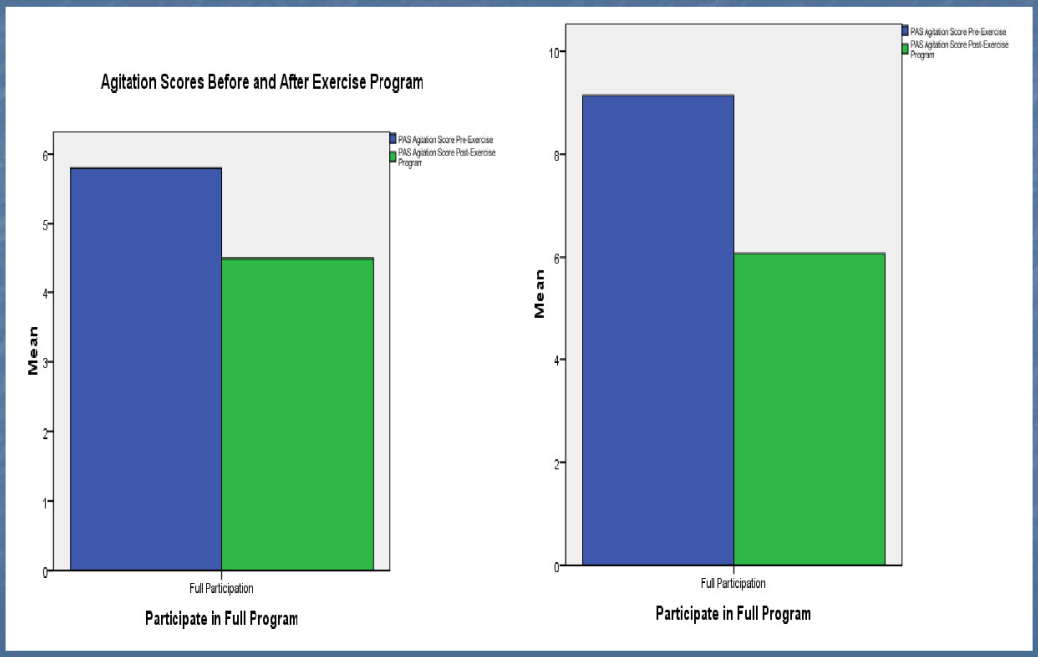
Exercise Program

Balance, Strength, and Aerobic Exercises

- 15 min walking outside
- 5 min of weight lifting
- 5 min of sit and stand
- 5 min of throwing a beach ball
- 30 min of exercise, 3 days per week for 3 weeks



All Subjects Agitated Subjects



Exercise and Mood

Williams et al, Am J Alz Dis Other Dementias 2007; 22:389

- Alameda County 1947 adults age 50 to 94 years…reduced physical activity associated with depression

  (Am J Epidemiology 2002; 150:328)

- Canadian Study of 4615 adults over 65 years…high levels of physical exercise associated with reduced cognitive impairment

  (Arch Neurol 2001; 58:498)

Exercise and Mood

- 85 depressed 34 weeks exercise to music. Ham D reduced 5.2 vs 3.7 in control

  Br J Psychiat 2000; 180:411
- 10 week resistance exercise decreased BDI by 11.5 vs 4.6 in controls ($p<0.002$)

  J Gerontol MS 1997; 52A:M27
- 439 elders 3 month aerobic exercise, resistance & health education ..less depression in aerobics

  J Gerontol B 2002; 57B:P124
- 40 older adults aerobic vs quiet rest…acute study…improved mood

  Med Sci Sports Exerc 2005; 37:2032

Exercise and Mood in Dementia

- 10 weeks lower extremity 3 times per week vs choice of walking or other activity improved depression

