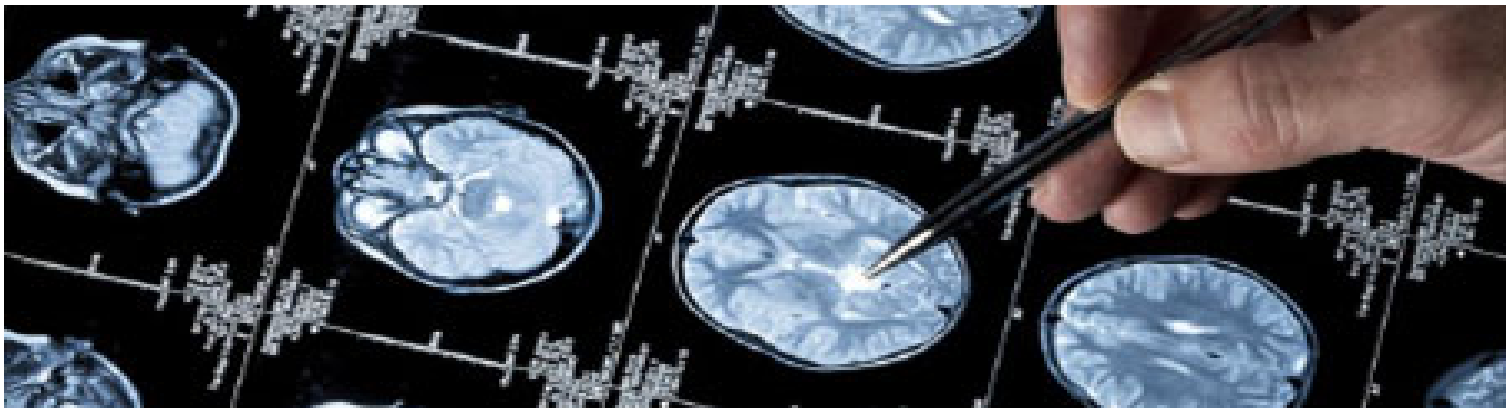
Yale Alzheimer's Disease Research Center (ADRC)



The Yale Alzheimer's Disease Research Center is one of a network of 32 centers across the United States funded by the National Institute on Aging. These centers bring together experts in the field to learn more about how Alzheimer's disease occurs, what manifestations it has, how to diagnose it, and how to treat it. For more details about the Yale ADRC and ADRC programs in general, please go to our website at **httsp://medicine.yale.edu/adrc/.** In this newsletter, we will highlight some of the exciting new studies being conducted by investigators at the Yale ADRC.

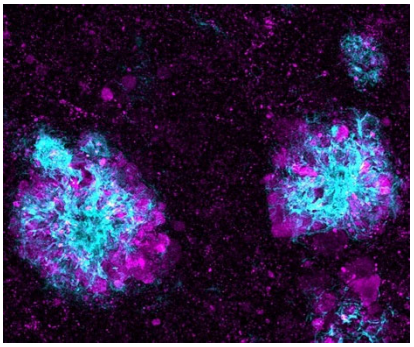


Image: Amyloid beta in blue and lysosomes in magenta

Title: Axonal Lysosome Dysfunction in Alzheimer's Disease

Investigators: Shawn Ferguson, Jaime Grutzendler, Pietro De Camilli

The goal of this research is to understand the relationship of amyloid plaques to lysosomes in surrounding nerve cells. Amyloid plaques are a characteristic feature of Alzheimer's disease (AD). These abnormal protein aggregates are surrounded by swollen axons of nerve cells. Such swellings contain numerous lysosomes. Lysosomes are normally involved in breaking down and recycling damaged proteins in the cells. However, the axonal lysosomes around amyloid plaques are lacking in degenerative activity. Why these lysosome-filled axonal swellings occur and whether they play a role in the symptoms or progression of AD are among the questions being addressed in this study. Once the mechanisms are better understood, interventions can be developed and tested in mouse models. Hopefully, this will eventually lead to new strategies to prevent and treat AD in humans.

Publications:

Gowrishankar S, Yuan P, Wu Y, Schrag M, Paradise S, Grutzendler J, De Camilli P, Ferguson SM. Massive accumulation of luminal protease-deficient axonal lysosomes at Alzheimer's disease amyloid plaques. Proc Natl Acad Sci U S A 2015;112(28):E3699- 3708.

Gowrishankar S, Wu Y, Ferguson SM. Impaired JIP3-dependent axonal lysosome transport promotes amyloid plaque pathology. J Cell Biol.2017;216(10):3291-305. doi:10.1083/jcb.201612148. PubMed: 28784610.

