The National Cell Repository for Alzheimer's Disease (NCRAD) is a data and specimen collection source for families with Alzheimer's disease (AD) or serious memory loss. Families having two or more living individuals with memory loss are encouraged to participate. We would like to thank the hundreds of families nationwide who are already participating in the National Cell Repository for AD. Many family members have provided blood samples, which researchers use to study AD and other related diseases. Our hope is that through the efforts of our participants, we will one day unravel the mystery of devastating diseases like AD. We are always eager to accept new families to help us move toward this goal.

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NCRAD Update

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Exercise and Cognition

There is growing evidence that exercise has a positive effect on health including brain health. Dr. Frederick W. Unverzagt, Professor in the Departments of Psychiatry and Medical and Molecular Genetics at the IU School of Medicine provides some reviews of recent research on the benefits of both cognitive and physical exercise.

Frederick W. Unverzagt, PhD, Professor of Clinical Psychology in Clinical Psychiatry and Professor of Clinical Medical and Molecular Genetics

Do cognitive exercises really help improve cognitive function?

A recent analysis of many studies showed that persons with mild cognitive impairment (MCI) did see some mild to moderate cognitive benefits by participating in cognitive training and those benefits lasted through follow-up [Li, H.J., et al., 2011]. The MCI patients given training actually showed improvement over baseline whereas control MCI subjects (those who did not receive training) declined in nearly all areas from the baseline measurements to the post-test. Also, significant net treatment gains were noted in those studies that included a follow-up but the average post-training interval is not specified. The analysis suggested no effect of subject age or years of education on outcomes and no differences between training delivered by computer versus in-person methods nor was there a difference between group versus individual instruction. Overall, **these findings strongly support the idea that patients with cognitive impairment and MCI do benefit from cognitive training and that the benefits last beyond the immediate post-training time frame.**

What about physical exercise…does that help?

A comparison of 18 studies examining the effect of physical exercise interventions on cognition in older adults found a result in favor of exercise over control activities [Colcombe, S. and A.F. Kramer, 2003]. The findings also indicated that executive cognitive ability (umbrella term for connecting past experience with present action) showed the largest response to exercise as compared to other cognitive domains (e.g. spatial skills). Gains were also greater for training that lasted 30-45 minutes (versus longer or shorter periods of time) and for older subjects (versus ones that were aged 55-65). A more recent analysis that used a broader set of inclusion criteria (subjects as young as 18 years of age and exercise programs as short as 1 month in duration) included 29 studies with data from 2049 participants [Smith, P.J., et al., 2010]. A significant effect of exercise on a range of cognitive performances (attention and processing speed, executive ability, and memory) was noted though the effect sizes were smaller. However, that was not unexpected given the inclusion of younger subjects and shorter training programs.

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It does seem that physical exercise produces a wide range of positive effects in older adults and those with MCI, and these benefits include improved cognitive function.

Of significant note, exercise improves brain structure as measured by frontal and temporal lobe gray matter volume [Colcombe, S.J., et al., 2006] and neural activation as measured by fMRI [Colcombe, S.J., et al., 2004; Nagamatsu, L.S., et al., 2012]. Aerobic and resistance exercise training have been found to produce improved physical and cognitive performance when compared to control interventions in persons with cognitive impairment. [Nagamatsu, L.S., et al., 2012 ; Heyn, P., et al., 2004; Lautenschlager, N.T., et al., 2012]. **This suggests that exercise actually changes the brain structure in a good way.**

The link between exercise and improved cognition includes activity-induced growth in neurons (neurogenesis).

In a large review of decades of animal research, Kempermann [Kempermann, G., et al., 2010] concludes that adult neurogenesis (the growth of nerve cells in the brain) occurs in an activity-dependent manner and that both physical and cognitive exercises generate nerve growth signals to the brain. Movement stimulates neural precursor cells to multiply while enriched environments (e.g., learning and thinking activities) promote survival of the new cells. Kempermann argues that the notion that physical activity can induce neurogenesis makes sense if one considers that activity is the basis of cognition: “Physical activity is required for providing relevant sensory information to the animal that is then used to construct a representation of the environment” in the brain. In this way, locomotion provides the basis for critical cognitively-mediated and survival dependent animal activities like food caching and territory establishment. Indeed, Kempermann makes the case that “… physical activity and its consequences are evolutionarily inseparable from cognition, training to improve cognition will inevitably benefit from, if not depend on, physical exercise”.

Additive effects were demonstrated in an animal study showing that the combination of exercise and enrichment (a surrogate for cognitive training in the human model) produced more neurons in adult mice than either intervention alone with each superior to a “standard” environment [Fabel, K., et al., 2009].

Therefore, exercise is a very good thing for the brain.

