A Picture of Memory: the MINA Study

Can we tell the difference between people who will get Alzheimer’s disease and people who won’t by looking at pictures of their brains?

If we could, how many years before the onset of dementia could we identify differences in the brains of people who are destined to become demented?

What other risk factors could help us identify these individuals?

Questions like these have inspired a unique study that aims at developing brain imaging techniques that can help us identify those people at risk for developing dementia later in life. The Memory Imaging of Normal Aging study (MINA) is a new study at the UCSD Shiley-Marcos Alzheimer’s Disease Research Center that is attempting to answer these important questions.

Exercise Slows Development of Alzheimer's-Like Brain Changes in Mice

According to a new study, physical activity appears to inhibit Alzheimer’s-like brain changes in mice, slowing the development of a key feature of the disease. The research demonstrated that long-term physical activity enhanced the learning ability of mice and decreased the level of plaque-forming beta-amyloid protein fragments—a hallmark characteristic of Alzheimer’s disease (AD)—in their brains.

A number of population-based studies suggest that lifestyle interventions may help to slow the onset and progression of AD. Because of these studies, scientists are seeking to find out if and how physically or cognitively stimulating activity might delay the onset and progression of Alzheimer’s disease. In this study, scientists have now shown in an animal model system that one simple behavioral intervention—exercise—could delay, or even prevent, development of AD-like pathology by decreasing beta-amyloid levels.
A Picture of Memory: the MINA Study (Continued from Page 1)

As new treatments for Alzheimer’s disease are being developed, our ultimate goal is not only to treat Alzheimer’s disease, but prevent it from happening in the first place. To do this we may need to start treatments ten, twenty, or even thirty years before the gradual onset of dementia. As new brain imaging technologies emerge, it is important for us to capitalize on their potential value for the use in preventing dementia.

The MINA study is using novel fMRI technology to take pictures of the memory centers of the brain as they are working. These exciting new techniques enable us to compare how the brain functions in people who are at increased risk for getting Alzheimer’s disease compared to those at low risk. New, more powerful fMRI machines, now available for research only at UCSD, make this work possible. We can see how the memory centers are activated by measuring blood oxygen content and blood perfusion to these key structures that are affected in Alzheimer’s disease. By looking at volunteers with various risk factors for AD but no memory problems, ages twenty-five to sixty-five, we may be able to reveal the footprints of dementia decades before its debilitating effects. Identifying such people and the early markings of AD is the first step to prevention and to the understanding of the complex architecture of dementia.

If you are in this age group and are interested in participating, call Susan Frye at (858) 622-5800.

Adam Fleisher, MD
MINA study Principal Investigator
Medical Director, Alzheimer’s Disease Cooperative Study

FOOTPRINTS OF DEMENTIA - A "BOLD" HYPOTHESIS

Exercise Slows Development of Alzheimer’s-Like Brain Changes in Mice (Continued from Page 1)

Results of this study, conducted by Paul A. Adlard, Ph.D., Carl W. Cotman, Ph.D., and colleagues at the University of California, Irvine, are published in the April 27, 2005, issue of The Journal of Neuroscience.

To directly test the possibility that exercise (in the form of voluntary running) may reduce the cognitive decline and brain pathology that characterizes AD, the study utilized a transgenic mouse model of AD rather than normal mice. The transgenic mice begin to develop AD-like amyloid plaques at around 3 months of age. Initially, young mice (6 weeks or 1 month of age) were placed in cages with or without running wheels for periods of either 1 month or 5 months, respectively. Mice with access to running wheels had the opportunity to exercise any time, while those without the wheels were classified as “sedentary.”

On 6 consecutive days after the exercise phase, the researchers placed each mouse in a Morris water maze to examine how fast it could learn the location of a hidden platform and how long it retained this information (this water maze task involves a small pool of water with a submerged platform that the mouse must learn how to find). The animals that exercised learned the task faster.

Thus the mice that used the running wheels for 5 months took less time than the sedentary animals to find the escape platform. The exercised mice acquired maximal performance after only 2 days on the task, while it took more than 4 days for the sedentary mice to reach that same level of performance. This suggests that exercise may help to offset learning/cognitive deficits present in AD patients.

Next, the investigators examined tissues from the brains of mice that had exercised for 5 months. They compared the levels of plaques, beta-amyloid fragments, and amyloid precursor protein, a protein found throughout the body and from which the beta-amyloid peptide is derived. In AD, beta-amyloid fragments clump together to form plaques in the hippocampus and cerebral cortex, the brain regions used in memory, thinking, and decision making.

