Published in final edited form as:
Alzheimers Dement. 2008 November ; 4(6): 443–446. doi:10.1016/j.jalz.2008.08.006.

Healthy Brain Aging: A Meeting Report From The Sylvan M. Cohen Annual Retreat Of The University of Pennsylvania Institute On Aging

Lisa J. Bain[1], **Kathy Jedrziewski**[1], **Marcelle Morrison-Bogorad**[2,†], **Marilyn Albert**[3], **Carl Cotman**[4], **Hugh Hendrie**[5], and **John Q. Trojanowski**[1*]

1*Institute on Aging, Center for Neurodegenerative Disease Research, and Department of Pathology and Laboratory, University of Pennsylvania School of Medicine, Philadelphia, PA*

2*National Institute on Aging, National Institutes of Health, Bethesda, MD*

3*Department of Neurology, John Hopkins University School of Medicine, Baltimore, MD*

4*University of California, Irvine, Irvine, CA*

5*University of Indiana School of Medicine Indianapolis, INI*

Since January of 2006, a baby boomer has turned 60 every seven seconds in the United States, according to Dr. John Trojanowski, director of the Institute on Aging at University of Pennsylvania, who introduced the theme of this public symposium on “Healthy Brian Aging”. And as these baby boomers get older, they are increasingly concerned about healthy aging, particularly healthy brain aging, and seek to avoid aging-related neurodegenerative disorders, like mild cognitive impairment (MCI), Alzheimer’s disease (AD) and other aging related neurodegenerative disorders associated with progressive brain degeneration and relentless declines in cognitive function.

AD is of particular concern because its prevalence increases exponentially with age after 65 and the world population is experiencing a longevity revolution in which the most rapidly expanding segment of the global population is that over age 65. There are a range of estimates on prevalence of AD in the United States, from 2.4 million[1] to 5.2[2] million, based on differing methodologies and approaches. But this notwithstanding, the number of people with AD is expected to explode in coming years as the population ages, unless ways to prevent or treat the disease are found. Indeed, someone develops AD in the United States approximately every 70 seconds, and AD has recently displaced diabetes as the 6th leading cause of death in the United States. By 2030, by one estimate, as many as 7.7 million people in the United States could have the disease, and by 2050 this number could rise to between 11 million and 16 million people[3]. It is currently estimated that the cost of AD in the U.S. exceeds $100 billion annually, and AD will likely affect the economies of other countries, including developing nations, as well. For example, the London-based Alzheimer’s Disease International has determined that

*Corresponding author, Institute on Aging & Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, HUP, Maloney 3rd Floor, 36th and Spruce Streets, Philadelphia, PA 19104-4283 USA, Tel: 215-662-6399; Fax: 215-349-5909, E-mail: trojanow@mail.med.upenn.edu.
†The listing of this participant should not be taken as this article’s representing the viewpoint of the U.S. Department of Health and Human Services, NIH, or the National Institute on Aging.

by 2040 the number of Alzheimer patients will more than triple in India, China and other countries in south Asia and the western Pacific[4].

With this in mind, the Penn Institute on Aging hosted some of the country's leading neuroscience researchers to discuss healthy brain aging at its Sylvan Cohen Annual Retreat on May 6, 2008. Facing an audience of some 400 attendees made up predominantly of the general public, Drs. Marcelle Morrison-Bogorad, Marilyn Albert, Carl Cotman, and Hugh Hendrie discussed both the science underlying brain aging as well as specific strategies that might reduce disabilities and enhance functional capacity.

How does the normal brain age?

Dr. Morrison-Bogorad, director of the Division of Neuroscience at the National Institute on Aging (NIA), began by focusing her comments on normal aging, which itself is associated with declining function in a number of areas. Normal cognitive changes associated with aging include a decreased speed of learning and processing of information, difficulty in performing several tasks at once, and changes in executive function, planning, sequencing, and working memory. At the same time, language functions, including vocabulary and syntax semantic processing, tend to be well preserved despite some difficulty with word retrieval[5].

