Quarterly news and updates from the
Stanford Alzheimer's Disease Research Center
and the Healthy Brain Aging Study

2022 Summer Issue

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MIND MATTERS

Updates in Research

Members of the Stanford ADRC have presented at several international and regional conferences this summer. The Bay Area Alzheimer's Researchers' Symposium took place on August 19th, drawing together researchers across institutions in Northern California. Dr. Beth Mormino, Imaging Core Lead, presented "Beyond Amyloid: APOE effects in clinically unimpaired cohorts", building on work in collaboration with postdoctoral scholar Dr. Ali Trelle. Additionally, Dr. Christina Young, instructor, presented "Divergent Cortical Tau PET patterns among patients with preclinical Alzheimer's Disease".

Drs. Christina Young and Yann Le Guen were amongst 7 recipients of the Young Investigator Award presented at this symposium.

Drs. Yann Le Guen and Christina Young

At the beginning of August, the Imaging Core group also presented at the Alzheimer's Association International Conference in San Diego to an international audience of researchers. Dr. Beth Mormino conducted an oral session entitled, "APOE2 is associated with amyloid independent effects on tau PET signal in preclinical Alzheimer's Disease". Dr. Christina Young presented "Short-term cognitive practice effects and their relation to amyloid and tau in preclinical Alzheimer's disease." This talk was focused on work showing that baseline computerized cognitive composite (C3) performance was related to both amyloid and tau burden in clinically unimpaired older adults. C3 practice effects over a month and a half captured additional unique information about tau burden in preclinical Alzheimer's disease. Together, these results show that computerized cognitive testing can be repeated over short follow-up periods to provide insight into early disease processes of Alzheimer's disease. Dr. Tammy Tran, postdoctoral scholar, also presented a poster entitled, "Hippocampal CA1 volume is associate with higher p-tau and diminished memory performance in normal older adults".

Presenting at these conferences furthers Stanford's participation in the world of cutting edge Alzheimer's research. We are grateful for the opportunity to be sharing our discoveries on the global stage.

Save the date

2022 Walk to End Alzheimer's—Silicon Valley

Join the Alzheimer's Association on **Saturday, October 15th, 2022** for their annual Walk to End Alzheimer's. Click here for more information and to register

5th Annual Participant Appreciation Day (Zoom Webinar)

Join us on **Wednesday, November 2nd, 2022** from **1:00 PM to 4:30 PM PDT** for our Annual Participant Appreciation Day. More details will be provided closer to the date

ADRC CORES

Data Management and Statistics Core (DMS)

The Data Management & Statistics Core of the Stanford Alzheimer's Disease Research Center (ADRC), is responsible for managing large volumes of clinical, neuropsychological, genetic, imaging, tissue biomarker, and associated research data. The Core provides anonymous data to the National Alzheimer Coordinating Center, National Centralized Repository for Alzheimer's disease, and to qualified researchers at Stanford and other universities. The DMS Core also processes requests for biomarker, clinical, neuropsychological, imaging, and basic demographic de-identified data from investigators within and external to the university. Please see "request for resources" link at: https://med.stanford.edu/adrc/researcher-resources.html

Core faculty work closely with other ADRC Cores in support of Center goals. They offer biostatistical consultation, support "big data" research using ADRC data, promote research on biostatistical methods tailored to ADRC data, provide statistical consultation to ADRC participating investigators, and offer biostatistical training for junior investigators.

The DMS Core is led by Lu Tian, ScD. Other faculty and staff members who are a part of DMS core include Zihuai He, PhD, Associate Core Leader; Serena Young, PhD; Janet Hwang, MS; and Amy Lin, MPH.

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ADRC SPOTLIGHT

Zihuai He, PhD
Assistant Professor of Neurology and Medicine (BMIR)
Data Management & Statistics Core Associate Leader

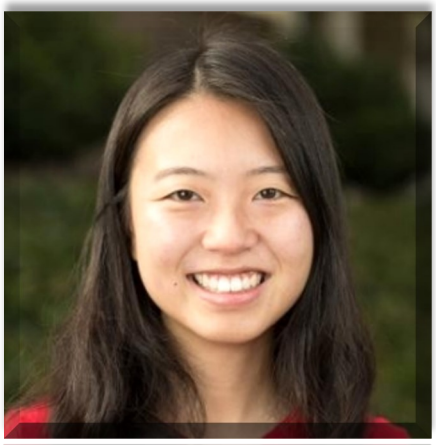
Large and complex data sets now drive nearly every aspect of science and discovery. Our focus is on the development of novel machine learning methods to rigorously identify causal features of AD, and to translate the discoveries into mechanistic insights and drug targets for the development of new AD therapies. Since genetic factors play an important role in the development of late-onset AD with heritability estimates of 58% to 79% (AD phenotypic variation due to genetic variation), we proposed to develop novel feature selection methods to detect and localize rare and common causal genetic variants of AD. This work led to a National Institutes of Health (NIH) sponsored R01 award (2019-2024). In an application to nine large scale AD genetic studies, we identified 31 new risk loci that were missed by existing analytical methods with ~70% of the proximal genes at these loci being validated in the scRNA-seq or proteomics analyses. The proposed feature selection framework has been published as a series of papers in high impact journals like *Nature Communications*, *The American Journal of Human Genetics* and *Nature Machine Intelligence*. Notably, our work that is to appear in *Nature Machine Intelligence* is the first to embark on deep learning methods to genetic data that can robustly detect putative causal variants of AD. We believe that these methods will significantly improve our understanding of the genetic architecture of AD and, critically, provide a credible set of well-defined, novel targets for the development of genomic-driven therapies.