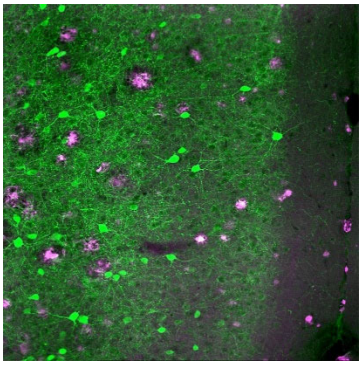


Image: Amyloid deposits (magenta) in a mouse model of Alzheimer's

Title: The role of cortical GABAergic neurons in Alzheimer's disease

Investigators: Alex Kwan, Marina Picciotto, Jamie Grutzendler

Problems with attention negatively affect the quality of life for AD patients, but why these problems occur is unclear. In mouse models, excitatory nerve cells are overactive near amyloid plaques, which might affect information processing and behavior. This study will explore how the circuitry and signaling among nerve cells may contribute to these changes and whether changing the signaling can improve symptoms.

References:

Siniscalchi MJ, Phoumthipphavong V, Ali F, Lozano M, and Kwan AC. Fast and slow transitions in frontal ensemble activity during flexible sensorimotor behavior. Nature Neuroscience, 19, 1234-1242 (2016).

Yuan P, and Grutzendler J. Attenuation of β-amyloid deposition and neurotoxicity by chemogenetic modulation of neural activity. Journal of Neuroscience, 36, 632-641 (2016).

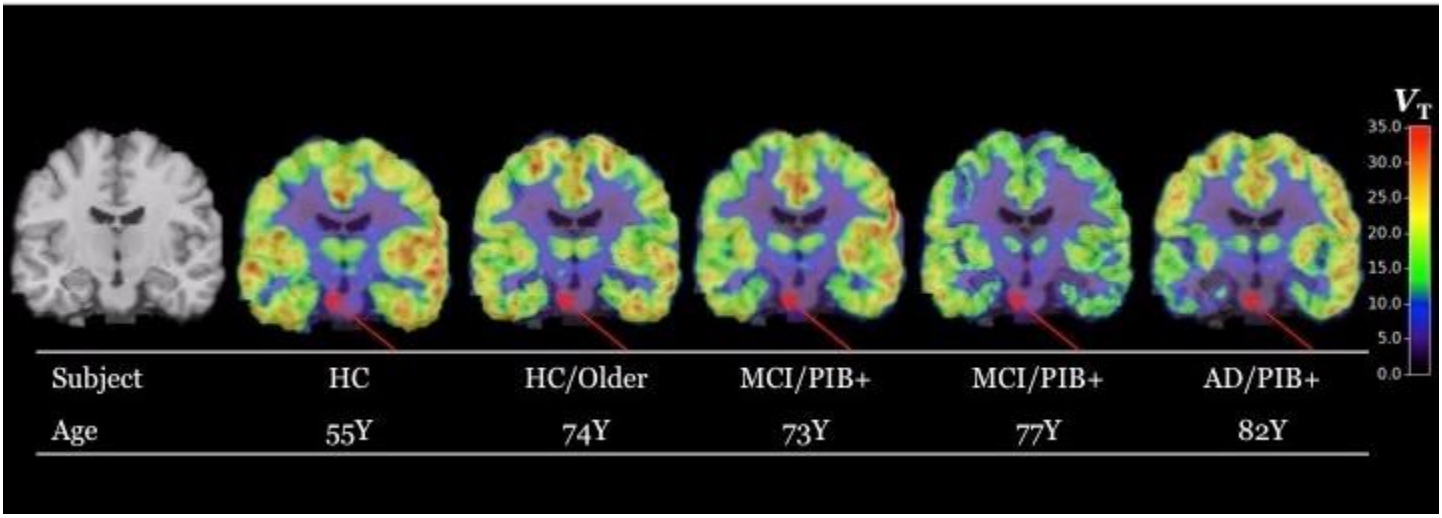


Image: Brain PET images in healthy controls, MCI, and AD

Title: Brain PET Imaging of Synaptic Density in Alzheimer's Disease

Investigator: Ming-Kai Chen, MD, PhD

The purpose of this study is to investigate a new way of diagnosing AD by using Positron Emission Tomography (PET) scans and a novel compound that bind to a biomarker that indicates how dense brain cell connections are. AD brains should have fewer connections. These images will be compared to measures of brain metabolism, which should also be lower in areas with fewer connections. Individuals with AD will be compared to those with mild cognitive impairment and to healthy controls of the same age.

Thank you for your interest in the Yale ADRC. For more information on our studies or to participate in studies please call or visit our website.

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