Compared to the sedentary animals, mice that had exercised for 5 months on the running wheels had significantly fewer plaques and fewer beta-amyloid fragments (peptides) in the cerebral cortex and hippocampus, by approximately 50 percent. Additional studies of exercised animals at 10 weeks old showed that the mechanism underlying this difference began within the first month of exercise.

“The results suggest that exercise—a simple behavioral strategy—in these mice may bring about a change in the way that amyloid precursor protein is metabolized,” says D. Stephen Snyder, Ph.D., director of the etiology of Alzheimer’s program in the National Institute on Aging’s Neuroscience and Neuropsychology of Aging Program. “From other research, it is known that in the aging human brain, deposits of beta-amyloid normally increase. This study tells us that development of those deposits can be reduced and possibly eliminated through exercise, at least in this mouse model. Further research will help us to understand those mechanisms, to learn how much and what kind of exercise is best, and to see if these same effects occur in humans.”

Excerpt courtesy of ADEAR, Alzheimer’s Disease Education and Referral Center, a service of the National Institute on Aging
Bits & Bites

and the Scientists from Mars, Inc.

by Ingrid Padilla, BA

Much to the delight of chocolate lovers everywhere, recent research has shown that eating chocolate may indeed be beneficial to your health. Already known to be heart friendly, antioxidants in cocoa (named flavanols) may in the future help treat diabetes, strokes, and vascular dementia. Some of these findings were reported at the 2005 Cocoa Flavanols Meeting held last July in Switzerland.

Convened by Mars, Incorporated, approximately 20 science and medical experts from around the world congregated in Lucerne, Switzerland to discuss the newest research regarding potential benefits from cocoa flavanols. Carl Keen, Ph.D., Professor of Nutrition and Internal Medicine at UC Davis, presented research that identified specific molecules which explain the aspirin-like antiagulant effects of cocoa flavanols. Two collaborative studies by the University of Nottingham, Harvard Medical School, and Brigham and Women’s Hospital in Boston support the positive impact of flavanols on brain blood flow, showing this powerful antioxidant increases blood flow to key areas of the brain. Another substantive finding by physicians from the University Hospital in Zurich and Harvard Medical School pointed to the effects of flavanols on the vascular complications of diabetes. The antioxidant properties of flavanols increase blood vessel synthesis of nitric oxide, thus diminishing oxidative damage and increasing blood flow.

Other research supporting cocoa’s potential role in the treatment of cardiovascular illnesses and diabetes has been published in several scientific and medical journals. Free Radical Biology and Medicine highlighted in November 2004 an article that established a relationship between ingestion of dark chocolate and increases in HDL (“good” cholesterol) concentration, and supported chocolate fatty acid’s ability to inhibit lipid peroxidation (fat oxidation) in healthy humans. In March of this year, the American Journal of Nutrition featured study findings that showed healthy persons experience a significant increase in insulin sensitivity and a decrease in blood pressure after short term administration of dark chocolate.

Scientists from Mars, Inc., along with other investigators in the field, have developed the ability to synthesize specific cocoa flavanol compounds that will enable mass production of related pharmaceutical products in the future. Considering recent study findings correlating diabetes, cardiovascular disease, and dementia (including, but not limited to Alzheimer’s disease), it would not be too far-fetched to speculate as to the possibility that cocoa may one day be utilized in the formulation of new medications to fight AD.

Before you rush to the nearest store to stock up on cocoa products, bear in mind most processed chocolate products are high in fat and sugar, and consequently calories. Moderation is key.

It would not be too far-fetched to speculate that cocoa may one day be utilized in the formulation of new medications to fight AD.

Dressed Up” Strawberries

1 pint large strawberries (preferably stemmed)  
1 cup semisweet chocolate (morsels or chopped)  
1 Tbsp canola oil  
- finely chopped toasted almonds

Line baking sheet with parchment or wax paper. Rinse strawberries and pat dry (make sure they are dry or the chocolate will not stick to them). Melt chocolate in a double boiler or a bowl over a pot of hot (not boiling) water. Mix in the canola oil. One by one, hold strawberry by the stem and dip into the melted chocolate to cover about ¾ of the berry. Let excess chocolate drip, dip into almonds, and lay on baking sheet.

