

# The Aging & Alzheimer's Update

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**Dr. Lisa Silbert**, Assistant Professor of Neurology, has recently been awarded a 2-year American Academy of Neurology Foundation clinical research training fellowship to support her research on the use of Transcranial Magnetic Stimulation (TMS) in obtaining an electrophysiologic measurement of central nervous system processing efficiency in the elderly. This fellowship will enable her to continue to pursue her research interest in studying the effects of subcortical white matter change on age-related cognitive and motor slowing. Dr. Silbert completed fellowship training in both Geriatric Neurology and Clinical Neurophysiology at OHSU.

In addition to the above AAN fellowship, Dr. Silbert has recently been awarded the 5-year Paul B. Beeson Career Development Award in Aging Research from the American Foundation for Aging Research and the National Institute on Aging. The study is titled, "White Matter change and CNS processing in the elderly".

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## Using TMS to study age-related cognitive change

Lisa Silbert, MD,  
Assistant Professor,  
Layton Aging & Alzheimer's Disease Center

It is commonly observed that advanced age is associated with slowing of our thinking and motor skills. In addition, brain images have shown changes in the white matter almost universally after age 85. In our research at the Layton Center, we are seeking to understand how changes in white matter are related to aging-related changes in non-demented elders. This region of the brain lies underneath the brain cell bodies, or neurons, and is responsible for the conduction of information from one part of the brain to another. Disruption of white matter tracks throughout the brain may lead to disorganized processing of information, resulting in slowing on tests of cognitive and motor function. We are currently investigating the effects of such white matter change on central nervous system processing speed using information obtained from subjects enrolled in ongoing Layton Aging and Alzheimer's Disease Center studies on aging.

Transcranial magnetic stimulation (TMS) is a tool that can be used to assess "cortical excitability." As such, it can be used to establish the level of stimulation required to activate brain cells. In our research, we are investigating the relationship between white matter change and cortical excitability with the cognitive and motor slowing that is commonly observed with increasing age. In our preliminary studies, we used magnetic resonance imaging (MRI) to look at TMS outcomes in a group

of elderly with normal memory and cognition. These studies suggest that decreased neuronal inhibition (resulting in increased cortical excitability) is associated with greater white matter change on MRI. These initial findings suggest that age-related cognitive and motor slowing may be the result of less inhibited and therefore less controlled and efficient processing of information in the brain.

We are continuing to examine TMS-derived measures of cortical excitability as a potential marker of central nervous system processing efficiency in the elderly. In this regard, our preliminary studies have shown that TMS markers of increased cortical excitability are associated with poorer performance on some tests of cognitive and motor function, particularly tests scored by performance based on the participant's time or speed. In addition, data analyzed from our pilot studies indicate potential right and left hemisphere differences in cortical excitability in nondemented elderly with white matter change. Future studies involving more subjects, and tracking changes in cortical excitability over time, are needed in order to fully understand these complex relationships.

Studies using TMS to investigate cognitive and motor function often use elderly subjects as age-matched controls to those with neurodegenerative diseases. Few, if any, have examined the effects of aging and white matter change on cortical excitability in the cognitively intact elderly. Accordingly, a more detailed understanding of normal age-related changes in cortical excitability would greatly assist in our understanding of cortical change that occurs in neurologic disease such as Alzheimer's disease. This may lead to therapeutic interventions aimed at specific neurotransmitter dysfunction. In addition, such investigations will be critical to understanding the underlying mechanisms behind age-related cognitive decline and white matter change in persons without dementia so that preventative therapies can be developed. TMS holds promise as a method to follow changes in cortical excitability and central nervous system processing over time. Thus, it may enable us to establish an objective, cost-effective biomarker of aging and white matter degeneration for use in future prevention and treatment trials aimed at improving age-related cognitive slowing.

