

# THE SCIENCE OF AGING

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// An Institute on Aging Newsletter

## Dissociation of tau pathology and neuronal hypometabolism within the ATN framework of Alzheimer's disease

While both amyloid (A) and tau (T) are hallmark pathologies associated with Alzheimer's disease (AD), tau is better correlated to neurodegeneration (N). However, tau and neurodegeneration have complex regional relationships in part related to non-AD factors that influence neurodegeneration.

In a recent study, Penn Medicine Researchers used machine learning to account for Alzheimer's Disease heterogeneity using two radioactive diagnostic agents, 18F-flortaucipir and 18F-fluorodeoxyglucose, in positron emission tomography (PET) as markers of tau (T) and neuronal hypometabolism (NM) -- decreased brain glucose consumption that is associated with cognitive decline -- in 289 symptomatic patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The team identified differing patterns of resilience and vulnerability in 6 T/NM clusters.

Their findings showed that groups resilient to tau had less hypometabolism than expected and displayed better cognition than a "canonical group" while groups with apparent greater susceptibility to tau had more hypometabolism than expected and exhibited worse cognitive decline, with imaging and clinical measures suggestive of concomitant non-Alzheimer's disease (AD) comorbidities. The observed T/Nm mismatch suggests distinct imaging signatures with pathobiological and prognostic implications for AD.

"One of the most vexing problems in developing therapeutics for Alzheimer's Disease is its marked heterogeneity, particularly with regard to the rate of progression and the presence of concomitant pathologies, for example, vascular disease or other neurodegenerative conditions that commonly co-occur with Alzheimer's Disease," said David A. Wolk, MD, IOA Co-director and a lead author on the study. "This work provides a template to account for differences in these co-pathologies and relative resilience to Alzheimer's Disease that may allow for more targeted therapies and enhanced design of clinical trials to account for heterogeneity."

// This study was published in *Nature Communications*.

## A LOOK INSIDE

### MEET THE IOA CO-DIRECTORS

A Q&A with David A. Wolk, MD and Edward B. Lee, MD, PhD

### TRANSCRANIAL MAGNETIC STIMULATION FOR APHASIA

### LOOKING AT THE LINK BETWEEN INFLAMMATION AND DEPRESSION IN OLDER ADULTS

### MAPPING THE PATH OF ALZHEIMER'S DISEASE



Institute on Aging  
UNIVERSITY OF PENNSYLVANIA



David A. Wolk, MD



Edward B. Lee, MD, PhD

### What is your vision for the IOA going forward?

**Dr. Wolk:** The core principle of improving the health of older adults remains in my current vision. I see the IOAs role as being a facilitator and promoter of highly impactful research that can be translated into clinical practice. This will be done by identifying gaps in expertise or new technologies that we want to bring to Penn, facilitating interactions and collaborations between investigators already at Penn with an eye towards those in different disciplines where synergies can occur, and by creating an environment where ideas are exchanged and transmitted to our next generation of researchers.

### Aside from neurodegeneration, what do you think are the most important issues that need to be addressed in the area of aging right now? And how, if at all, do you see this evolving in the next several years?

**Dr. Lee:** It is vitally important to uncover the fundamental mechanisms that lead to the generalized decreased physiologic function of cells and organs that occurs during the aging process. Understanding these basic mechanisms will have profound implications in understanding all aging related diseases.

### What research advances or recent discoveries are you most excited or hopeful about right now?

**Dr. Wolk:** Within the neurodegenerative field I am very excited about a number of advances, including the explosive growth in our knowledge of genetic and epigenetic factors associated with Alzheimer's Disease and Related Dementias (ADRD) that are pointing to new mechanisms, the development of numerous new biofluid and imaging biomarkers, including those in the blood, that will revolutionize not only how we diagnose disease, but enhance our ability to effectively test new drugs, and the number of new therapeutic interventions that are in various phase of study that have a panoply of targets driven by new discoveries in the biology of ADRD.