Chocolate recipes abound and are usually fat and sugar laden. Some of us may not be able to indulge our “chocolate tooth” (due to allergies and/or other food intolerances); yet those who are able to consume chocolate may want to try this recipe for a quick, easy and guilt-free chocolate treat. The strawberries provide soluble fiber, and are high in vitamin C, antioxidants (lutein and zeaxanthin), and potassium; the almonds are a great source of protein, magnesium, zinc, vitamin E, phosphorus and potassium. Enjoy these and reap the flavanol antioxidant benefits from the dark chocolate!
Clinical Trials

If you are interested in participating or would like more information, please contact the Study Coordinator listed with each trial.

- They may all be reached at the Shiley-Marcos ADRC.
- There is no cost to participate in any of these research protocols.

CLASP Study
Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease

STUDY DIRECTOR: Gang Tong, M.D., Ph.D.

TIME INVOLVED: This study involves 8-9 visits over 20 months.

DESCRIPTION: Statins are drugs that are used to lower cholesterol to reduce the risk of heart disease. This study will investigate the safety and effectiveness of simvastatin (Zocor) in lowering cholesterol to reduce the risk of Alzheimer's disease. This study will measure levels of a cholesterol drug, you may be eligible and are not currently taking a placebo.

Huperzine A

STUDY DIRECTOR: Jody Corey-Bloom, M.D., Ph.D.

TIME INVOLVED: Study participation will be 24 weeks.

DESCRIPTION: This study is to determine whether huperzine A is beneficial in the treatment of mild to moderate Alzheimer's disease. This effect has not been approved by the Food and Drug Administration (FDA). Study participation will be provided at no cost.

VALID
VALproate In Dementia

STUDY DIRECTOR: Jody Corey-Bloom, M.D., Ph.D.

TIME INVOLVED: Study participation will be 26 months.

CONTACT: Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5822 and ask for the "Huperzine A Study".

ONO-2506

STUDY DIRECTOR: Jody Corey-Bloom, M.D., Ph.D.

CONTACT: Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5822 and ask for the "VALID Study".

Lecozotan

STUDY DIRECTOR: Jody Corey-Bloom, M.D., Ph.D.

CONTACT: Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5822 and ask for the "ONO-2506 Study".

Biomarkers
In Aging, MCI, and Alzheimer’s Disease

STUDY DIRECTOR: Douglas Galasko, M.D.

DESCRIPTION: This study will measure levels of a number of different proteins in cerebrospinal fluid (CSF) and in blood in order to compare these biomarker levels amongst people who have normal cognitive ability, mild memory problems, or early Alzheimer's Disease. All participants must be accompanied by someone who can answer questions about them and who can make sure they are taking the study drug. They may all be reached at the Shiley-Marcos ADRC.

COMPENSATION: There will be no payment for participation in this study; however, all tests, examinations, and medical care required as part of the study will be provided at no cost.

Passive Immunization
STUDY DIRECTOR: Jody Corey-Bloom, M.D., Ph.D.

CONTACT: Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5822

DESCRIPTION: The safety, tolerability and effectiveness of an experimental drug, AAB-001, is being studied in individuals with mild to moderate Alzheimer's disease (AD). The study is sponsored by Elan Pharmaceuticals. AAB-001 is an antibody (a type of protein usually produced by white blood cells to destroy other substances in the body). In AD, a protein called amyloid gathers in the brain and is thought to cause symptoms like memory loss and confusion. It is hoped that AAB-001 will bind to the protein in the brain and help the body remove it.

CURRENT treatment with Vitamin E, Aricept, Razadyne and Exelon and/or Namenda are allowed. Participants will continue to receive their current treatment and will be randomly assigned to receive one of three possible doses of the experimental drug (AAB-001) or placebo. AAB-001 is given by intravenous infusion (given into a vein) and cannot be taken by mouth.

COMPENSATION: There will be no payment for participation in this study; however, all tests, examinations, and medical care required as part of the study will be provided at no cost.

CONTACT: Karen Wetzel, M.P.A.S., PA-C, at (858) 622-5822 and ask for the "Biomarkers Study".
Does Memory Affect our Appreciation of Pleasantness?

Research suggests that certain parts of the brain are involved in how we appreciate pleasantness. These brain regions, which include the amygdala and the basal forebrain, are sites of neuropathological change in Alzheimer’s disease (AD). Yet little research has been done on how people with AD process the pleasantness value of stimuli. Patients with AD often demonstrate changes in motivational behaviors during the course of their disease; apathy and weight loss in particular are two of the most common behavioral disturbances. Given the brain regions affected by AD and the behavioral changes observed, we hypothesized that the disease may adversely affect patients’ experience of pleasure.

A recent project at UCSD studied the appreciation of pleasure (a.k.a., hedonic processing) in older adults with mild to moderate AD, testing the hypothesis that patients would show impaired judgment of pleasure relative to a cognitively healthy older adult control group.