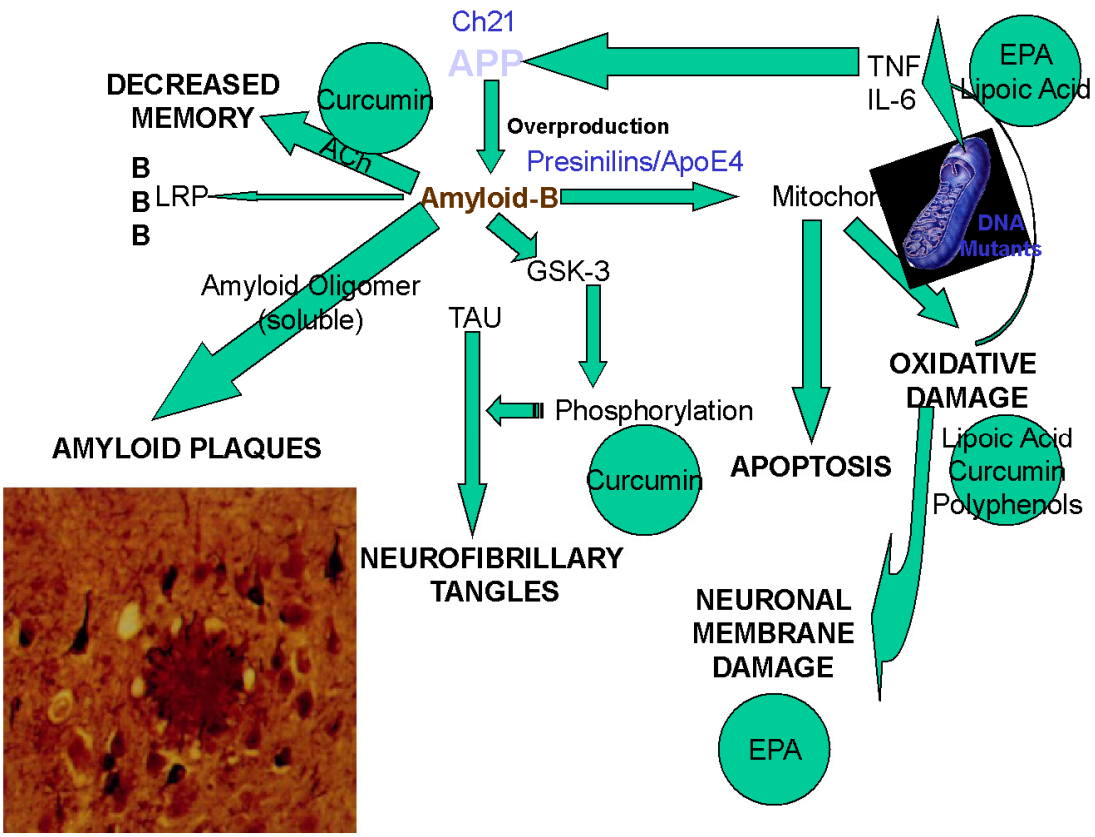
  NEJM 1994; 330:1769
- 12 hours mixed exercise over 12 weeks reduced depression

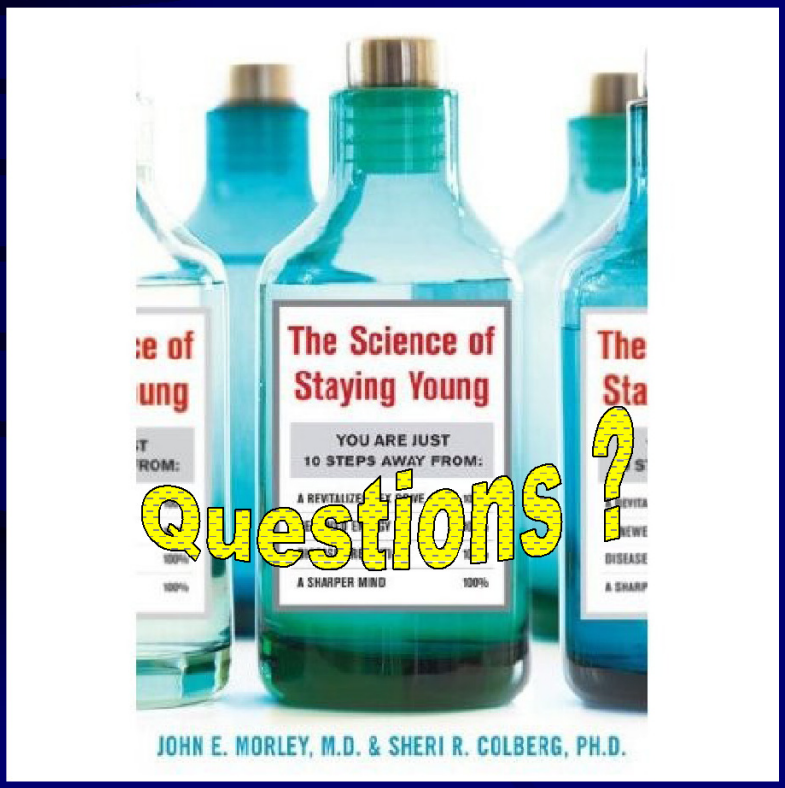
  JAMA 2003; 290:2
- Two other studies showed no effect

  JAGS 1996; 44:175

  JAGS 1988; 36:29

"We dance not only for ourselves but for the good of the people"
- Zuni





Dietary Factors

- Omega 3 PUFA were associated with reduced risk of cognitive impairment
- High cholesterol and saturated fats were associated with a poor memory
- Moderate alcohol intake was associated with better cognitive test scores

Notes

Notes