In human studies, exercise increases frontal and temporal lobe gray matter volume [Colcombe, S.J., et al., 2006] and the studies indicating that the exercise effect on cognition may be mediated by changes in brain-derived neurotrophic factor (BDNF) are consistent with the idea that exercise may fundamentally enhance the neural substrate in a way that could maximize the effects of future cognitive stimulation [Voss, M.W., et al., 2011]. Exercise training also appears to alleviate endothelial dysfunction and vascular wall inflammation [Ribeiro, F., et al., 2010]. It seems that the beneficial effects of exercise on cognition may operate through multiple pathways. **Therefore, exercise is a very good thing for the brain.** ■

BENEFITS OF PHYSICAL ACTIVITY

Increasing physical activity through walking can help with:

- Decreasing blood glucose levels
- Decreasing systolic blood pressure
- Reducing the risk of coronary heart disease
- Reducing high cholesterol
- Reducing body fat
- Bone density
- Flexibility
- Osteoarthritis

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APOE and Alzheimer Disease

Alzheimer's disease (AD) is a progressive brain disease, characterized by the development of amyloid plaques and neurofibrillary tangles. This disease results in a loss of connections between nerve cells in the brain, and the death of these cells. There are two types of AD: early-onset and late-onset. Both types are caused by genetic factors.

Most cases of AD are the late-onset form, with an onset of disease after the age of 60. The cause of late-onset AD is unknown but is thought to be a combination of genetic, environmental, and lifestyle factors that influence a person's risk for developing the disease.

Researchers have not found a specific gene that causes late-onset AD. However, several genetic variants have been found that increase the risk of developing AD. ***Apolipoprotein E (APOE)*** is the first risk gene identified, and remains the gene with strongest impact on risk. ***APOE*** contains the instructions for making a protein that helps carry cholesterol and other types of fat in the bloodstream including the brain.

APOE has three common forms: ***APOE ε2***, ***APOE ε3***, and ***APOE ε4***. Each person has two copies of the ***APOE*** gene, one from the father and one from the mother. The ***APOE ε4*** form is considered a risk-factor gene for AD and appears to influence the age at which the disease begins. Those who inherit one copy of ***APOE ε4*** have an increased risk of developing AD. Those who inherit two copies have an even higher risk. In addition, people who have ***APOE ε4*** tend to develop the disease at an earlier age than those who do not have any ***APOE ε4*** alleles.

- ***APOE ε2*** is relatively rare and may provide some protection against the disease. If AD occurs in a person with this form, it develops later in life than it would in someone with the ***APOE ε4*** gene.
- ***APOE ε3***, the most common form, is believed to play a neutral role in the disease—neither decreasing nor increasing risk.
- ***APOE ε4*** is present in about 25 to 30 percent of the population and in about 40 percent of all people with late-onset AD. People who develop AD are more likely to have an ***APOE ε4*** form than people who do not develop the disease.

Jill Murrell, PhD, Associate Professor, Department of Pathology & Laboratory Medicine and Medical and Molecular Genetics, Indiana University School of Medicine

Numerous studies have confirmed that the ***APOE ε4*** form increases the risk of developing AD, but how that happens is not yet understood. ***APOE ε4*** is called a risk-factor gene because it increases a person's risk of developing the disease. However, inheriting an ***APOE ε4*** gene does not mean that a person will definitely develop AD. Some people with one or two ***APOE ε4*** genes never get the disease, and others who develop AD do not have any ***APOE ε4*** genes.

Although a blood test can identify which ***APOE*** type a person has, it cannot predict who will or will not develop AD. Because of this uncertainty, ***APOE*** testing is not recommended for people at risk for AD. Many experts have suggested that some individuals with the ***APOE ε4*** allele will never develop the disease and will therefore become unnecessarily concerned about their health, while those without the ***APOE ε4*** allele will be falsely reassured that they will never develop the disease. It is unlikely that genetic testing will ever be able to predict the disease with 100 percent accuracy because too many other factors may influence its development and progression.

Presently, ***APOE*** testing may be done in a clinical setting along with other diagnostic tests in patients with dementia. This test aids the clinician because the presence of the ***APOE ε4*** allele increases the likelihood of a diagnosis of AD if the patient already has dementia.

In addition, ***APOE*** testing is often performed in research settings to identify study participants who may have an increased risk of developing AD. This knowledge helps scientists look for early brain changes in participants and compare the effectiveness of treatments for people with different ***APOE*** profiles. For those studies that perform ***APOE*** testing, the results of these tests are not given to the participants. Most researchers believe that ***APOE*** testing is useful for studying AD risk in large groups of people but not for determining any one person's specific risk.

Most researchers believe that APOE testing is useful for studying AD risk in large groups of people but not for determining any one person's specific risk.