In one experiment, participants made two-choice preference decisions about “First Taste.” People with early Alzheimer’s disease show this unique contrast effect is evident. Notice that Person A and Person B taste just fine. The diagram shows generalized responses to drinks when a contrast effect occurs (see diagram). We found that patients and their control group showed the same contrast effects in their pleasantness judgments of drinks, even though the patients had poor memory for doing the experiment.

Taken together, these results suggest that patients with AD judge pleasantness as effectively as people with normal memory, and they have a preserved capacity to be influenced by the pleasantness of prior experience even when they are unable to recall those experiences. A person who has enjoyed pancakes with syrup all their life will continue to enjoy it if they develop AD. These findings provide scientific support for the need for emotionally sensitive patient care. Our results also suggest that changes in motivated behaviors, such as apathy and weight loss, are not necessarily due to patients’ inability to appreciate pleasurable activities and food items. This work is ongoing at UCSF, where we are studying other bias phenomena and are continuing to clarify brain regions and systems involved in hedonic processing.

What is your education/background? I was born in South Korea, where I lived the first 8 years of my life. I spent the next 8 years in Africa (Nigeria) where my parents served as Christian missionaries and where I attended boarding schools for missionary kids. I came to the US at the age of 16, where I completed my education from high school to post-doctoral training. I received my bachelor’s degree in Natural Science and Psychology from Illinois Wesleyan University. In 1993, I joined the Graduate Program in Neurosciences at UCSD committed to continuing my research on Alzheimer’s disease that I began as an undergraduate. At UCSD I studied in the labs of Drs. Tszanu Saitoh and Edward Koo looking at the genetic basis of Alzheimer’s disease, as well as the molecular cell biology of presenilins. Based on these studies, I completed my PhD training in 1999 and post-doctoral research in 2002.

What prompted your interest in the field of Alzheimer’s disease? My interest in the field of Alzheimer’s disease research stemmed from my fascination with the biological basis of learning and memory. Knowing that connections between neurons (synapses) that form memory are disrupted or destroyed by plaques and tangles, it became clear to me that I wanted to understand the mechanisms by which these pathologies drive the disease process and how best to prevent or reverse them.

What are your particular areas of interest with regards to AD research? The pathological hallmarks of Alzheimer’s disease are the plaques and tangles. Previous genetic and biochemical studies together have clearly shown that the action of amyloid is a critical and early event in the development of AD. Many researchers, including me, are working on ways to prevent or reverse amyloid accumulation. In contrast, there is very little known as to how the tau/tangle pathology develops. This is an important area of study, because we know that accumulation of amyloid beta protein in the absence of tangles is not sufficient to cause AD. There is some evidence that amyloid beta protein can worsen tangle pathology in experimental rodent models. There is also evidence that tangle pathology can also be driven by factors other than the amyloid beta protein. One of my interests is to study the regulation of biochemical pathways that control the tau protein. Looking at the normal and abnormal biology of tau, I hope to study the network of proteins or genes involved and learn how they interact. This work may lead to the identification of future targets for therapy that might prevent the formation of tangles.

Who funds your work? My research is partly supported by the Alzheimer’s Association. The support for this particular research is expected to continue until 2008. I expect to garner new funds to support stem cell research related to replacement of neurons lost in neurodegeneration, such as AD. We scientists have a mandate in AD research and encourage you to support research to help people you care about.
The Alzheimer’s Association San Diego Chapter is a nonprofit 501 (c)(3) voluntary health organization whose mission is to enhance care and support for individuals, their families and caregivers coping with Alzheimer’s disease, and to reduce the risk of dementia through the promotion of brain health as we research to find a cure. The chapter provides a number of free services to help caregivers in addition to individuals with Alzheimer’s disease. Services include 24-hour Helpline information and referrals, support groups, personalized care consultations, educational seminars, Memories in the Making art program, library, and safe return program.

For more information visit the Web site at www.sanalz.org or call 1-800-272-3900

WORKSHOPS FOR FAMILY CAREGIVERS AND HEALTHCARE PROFESSIONALS

Making the Placement Decision

The decision to move a loved one into any type of long-term care facility—whether an assisted living setting, skilled nursing facility, or dementia care unit—can be a complicated and overwhelming one. After attending this workshop, participants will be able to identify some of the emotional issues involved in placement, distinguish among various options for assistance along a continuum of care, articulate questions to ask when searching for a facility, and recognize methods to assist in easing the transition to placement.