Scientists are now asking what, at a biological level, accounts for the "normal" declines with aging and their relationship to the pathological symptoms of neurodegenerative disease. We have known for some time, from examination of brain tissue at autopsy, that AD brains are characterized by amyloid-beta (Aβ) plaques and neurofibrillary tangles made up of phosphorylated tau protein. In recent years, we have been able to "see" amyloid burden in the living brain through positron emission tomography (PET) imaging using the PET tracer ^{11}C-labeled Pittsburgh Compound-B (^{11}C-PIB), which specifically binds to fibrillar amyloid-beta (Aβ). The technique appears to offer the potential to detect Alzheimer's disease even in the preclinical stages of the disease. Studies using this test have shown as well that many cognitively normal older adults over the age of 60, with no signs of dementia, have plaques[6].

To better understand what happens in the brain that leads to AD, the National Institutes of Health, academic medical centers and research institutes, the pharmaceutical industry, and private foundations have joined in a unique public/private partnership, the Alzheimer's Disease Neuroimaging Initiative (ADNI), to identify the best combination of biomarkers, both brain imaging and biological markers in body fluids, that can be used both to diagnose AD and to monitor the effectiveness of treatments in drug trials more efficiently and perhaps even to diagnose AD earlier in its course[7]. At the same time, researchers are exploring a wide range of interventions, including drugs that may target the variety of brain changes associated with aging and AD as well as lifestyle therapies including dietary changes, behavioral enrichment, and exercise. Dr. Morrison-Bogorad also noted that while a number of observational and animal studies have pointed to possible approaches for reducing risk of AD, further testing will be needed to demonstrate effectiveness, dosages, and, in some cases, safety. Combinations of multiple interventions are likely to be required.

Vascular risk factors

Theories about the association between cardiovascular disease and dementia have evolved over time, but have garnered renewed interest in recent years. Forty to 50 years ago, people thought cognitive decline was related to hardening of the arteries, said Dr. Marilyn Albert, Director the Division of Cognitive Neuroscience at Johns Hopkins University School of Medicine. This was followed by a period where people began to think of AD pathology as the primary cause of dementia, with vascular disease playing little if any role. Now, she said, people are becoming increasingly aware that vascular disease and AD both contribute to cognitive decline, and in

fact seem to be additive. The importance of this realization is that since many vascular risk factors, such as high blood pressure, high cholesterol, diabetes, obesity, and smoking can be modified through lifestyle changes, and it is hoped that such changes may also have an impact on cognitive decline.

Dr. Albert cited a number of studies showing that people with multiple vascular risk factors are also at a greater risk for cognitive decline. For instance, one study conducted at Johns Hopkins compared people with heart disease who underwent coronary bypass grafting (CABG) surgery, off-pump surgery, or no surgery to heart-healthy individuals[8]. The study was prompted by concerns that surgery itself resulted in cognitive decline among cardiac patients. However, the study showed that after three years, people with vascular disease, regardless of whether they underwent surgery, performed slightly worse on cognitive tests compared to the heart-healthy control group. A follow up study after six years showed increased cognitive decline in multiple domains among those individuals with coronary artery disease, again regardless of whether they had surgery[9].

How might vascular disease contribute to cognitive decline? One possibility is that people with heart disease are more likely to have “silent strokes.” In fact, studies have shown that both silent and frank strokes cause an increase in the risk of dementia[10]. While dementia severity tends to be greater when vascular pathology is also present, vascular pathology and AD pathology (e.g., plaques and tangles) appear to be independent and additive[11]. The implications of these studies, said Dr. Albert, are that prevention of heart disease through multiple types of interventions may not only improve heart health but promote healthy brain aging as well. Randomized clinical trials, using medications that lower blood pressure or cholesterol, have shown a major impact of risk for coronary disease and stroke, but not cognitive decline. Options for future clinical trials include treating individuals with vascular risk factors in middle age or using combinations of medications. The potential benefits appear substantial given the evidence that vascular factors are associated with increased risk of cognitive decline.

Are exercise and diet the answer?

Dr. Carl Cotman, Director of the Institute for Brain Aging and the Alzheimer’s Disease Research Center at the University of California, Irvine, argued that physical exercise builds brain health, at least in animal models. In AD mouse models, exercise has been shown to reduce amyloid accumulation and inflammation, enhance synaptic plasticity, induce brain growth factor, and enhance communication among neurons in the brain, resulting in improved learning (reviewed in Cotman et al.[12] and Jedrziewski et al.[13]). In a large Nurses’ Health Study that enrolled over 18,000 women, those who reported merely walking several times a week showed improved cognitive function[14]. Significant benefits, he said, were achieved by walking as little as 1.5 to 2.8 hours per week. Other studies have shown other brain benefits from exercise, including a reduced risk of AD [15]and larger brain volume[16].