Modified from http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-genetics-fact-sheet ■

Research Opportunities:

4 Repeat Tauopathy Neuroimaging Initiative (4RTNI)

- Purpose: To identify the best methods of analysis for tracking PSP and CBD over time. The results from this study may be used in the future to calculate power for clinical drug trials, as this study aims to identify the most reliable outcome measures.
- Eligibility: Men and women ages 45 to 90 years, diagnosis of Progressive Supranuclear Palsy or Corticobasal Degeneration (CBD)
- Locations: CA
- Contact: PH: 415-476-9578 or 4RTNI webpage: www.memory.ucsf.edu/research/studies/4rtni

Dominantly Inherited Alzheimer Network (DIAN)

- Purpose: To study brain changes in people who carry an Alzheimer's disease mutation in order to determine how the disease process develops before the onset of symptoms.
- Eligibility: Men and women ages 55 to 80 years, diagnosis of mild to moderate Alzheimer's disease, good general health and medically able to undergo neurosurgery.
- Locations: USA - CA, IN, MA, MO, NY, RI; United Kingdom; Australia
- Contact: PH: 314-286-2683 or DIAN webpage: http://www.dian-info.org

Neuroimaging in Frontotemporal Dementia (NIFD)

- Purpose: To identify the best methods for imaging and analysis for tracking frontotemporal lobar degeneration (FTLD) over time.
- Eligibility: Individuals between the ages of 45 and 90 who meet the criteria for behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), progressive nonfluent aphasia (PNFA), or healthy aging. A study partner who has frequent contact with the volunteer and can provide information about them and accompany them to study visits is also required. All volunteers must be willing and able to undergo testing procedures and agree to follow-up.
- Locations: CA, MN, MA
- Contact: Aly Caplan,
  PH: 415-476-0670,
  e-mail: acaplan@ucsf.edu

Brain Health Registry

- Purpose: Promote healthy brain function through the prevention of brain diseases, brain disorders and brain injuries that affect brain function in adults
- Eligibility: Anyone 18 years and older, men and women
- Please visit the following website for more information: http://www.brainhealthregistry.org/

Alzheimer Disease Centers

- Purpose: Working to translate research advances into improved diagnosis and care for Alzheimer's disease patients, while at the same time, trying to find a way to cure and possibly prevent AD.
- Eligibility: Varies by center; cases, families and controls.
- Locations: At major medical institutions across the U.S., please visit the following website for locations: http://www.nia.nih.gov/alzheimers/alzheimers-disease-research-centers

NCRAD Welcomes Your Ideas and Suggestions

We hope that you and your family find the NCRAD Newsletter informative. We would welcome suggestions on future topics for articles, questions you would like to ask the NCRAD doctors or anything you would like shared with our readers about your family's experience with Alzheimer disease. Please send us your ideas by email or by phone.

Phone: 1-800-526-2839 **Email:** alzstudy@iupui.edu **Website:** www.ncrad.org

Sources for Information and Support

***Alzheimer's Association**
http://www.alz.org
Tel: 312-335-8700 or 800-272-3900

***Alzheimer's Disease Education and Referral Center (ADEAR)**
http://www.nia.nih.gov/Alzheimers
Tel: 301-495-3311 or 800-438-4380
** ADEAR lists all 29 Alzheimer Disease Centers (ADCs) and their contact information.

Assisted Living Directory, Assisted Living Facilities Information & Senior Care
http://www.assisted-living-directory.com/

The Association for Frontotemporal Dementias (AFTD)
http://www.theaftd.org
Tel: 267-514-7221 or 866-507-7222

Family Caregiver Alliance
http://www.caregiver.org
Tel: 415-434-3388 or 800-445-8106

National Parkinson Foundation
http://www.parkinson.org/
Tel: 305-547-6666 or 800-327-4545

Parkinson's Disease Foundation (PDF)
www.pdf.org
Tel: 212-923-4700 or 800-457-6676

Society for Progressive Supranuclear Palsy
http://www.psp.org
Tel: 410-486-3330 or 800-457-4777

National Organization for Rare Disorders (NORD)
http://www.rarediseases.org
Tel: 203-746-6518 or 800-999-NORD (6673)

Center for Disease Control and Prevention (CDCP)
http://www.cdc.gov
Tel:800-311-3435

Creutzfeldt- Jakob Foundation Inc. (CJD)
http://cjdfoundation.org
Tel: 954-704-0519 or 305-891-7579

***ClinicalTrials.gov** is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals.
http://www.clinicaltrials.gov/

***Research Match** is a free service that pairs volunteers interested in participating in research opportunities from surveys to clinical trials with researchers. Open to all, including healthy volunteers.
http://www.researchmatch.org

National Society of Genetic Counselors
http://www.nsgc.org/
Tel: 312-321-6834

*These are good sources for research opportunities in your area.

10 Signs of AD

1. Memory loss
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time and place
5. Poor or decreased judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in personality
9. Changes in mood or behavior
10. Loss of initiative

For more information, call the Alzheimer's Association at (800) 272-3900

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