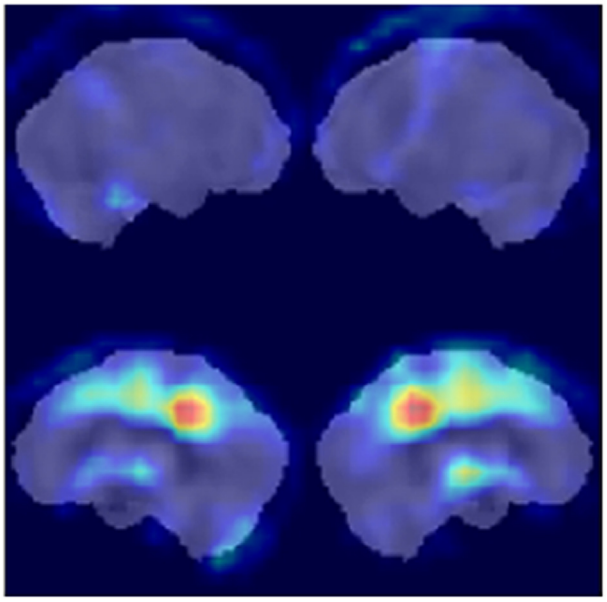
discrimination. Visualization of learning process by guided Grad-CAM revealed that CIS became more focused by the CNN as the training progressed. DLB/AD score was significantly associated with three core-features of DLB. **Conclusions:** Deep learning-based imaging classification was useful not only for objective and accurate differentiation of DLB from AD but also for predicting clinical features of DLB. The CIS was identified as a specific feature during DLB classification. The visualization of specific features and learning process could have important implications for the potential of deep learning to discover new imaging features.



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ADVANCING CLINICAL AND BIOMARKER RESEARCH IN AD: THE LEAD STUDY

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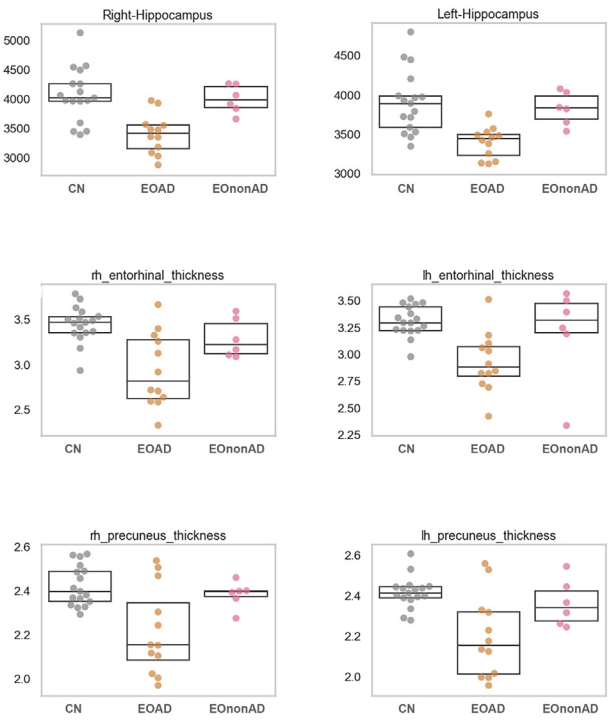
Background: Approximately 5% of the 5.6 million (~280,000) Americans with Alzheimer's disease (AD) develop symptoms at age 65 or younger and are classified as early-onset AD (EOAD). Compared to late-onset AD (LOAD), EOAD patients show lower prevalence of amnestic versus non-amnestic presentations, more rapid cognitive decline, more severe AD pathology and higher heritability. Sporadic EOAD phenotypes are commonly excluded from observational biomarker studies (e.g. ADNI) and therapeutic trials due to their age and atypical presentation. Objective: The goals of the Longitudinal Early-onset AD study (LEADS) are to 1) advance knowledge about EOAD diagnosis, 2) develop sensitive clinical and biomarker tools that capture EOAD progression, 3) establish EOAD site network for interventional studies and 4) explore for novel genetic risk variants.

Table. Demographic Characteristics

	CN	EOAD	EAnonAD	EOADvsCN	EOnonADvsCN
N	16	12	6	-	-
Age	54.6 (6.8)	59.2 (3.6)	56.2 (7.9)	**0.032**	n.s.
Sex (M/F)	7/9	4/8	3/3	n.s.	n.s.
Education yrs	16.1 (2.7)	15.0 (2.8)	15.3 (2.5)	n.s.	n.s.
MMSE	29.1 (0.5)	21.4 (5.0)	25.3 (3.2)	**<0.001**	**0.033**
AmyPos 1.21 (y/n)	0/16	12/12	0/6	**<0.001**	**<0.001**
Tau-PET Available	11/16	10/12	4/6	-	-