Dr. Cotman and others are trying to understand the mechanism by which exercise may improve brain health. A number of functional changes are seen in brains from exercised animals, such as improved learning, increased synaptic plasticity and numbers of neurons, protection from injury, and resistance to depression. Dr. Cotman suggested that a common mechanism for these effects could be BDNF (brain-derived neurotrophic factor), what he calls “brain fertilizer”. To see if exercise increases brain BDNF, Dr. Cotman provided running wheels to a group of rats. Each night, the rats run several kilometers, and after only one week showed increased levels of BDNF in the hippocampus, which is involved in learning and memory. Tested in the Morris water maze, the rats also showed an improved ability to learn where the escape platform was located. Moreover, when an antibody against the BDNF receptor (TrkB) was injected into these

animals, they could no longer find the platform, demonstrating that BDNF was responsible for their improved learning.

Whether these rat studies can be extrapolated to humans remains an unanswered question. Studies in higher animals, such as dogs, have attempted to answer this question. Dogs have several advantages: they have some of the same genes as those implicated in human AD, such as the gene for the amyloid precursor protein (APP); they naturally deposit amyloid in the brain similar to that seen in humans; they show age-related declines in cognition, and they can perform many of the same learning tasks as humans. Studies in beagles, for example, have shown that learning is improved by providing an enriched stimulating environment and a diet rich in antioxidants, said Cotman. Moreover, these "lifestyle" modifications resulted in increased production of BDNF, reduced production of free radicals, increased energy metabolism, a reduction in beta amyloid pathology, and reduced brain cell loss.

Happiness may be good for your brain

Attention to heart health, including diet and exercise, may not be the only path to healthy brain aging. According to Dr. Hugh Hendrie from the Center for Aging Research at Indiana University, attention to emotional health is also important. Yet although several studies showing that a good, meaningful life enables both individuals and communities to thrive, emotional health has generally been ignored as a means of promoting healthy brain aging. Dr. Hendrie chaired a committee of the NIH's Cognitive and Emotional Health Project, which was charged with assessing the state of the science in this area and making recommendations about future research priorities. Among the committee's conclusions was that cognitive and emotional health must be studied simultaneously[17]; however, Dr. Hendrie said this idea was not widely accepted and there is still resistance to the idea that emotional health influences cognitive function.

Nevertheless, he thinks this is an idea whose time has come. Studies suggest that a positive affect has a positive influence on health outcome, he said, and that this association is independent of the influence of negative affect[18]. In other words, while depression and anxiety are known to be detrimental to health, the effects of happiness and optimism are less widely accepted. Moreover, he noted that interventions are unlikely to succeed if they do not involve population-wide changes. In other words, an individual's mental health is strongly related to the mental health of the community at large, so interventions that attempt to improve the well being of larger communities are important[19]. Moreover, emerging evidence indicates that other lifestyle factors also may influence cognitive health and the risk for AD [20]. The table below summarizes some of the more commonly recognized lifestyle and environmental factors that association studies suggest are linked to risk for AD [20].

Because of emerging scientific and public interest in brain health, an Alzheimer's Association/Centers for Disease Control and Prevention initiative is underway to promote research, improve public health surveillance, and develop initiatives in the area. As these and other efforts move forward, all of the speakers agreed that more data, in particular, controlled trials that test both the efficacy and effectiveness of the proposed interventions, are needed to prove that a positive attitude, stimulating environment, and exercise can promote healthy brain aging; yet such large studies are difficult to conduct and enormously expensive. In the meantime, Ms. Nora Dowd Eisenhower, Secretary of the Pennsylvania Department of Aging, asked the panelists what they would advise people to do today. Dr. Albert gave what was perhaps the most practical response: "I think it's important to be mentally and physically active and socially engaged, and the activity that I think best combines all of those is shopping" she said. "This was inspired by my mother-in-law who is currently 97. She shops every day, she carries a heavy bag, she walks

long distances, and she debates at great length, comparing and contrasting what she ought to buy. And when she finally makes a purchase she feels very good about herself!"