## **A New Medication for the Treatment of Alzheimer's Disease: Memantine (Namenda)**

Georgene C. Siemsen, M.S., APRN BC Geriatric Nurse Practitioner

In September 2003, the FDA's Peripheral and Central Nervous System Drug Advisory Committee supported the use of memantine (Namenda) for the treatment of moderate to severe Alzheimer's disease. Some advisory committee members considered memantine's effect to be modest, similar to cholinesterase inhibitors such as donepezil (Aricept), rivastigmine (Exelon), and Reminyl (galantamine). Memantine was approved by the Food and Drug Administration (FDA) in October 2003.

Memantine is classified as a NMDA receptor blocker, believed to work by protecting the brain from exposure to damaging chemicals that result from disrupted nerve function in the brain. While memantine may improve symptoms in persons with Alzheimer's disease, it does not cure or stop the progressive decline seen in the course of the illness. Research findings found the possible benefit of treatment with memantine (Namenda) includes a modest improvement in ability to manage activities of daily living. This benefit has the potential to improve the affected person's quality of life.

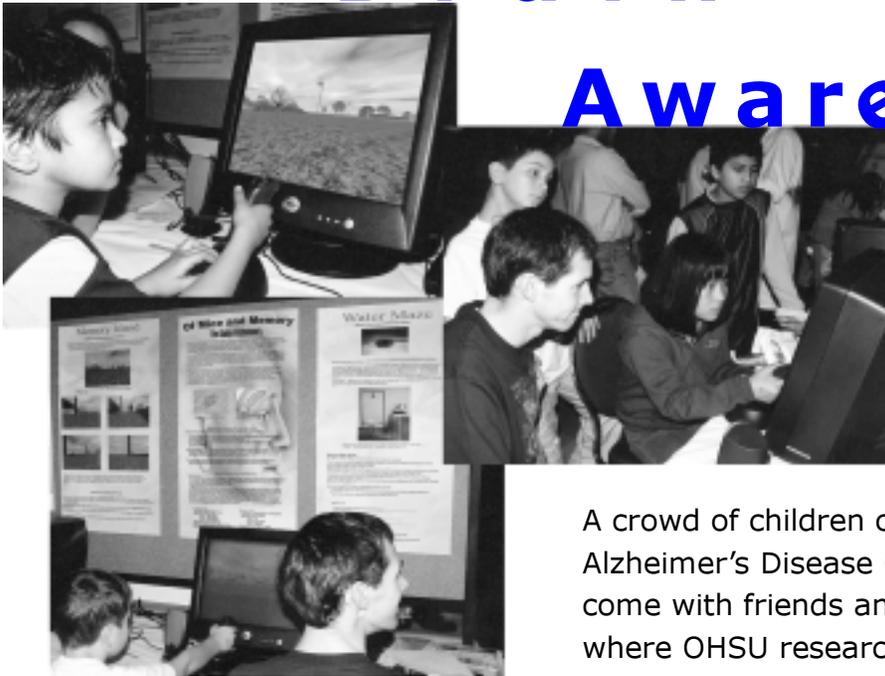
Memantine is a medication that is used only when prescribed and monitored by a medical provider. The medication is in tablet form, started at a low dose to minimize side effects, and gradually increased over time. The medical provider will oversee treatment to assess effectiveness and tolerance.

Alzheimer's disease is a complex illness. It is involvement of people and families affected by the illness in research that makes new treatments possible. Treatment may not be a cure, but it can still be valuable in improving the quality of life of the person affected, and decreasing the burden of family, friends, and others involved with them.

# Brain

# Awareness

# Week, 2004



A crowd of children collected around the Layton Aging & Alzheimer's Disease Center's display on March 14. They had come with friends and family to OMSI's yearly Brain Fair, where OHSU researchers were presenting displays designed to spark children's scientific interest.

The Layton Center's display, "Of Mice and Memory," encouraged visitors to explore their spatial memories using a joystick. The visitors navigated across Memory Island, a virtual environment designed by the lab of Dr. Jacob Raber. The players' task was to remember the location of a previously marked object. The game attracted old and young alike.