Figure 1. Mean hippocampal volume, entorhinal and precuneal thickness



Methods: LEADS will recruit and longitudinally follow approximately 400 amyloid-positive (EOAD), 100 amyloid-negative cognitively impaired subjects (EOnonAD) and 100 age-matched controls. Participants will undergo clinical and psychometric assessments, MRI, amyloid ([18F]Florbetaben) and tau ([18F]AV1451) PET, CSF, DNA, RNA, plasma, serum and peripheral blood mononuclear cells collection at three time points. Methods are harmonized with ADNI and DIAN to facilitate scientific comparisons. **Results:** LEADS enrollment is ongoing. Demographics of the current sample are shown in Table. Figure1 presents mean hippocampal volume as well as the mean entorhinal and precuneal cortical thickness in the 17 CN, 12 EOAD and 6 EOnonAD with available MRI data. Group comparisons projected on Freesusrfer-rendered 3D brain hemispheric models can be seen in Figure 2. Figure 3 presents the mean global amyloid PET SUVR and Figure 4 the mean tau PET deposition by early-, mid- and late-stage Braak regions in 13 CN, 11 EOAD, 6 EOnonAD with both amyloid and tau PET data availability. The latest enrollment and study participant updates will be presented at the meeting. **Conclusions:** LEADS will develop a publicly available natural history biomarker and clinical data set in EOAD and will enable future planning and implementation of clinical trials in EOAD. Successful completion of this project will address several substantial gaps in our understanding of EOAD and AD research in general.

Figure 2. Between group comparison of cortical thickness

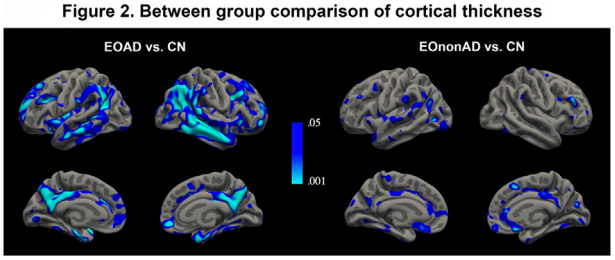


Figure 3. Mean global amyloid PET SUVR by diagnosis

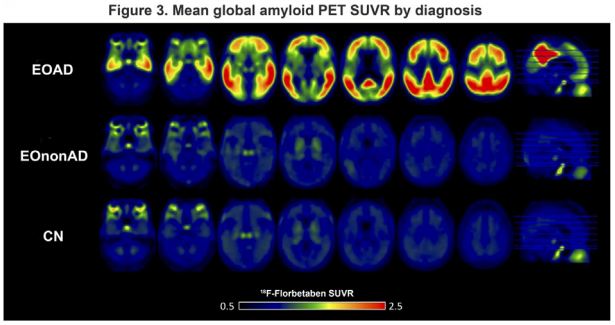
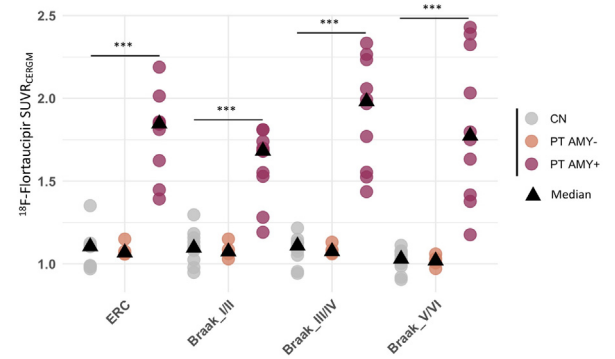


Figure 4. Mean tau PET SUVR in early-, mid- and late-stage Braak regions by diagnosis



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HIPPOCAMPAL INTRINSIC CONNECTIVITY SUPPORTS COGNITIVE RESERVE IN AMYLOID-POSITIVE COGNITIVELY NORMAL SUBJECTS AND ALZHEIMER'S DISEASE PATIENTS

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Background: Cognitive reserve (CR) accounts for maintaining functionality despite brain pathology. Recently, a residual approach was introduced as a more specific measure of CR. This approach considers the variance in cognition not being explained by demographic and neuroimaging predictors as CR measure. Here, we aimed to determine a functional neuronal correlate of CR from resting-state functional MRI (rs-fMRI). **Methods:** 103 cognitively normal subjects (*mean age* 72.01 ± 5.98) and 36 early amyloid-positive Alzheimer's disease (AD) patients (74.08 ± 7.33) were included, for whom neuropsychological data, an amyloid PET, and a rs-fMRI scan were available at the Open Access Series of Imaging Studies (OASIS; https://www.oasis-brains.org/). Information on global amyloid load was assessed based on the Freesurfer-ROIs available in OASIS. Cognition residuals were computed regressing global amyloid, ApoE status, age and sex onto cognitive test performance using an exponential model fit. Positive residuals indicate higher cognitive performance than predicted. Intrinsic connectivity (IC) maps were extracted based on the pre-processed rs-fMRI data using the CONN toolbox. Using general linear modeling in SPM12 ($p < .0001$, *uncor.*), we first examined the voxel-based association between the individual IC maps and the cognition residuals in the early AD group, assuming this group requires a high need for reserve. To determine if the identified neuronal CR correlate extends to the preclinical phase of AD, we extracted the beta values of IC of the identified neuronal CR correlate in the amyloid-positive cognitively normal group (SUVR > 1.1, n=57) and examined the relationship between cognition residuals and IC. **Results:** Only increased IC in the right hippocampus was associated with higher residuals in the early AD group. In the amyloid-positive cognitively normal group, the IC in this area was also correlated with greater residuals ($r=.34$, $p<.05$). The effect of the neuronal correlate and the residuals was stronger in the AD group when comparing both groups in terms of their correlation strengths. **Conclusions:** The findings indicate that intrinsic hippocampal connectivity might