He, Z., Liu, L., Wang, C., Le Guen, Y., Lee, J., Gogarten, S., Lu, Fred., Montgomery, S., Tang, H., Silverman, E., Cho, M.H., Greicius, M.D., Ionita-Laza, I. (2021). Identification of putative causal loci in whole-genome sequencing data via knockoff statistics. *Nature Communications*, 12(1), pp.1-18.

He, Z., Le Guen, Y., Liu, L., Lee, J., Ma, S., Yang, A.C., Liu, X., Rutledge, J., Losada, P.M., Song, B., Belloy, M.E., Butler III, R.R., Longo, F.M., Tang, H., Mormino, E.C., Wyss-Coray, T., Greicius, M.D., Ionita-Laza, I. (2021). Genome-wide analysis of common and rare variants via multiple knockoffs at biobank scale, with an application to Alzheimer disease genetics. *The American Journal of Human Genetics*, 108(12), pp.2336-2353.

Kassani, P.H., Lu, F., Guen, Y.L. and He, Z. (2022). Deep neural networks with controlled variable selection for the identification of putative causal genetic variants. *Nature Machine Intelligence,* in press.

ADRC SPOTLIGHT



Serena Yeung, PhD
Assistant Professor of Biomedical Data Science

The Yeung group's research is focused on developing computer vision algorithms to interpret and analyze biomedical image and video data. With the ADRC, we are developing computer vision and deep learning algorithms to modernize the neuropathologic evaluation of Alzheimer's disease and related dementias. Specifically, we are working with neuropathologist and ADRC REC fellow, Dr. Jeff Nirschl, to investigate Alzheimer's disease and Lewy body disease, which often occur together but the shared molecular pathways are unclear. In a complementary line of work, we are developing computer vision and deep learning algorithms to annotate and model subcellular structures in 3D cryo-electron microscopy (EM) tomograms of neurons in Huntington's disease. We are using these automated techniques to quantitatively characterize these structures and how they change across different disease states. This can provide insight into mechanisms underlying the disease process and provide bases for novel pathways of therapeutic targeting. These data and workflows could also open the opportunity for broader application of cryo-EM technologies to other neurodegenerative diseases.

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Additional Opportunities to Participate in Research

Stanford ADRC Affiliated Studies

Study: Healthy Brain Aging Study **Study status:** Open, enrollment ongoing

Contact: Isabelle Yi isayi@stanford.edu or (650) 721-2409

Study: Alzheimer Gut Microbiome Project **Study status:** Open, enrollment ongoing

Contact: Veronica Ramirez vramirez1@stanford.edu or (650) 721-5354

Study: Sleep and Physical Activity Study **Study status:** Open, enrollment ongoing

Contact: Joseph Winer jwiner@stanford.edu

Study: Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) **Study status:** Open, enrollment ongoing

Contact: Savneet Takhar sktakhar@stanford.edu or (650) 304-7428

Contact: Stephanie Tran trans@stanford.edu or (650) 521-7287

Study: Asian Cohort Study **Study status:** Open, enrollment ongoing

Contact: Veronica Ramirez vramirez1@stanford.edu or (650) 721-5354

Study: Neighborhoods Study **Study status:** Open, enrollment ongoing

Contact: Nicole Caceres ncaceres@stanford.edu or (650) 736-2893

Study: Eyes in Alzheimer's Disease and Mild Cognitive Impairment **Study status:** Open, enrollment ongoing

Contact: Moss Lab moss_lab_studies@stanford.edu

Study: Caregiver Study (Auracle) **Study status:** Open, enrollment ongoing

Contact: Dulce Garcia dulce.garcia@stanford.edu or (650) 463-6182

Clinical Trials

Study: Janssen Research & Development (Autonomy Study) **Study status:** Open, enrollment ongoing

Contact: Savneet Takhar shtakhar@stanford.edu or (650) 304-7428

Study: Eisai and NIH (AHEAD 3-45 Study) **Study status:** Open, enrollment ongoing

Contact: Anthony Velasquez anthgv@stanford.edu or (650) 206-0963