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## **New driving law in effect**

Katherine Wild, Ph.D.  
Assistant Professor, Neurology

A new law governing the reporting of impaired drivers is being phased in around the state, and will be in effect in all counties by June 1 of this year. Based on a law passed by the Oregon State Legislature in 2001, physicians and other health care providers will be required to report to DMV any "severe or uncontrollable" physical or mental impairments that may impede one's ability to drive safely. These reporting requirements are not based on age or medical diagnosis, and are intended to help health care providers focus on specific problems that may pose a risk.

Because of the wide range of impairments and rates of progression in Alzheimer's disease, the new regulations were intended to allow those

with AD who are still competent drivers, to keep their driving privileges as long as they remain safe behind the wheel. But when changes in vision, reaction time, or judgment, begin to affect the skills required for driving, a report to DMV will start a process that may result in suspension of the driver's license.

What are some of the signs of unsafe driving to be aware of? The majority of accidents involving older drivers occur at intersections. If someone you know is having difficulty judging when it is safe to make a left turn across oncoming traffic, it may be time for a re-evaluation by the DMV. Other common problem areas include failure to check your "blind spot" when changing lanes, drifting into other lanes, failure to yield right of way, and failure to observe traffic signs or signals. Some warning signs of unsafe driving may be an increasing number of citations or warnings, occasional "fender benders," or becom-

ing unusually flustered or irritated in heavy traffic.

If a family member is concerned about a loved one's driving competence, he or she can utilize the voluntary reporting system of the DMV by completing a Driver Evaluation Request form, available from any local field office. The DMV will then contact the driver either for re-testing or to require a medical examination. Based on test results, the DMV will make recommendations about the person's ability to continue driving.

The DMV has launched a campaign called "Shifting Gears in Later Years" to familiarize the public with their new reporting system. For more information, log on to their website at [www.oregonsafemobility.org](http://www.oregonsafemobility.org). All reporting forms are available at this site.

Alternatively, a Driver Rehabilitation Specialist can assess driving safety for a fee. Typically, these evaluations are not reimbursed by Medicare or private insurance. To locate a driver rehabilitation specialist in your area, contact the Association for Driver Rehabilitation Specialists, 1-800-290-2344.

### **Mouse Model Genetics Study Identifies Early Gene-markers of Alzheimer's Disease**

P. Hemachandra Reddy, Ph.D., Assistant Scientist, Principal Investigator of Neurogenetics Laboratory at the Neurological Sciences Institute, West Campus, OHSU

A major research project under way in the Reddy laboratory is investigating how genes are expressed in brain cells during the progression of Alzheimer's disease. The focus of this research is on a mouse model of Alzheimer's disease.

To determine early cellular changes connected to Alzheimer's disease, Reddy's laboratory studied mice that express human mutated amyloid precursor protein. Animal tissue was provided from the lab of Dr. Joseph Quinn of the Oregon Alzheimer's Disease Center and the study was carried out in collaboration also with scientists at the Gene Expression Core Facility, the

OHSU Department of Neurology, and Portland Veteran Affairs Medical Center. The genetically-altered mice produce heightened levels of amyloid precursor protein. Over time, higher than normal levels of this protein can result in structures in the brain called beta amyloid plaques. By studying 11,283 mouse genes and using a gene chip technology called microarray, Reddy's laboratory was able to identify a much smaller set of distinct genes that functioned differently in the diseased mice from those in healthy mice. These genes are involved in mitochondrial energy metabolism and programmed cell death.

"We studied gene expression levels at three distinct stages of disease progression in the genetically-altered mice relative to age-matched wild-type normal mice," explained Reddy. "We conducted gene expression analysis long before (2 months of age), immediately before (5 months) and after (18 months) the appearance of beta amyloid plaques. In doing this, we found that these mitochondrial genes were more active at 2 months of age when compared to normal mice, and in some cases their activity heightened as the disease progressed. We believe the abnormal gene expression comes in response to beta amyloid-induced mitochondrial dysfunction, even in its early stages.