### Are there are particular centers or institutes that you would like to see the IOA collaborate with more closely?

**Dr. Lee:** There are so many opportunities at Penn. We already have relationships with some centers such as the Center for Brain Injury and Reserve, Center for Clinical Epidemiology and Biostatistics, the Population Aging Research Center, the Penn Medicine Translational Neuroscience Center, Mahoney Institute for Neurosciences, and others. We have been participating in a "listening tour" to meet various Institute/Center/Department leaders to better understand what the research landscape and there are collaborative opportunities that I did not realize existed and I think aging/neurodegeneration touches on many fields including DNA damage (Penn Center for Genome Integrity), epigenetics (Penn Epigenetics Institute), immunology (Institute for Immunology), translation (Institute for Translational Medicine and Therapeutics) and others. I hesitate to limit this list because I think there can be fruitful interactions with essentially every other center/institute at Penn.

### What are your thoughts on the public's knowledge and awareness of neurodegenerative conditions? Is this an area you think the IOA can expand upon?

**Dr. Wolk:** It is remarkable how much more awareness and sophistication the public has about Alzheimer's Disease and Related Dementias over the last decade or longer. When we have public events, the questions have become increasingly more informed and challenging! A lot of this is credit to outreach at many institutions such as our own and the growing awareness of the public health crisis caused by our aging demographics. That said, with the rapid way neurodegenerative research is evolving, there needs to be an active dialogue with the public and the Penn IOA has an important role in disseminating this knowledge. We plan for the IOA to continue its strong communication presence to allow the public to learn about many of the exciting research areas being pursued at Penn and beyond, as well as the importance of clinical research to translate these discoveries into practice which requires an engaged public. Additionally, we will continue to increase efforts to reach communities that have traditionally had less access to these research discoveries which we hope will help in ultimately reducing disparities in care.

### What inspired you to focus your research/work on neurodegenerative diseases?

**Dr. Lee:** I have always found science to be fascinating, and particularly found the brain to be a remarkable organ that interprets the environment around us and controls everything we choose to do. Much of my life has been dependent on using my brain to think about science and health, and so I have a hard time thinking about what would happen if I lost my brain function. Knowing the impact that neurodegenerative diseases have on individuals, families, and caretakers, I could think of no better topic to concentrate my research efforts. Being able to give answers to families affected by aging-related neurodegenerative diseases has been the most satisfying aspect of what I do.

David A. Wolk, MD, and Edward B. Lee, MD, PhD, have been named Co-Directors of the Institute on Aging, succeeding Dr. John Q. Trojanowski.

Dr. Wolk, who serves as director of the Penn Alzheimer's Disease Research Center (PADRC) and co-director of the Penn Memory Center, is Professor of Neurology and Chief of the Division of Cognitive Neurology. Dr. Lee, who is the PADRC co-associate director, is an Associate Professor in the Department of Pathology and Laboratory Medicine. In their new roles as IOA co-directors, Dr. Wolk will serve as Director of Clinical Research and Dr. Lee will serve as Director of Mechanistic Research. Their combined leadership marks the beginning of new era in aging related research at Penn that will further enhance multidisciplinary collaborations and accelerate translational impact.

## PENN MEDICINE RESEARCHERS STUDY TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR APHASIA

Aphasia -- the loss or impairment of the ability to speak or write -- results from damage to the area of the brain that controls language expression and comprehension as a result of a stroke, brain tumor, infection, head injury, or dementia. While the only current treatment for patients with aphasia is speech and language therapy, Penn's Brain Science, Translation, Innovation, and Modulation (brain-STIM) Center is studying another potential option, transcranial magnetic stimulation (TMS).

TMS, which is already FDA approved to treat major depression and pain associated with migraines, is a non-invasive procedure using electromagnetic pulses to stimulate nerve cells in the brain.

"Our research, which is currently under a phase II clinical trial, shows promising evidence that when we use TMS to target the damaged areas of a patient's brain that is causing aphasia, the brain is able to recruit different, healthy parts of itself, and create new pathways, bypassing the injured area,"

explained Roy Hamilton, MD, MS, an associate professor of Neurology and Physical Medicine and Rehabilitation, and director of the brain STIM Center in a Penn Medicine news blog.