Date: Tuesday, December 6, 2005
Time: 9:30 AM - 12:30 PM
Place: Grossmont Health Care Center, Conference Center
9001 Wakarusa St.
La Mesa, CA 91942
Call: (858) 492-4400 ext. 122 to register

This workshop meets the qualifications for three hours of continuing education credit for MFTs and LCSWs as required by the California Board of Behavioral Sciences (PCE 1507). Provider also approved by the California Board of Registered Nursing (CEP 12772) for three hours of continuing education credit for MFTs and LCSWs as required by the California Board of Behavioral Sciences (PCE 1507). Provider also approved by the California Board of Registered Nursing (CEP 12772) for three contact hours. Cost is $30 for professionals requesting CEUs. No charge for family caregivers and the general public.

Medications and Alzheimer’s Disease

Understanding the variety of medications available for treating behaviors associated with Alzheimer’s disease can be puzzling. Upon completing this workshop, attendees will learn about medications which are appropriate for treating behavioral issues, identify tips on medication compliance for someone living with dementia, recognize medications used to enhance cognitive abilities, and learn ways to work cohesively with your pharmacist.

Date: Wednesday, December 7, 2005
Time: 5:00 PM - 7:00 PM
Place: Sunrise Senior Living - La Costa
7020 Manzanita St.
Carlsbad, CA 92009
Instructor: David Dirig, RPh, Ph.D, CGP
Call: (760) 930-0060 to register

This workshop meets the qualifications for two hours of continuing education credit for MFTs and LCSWs as required by the California Board of Behavioral Sciences (PCE 1507). Provider also approved by the California Board of Registered Nursing (CEP 12772) for two contact hours. Cost is $20 for professionals requesting CEUs. No charge for family caregivers and the general public.

An Income That Can’t Shrink

You could arrange for a dependable supplemental income stream that would continue as long as you live?

The same plan freed you from worries about outliving your resources, fluctuating interest rates and the performance of your investments?

There was a way to do this while making a meaningful, charitable gift to the Alzheimer’s Disease Research Center of the University of California, San Diego?

There Is Such A Plan.

Charitable gift annuities offer a way to supplement your income, reduce gift, estate and income taxes while supporting something that means a great deal to you, such as our Alzheimer’s disease research.

How Do Gift Annuities Work?

Under a gift annuity’s terms, you make a gift of cash or appreciated securities through a simple agreement that provides you with quarterly payments, backed by UCSD, which will never decrease in size or frequency, regardless of changes in the economy. See the table for examples of rates you can receive.

Gift Annuities Offer Other Benefits Also:

- An income tax deduction is available for a portion of your charitable gift.
- Part of each payment is free from federal income tax for a period of time.
- You may enjoy capital gains tax savings.
- Estate taxes generally will not be due on amounts used to fund your annuity.
- Payments could also benefit loved ones and friends, if you wish.

For a customized illustration of your potential financial and tax benefits please call Dana Weintraub, Director of Development, at (858) 822-4197 or email her at dweintraub@ucsd.edu.

**SELECTED GIFT ANNUITY PAYMENT RATES**

<table>
<thead>
<tr>
<th>Age</th>
<th>Rate</th>
<th>Ages</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>5.5%</td>
<td>55</td>
<td>5.0%</td>
</tr>
<tr>
<td>60</td>
<td>5.7%</td>
<td>60</td>
<td>5.4%</td>
</tr>
<tr>
<td>65</td>
<td>6.0%</td>
<td>65</td>
<td>5.6%</td>
</tr>
<tr>
<td>70</td>
<td>6.5%</td>
<td>70</td>
<td>5.9%</td>
</tr>
<tr>
<td>75</td>
<td>7.1%</td>
<td>75</td>
<td>6.3%</td>
</tr>
<tr>
<td>80</td>
<td>8.0%</td>
<td>80</td>
<td>6.9%</td>
</tr>
<tr>
<td>85</td>
<td>9.5%</td>
<td>85</td>
<td>7.9%</td>
</tr>
<tr>
<td>90</td>
<td>11.3%</td>
<td>90</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

For a customized illustration of your potential financial and tax benefits please call Dana Weintraub, Director of Development, at (858) 822-4197 or email her at dweintraub@ucsd.edu.

**Shiley-Marcos Alzheimer’s Disease Research Center**
YOU'RE INVITED!

DECEMBER 7, 2005
10:00 AM - 11:30 AM

Radisson Hotel
3299 Holiday Court
La Jolla, CA 92039

(Across the street from the ADRC, behind the gas station as you're coming up the hill)