"Prior research has linked Alzheimer's to mitochondrial function. However this is the first time genes that are responsible for early cellular change in Alzheimer's disease pathogenesis have been identified", said Reddy. If humans consistently show similar abnormal mitochondrial gene expressions at early stages, the discovery could lead to a test for early detection of Alzheimer's in humans.

The research was supported by the National Institute on Aging, the Alzheimer's Association of Oregon, the Medical Research Foundation of Oregon, the American Federation for Aging Research, the Layton Aging and Alzheimer's Disease Center at OHSU, and an Advanced Research Career Development Award provided by the Department of Veterans Affairs. This research has been published in the last week of April, 2004 in *Human Molecular Genetics* (Advance Access).

**Title:** Study of the Effects of Fish Oil & Alpha Lipoic Acid in Mild Alzheimer's Disease

**IRB #:** 8065

**Sponsor:** National Institute on Aging (NIA)/National Institute of Health (NIH)

**Principle Investigator:** Dr. Lynne Shinto

**Length:** 12 months

**Visits:** Six one-half to 3 hour visits over 12 months at the Layton Aging and Alzheimer's Disease Center located at Oregon Health & Science University

**Purpose:** The purpose of this study is to determine the effects of fish oil alone and fish oil plus alpha lipoic acid on substances in the blood that are associated with the progression of Alzheimer's disease. We will also determine the safety of using fish oil alone and fish oil plus alpha lipoic acid in AD.

**Study Design:** Two thirds (67 percent) of the study participants will be assigned to receive either an active supplement of fish oil alone or fish oil combined with alpha lipoic acid; one third (33 percent) of the study participants will be assigned to a placebo (inactive pill). Participants will be assigned at random, like the roll of a dice.

### **Seeking Volunteers**

- \* 55 years of age or older
- \* Diagnosed with probable AD and having mild cognitive impairment
- \* Able to speak English
- \* Not on lipid lowering medication
- \* Not on omega-3 (e.g. fish oil, cod liver oil, flax seed oil, evening primrose oil) and lipoic acid supplementation
- \* Does not consume fish (e.g. tuna, herring, salmon, sardines, others) more than two times a week.
- \* Having a general health status that will not interfere with his/her ability to complete the study
- \* Has a study partner willing to accompany him/her to visits and complete informant-based assessments
- \* Not enrolled in another study

**Study Care:** All study related visits, laboratory tests, and supplements will be provided at no cost.

**Contact:** Sara Baldauf-Wagner at (503) 494-3549, Oregon Health & Science University. Callers will be given an initial qualifying screen over the phone.



**Layton Aging & Alzheimer's Disease Center**

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**Will omega-3 fatty acids and antioxidants slow the progression of Alzheimer's disease?**

This is a key research question underlying a pilot study by Lynne Shinto, ND, principal investigator of a pilot study funded by the National Institutes of Health looking at the effects of omega-3 fatty acids and alpha lipoic acid in mild Alzheimer's disease (AD). The study will determine if fish oil alone or fish oil plus alpha lipoic acid can decrease blood markers of oxidative stress, inflammation, and lipid levels in people diagnosed with AD. These markers have been associated with the disease process in AD. Fish oil and alpha lipoic acid contain anti-oxidant, anti-inflammatory and lipid lowering properties. The omega-3 fatty acids found in cold watercold-water fish, such as salmon, mackerel, and tuna, have been found to

be anti-inflammatory and decrease lipid levels. Alpha lipoic acid, which is found in foods such as broccoli, eggs, and certain types of meats, is a strong antioxidant.

As more people are diagnosed with AD, slowing down the progression of the disease is of high priority. This is a double blind placebo controlled pilot study that will enroll 39 individuals diagnosed with mild AD for a 1-year treatment.

**If you are interested in learning more about research and clinical drug trials at the Layton Aging & Alzheimer's Disease Center, check our web site (<http://www.ohsu.edu/research/alzheimers>) or call Joyce Lear at (503) 494-7615.**