References

1. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, Steffens DC, Willis RJ, Wallace RB. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007;29(1–2):125–132. [PubMed: 17975326]
2. Alzheimer's Association. Alzheimer's Disease Facts and Figures. Alzheimers Dement 2008;4:110–133. [PubMed: 18631956]
3. Hebert LE, Beckett LA, Scherr PA, Evans DA. Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050.". Alzheimer Disease and Associated Disorders 2001;15:169–173. [PubMed: 11723367]
4. Edelson E. Huge increase in Alzheimer's, dementia predicted. NY Times 12/16/2005
5. Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK. Models of visuospatial and verbal memory across the adult life span. Psychol Aging 2002 Jun;17(2):299–320. [PubMed: 12061414]
6. Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, Klunk WE, Mathis CA, DeKosky ST, Morris JC. [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. Neurology 2006 Aug 8;67(3):446–452. [PubMed: 16894106]
7. Shaw LM, Korecka M, Clark CM, Lee VM, Trojanowski JQ. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. Nat Rev Drug Discov 2007 Apr;6(4):295–303. [PubMed: 17347655]Epub 2007 Mar 9
8. Selnes OA, Grega MA, Bailey MM, Pham L, Zeger S, Baumgartner WA, McKhann GM. Neurocognitive outcomes 3 years after coronary artery bypass graft surgery: a controlled study. Ann Thorac Surg 2007 Dec;84(6):1885–1896. [PubMed: 18036903]
9. Selnes OA, Grega MA, Bailey MM, Pham LD, Zeger SL, Baumgartner WA, McKhann GM. Cognition 6 years after surgical or medical therapy for coronary artery disease. Ann Neurol 2008 May;63(5):581–590. [PubMed: 18481292]
10. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003 Mar 27;348(13):1215–1222. [PubMed: 12660385]
11. Launer LJ, Petrovitch H, Ross GW, Markesbery W, White LR. AD brain pathology: Vascular origins? Results from the HAAS autopsy study. Neurobiol Aging. 2007 Apr 25;[Epub ahead of print]
12. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 2007 Sep;30(9):464–472. [PubMed: 17765329]Epub 2007 Aug 31
13. Jedrziewski MK, Lee VM, Trojanowski JQ. Physical Activity and Cognitive Health. Alzheimers Dement 2007 Apr;3(2):98–108. [PubMed: 18379636]
14. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. JAMA 2004 Sep 22;292(12):1454–1461. [PubMed: 15383516]
15. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006 Jan 17;144(2):73–81. [PubMed: 16418406]
16. Kramer AF, Colcombe SJ, McAuley E, Eriksen KI, Scalf P, Jerome GJ, Marquez DX, Elavsky S, Webb AG. Enhancing brain and cognitive function of older adults through fitness training. J Mol Neurosci 2003;20(3):213–221. [PubMed: 14501000]
17. Hendrie HC, Albert MS, Butters MA, Gao S, Knopman DS, Launer LJ, Yaffe K, Cuthbert BN, Edwards E, Wagster M. The NIH Cognitive and Emotional Health Project. Report of the Critical Evaluation Study Committee. Alzheimers Dement 2006;2:12–32.
18. Pressman SD, Cohen S. Does Positive Affect Influence Health ? Psychol. Bull 2005;131:925–971. [PubMed: 16351329]

19. Huppert, F.; Baylis, N.; Keverne, B. The Science of Wellbeing. USA: Oxford University Press; 2006.
20. Jedrziewski MK, Lee VM, Trojanowski JQ. Lowering the risk of Alzheimer's disease: Evidence-based practices emerge from new research. Alzheimers Dement 2005;1:152–160.

TABLE

- **Cognitively stimulating activities –** e.g. read, do crossword puzzles, play cards.
- **Education –** e.g. take a class or attend lectures and advise the next generation to stay in school.
- **Exercise –** e.g. an exercise program as brief as 30 minutes ~3 times per week may benefit.
- **Head injury –** e.g. avoid traumatic brain injury.
- **Good nutrition –** e.g. a heart healthy diet also may benefit brain health.
- **Cholesterol and blood pressure –** e.g. cholesterol levels and blood pressure within normal limits are associated with reduced risk for AD.