According to the blog, current findings sound promising but it will likely still be some time before TMS is an approved and widely adopted treatment for aphasia. "Each person's brain reorganizes differently after a stroke or other injury," said Dr. Hamilton. "Part of our research in the brainSTIM Center is an attempt to gain a fundamental understanding of how stimulation affects the brain, and what underlying properties make it more likely that one part of the brain will take on the function of the damaged area of the brain." His hope is that their findings will allow them to take a precision medicine approach and tailor treatments to individual needs.

// A PENN MEDICINE NEWS BLOG BY KELSEY ODOROZYK

RESEARCH @ PENN



## PENN MEDICINE STUDY FINDS INFLAMMATION IS NOT ALWAYS LINKED TO DEPRESSION IN OLDER ADULTS

Multiple prior studies have found higher levels of inflammation in older individuals with depression. Now, a new Penn Medicine study has found that clinically depressed older individuals, on average, don't have elevated levels of inflammation if they don't already have other inflammatory conditions such as arthritis.

The new study, published in Nature Translational Psychiatry, suggests that depression occurs independently of inflammation for many older adults. Furthermore, depression-inflammation links are due to the greater incidence of inflammatory conditions, which in general are common in older people.

"It is still true that inflammatory illnesses can contribute to depression, but our findings suggest that there is a subset of individuals with late-life depression who do not have elevated levels of inflammation," said study senior author Yvette Sheline, MD, McLure Professor of Psychiatry and

Behavioral Research in the Perelman School of Medicine at the University of Pennsylvania. The study therefore suggests that, in many older adults, depression occurs independently of inflammation, and probably won't be alleviated by anti-inflammatory treatments unless inflammation is present in addition to depression.

The researchers note, however, that because their study excluded late-life depression patients who have inflammatory disorders, it leaves open the possibility that inflammation from such disorders can contribute to depression. "Our study supports the view that depression consists of different sub-categories, some with inflammation and some without," said Sheline, who is also director of Penn's Center for Neuromodulation in Depression and Stress. "People who have depression should consult with their doctor to see if they have other illnesses that could cause inflammation, since there is evidence that increased inflammation can cause depressive symptoms."

// A PENN MEDICINE NEWS RELEASE BY HANNAH MESSINGER

## MISSION

The mission of the Institute on Aging (IOA) at the University of Pennsylvania is to improve the health of older adults by increasing the quality and quantity of clinical and basic research as well as educational programs focusing on normal aging and aging-related diseases across the entire Penn campus.

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## LEARN MORE

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# PENN'S 'HIPPOCAMPUS GANG' MAPS POSSIBLE PATHS OF ALZHEIMER'S

Your brain is like a road map. Information travels between areas through different routes, or networks of brain cells. For individuals with Alzheimer's disease, this travel can become difficult. A team of researchers at the Penn Memory Center (PMC) is striving to understand the networks of the medial temporal lobe (MTL) in people living with Alzheimer's.

"Ultimately, this may allow for insights of disease mechanisms that will hopefully help in developing more targeted therapies," said PMC Co-Director and leader of the study, Dave Wolk, MD.

Their study, which is based off of data from over five hundred individuals, has three primary aims: 1) to distinguish the anterior-temporal (AT) network and posterior-medial (PM) network, 2) evaluate how they deteriorate, and 3) compare different protein levels within them.

"This was a really complex and comprehensive study which involved brain scans from both our Aging Brain Cohort and the Alzheimer's Disease Imaging Initiative," said Dr. Wolk. Using different forms of imaging, such as MRI and PET, the team concluded that the AT and PM networks are distinct from one another.

"What's exciting about these data is that they provide imaging support for the idea that memory is supported by dissociable systems, or networks, which are highly connected brain structures that support different aspects of memory," said Dr. Wolk.

When comparing networks, researchers found that if one part of either the AT or PM network was deteriorating, other distant regions within that respective network were more likely to be deteriorating too. The team also found that tau protein levels are higher in the AT network and amyloid is higher in the PM network.

"This supports the notion that the pathology of Alzheimer's disease spreads along connected brain regions, consistent with theories from animal models, and provides evidence for differences in how tau and amyloid spread in the brain," said Dr. Wolk.

This publication is the first long-term study of MTL networks, and is a next step to creating more specific treatments for AD in the future.

// A PENN MEMORY CENTER ARTICLE BY MEGHAN MCCARTHY



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