Alzheimer's
Research & Therapy

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Heterogeneous clinical phenotypes of sporadic early-onset Alzheimer's disease: a neuropsychological data-driven approach

Deepti Putcha[1*], Yuta Katsumi[1], Alexandra Touroutoglou[1], Ani Eloyan[2], Alexander Taurone[2], Maryanne Thangarajah[2], Paul Aisen[3], Jeffrey L. Dage[4,5], Tatiana Foroud[5], Clifford R. Jack Jr.[6], Joel H. Kramer[7], Kelly N. H. Nudelman[5], Rema Raman[3], Prashanthi Vemuri[6], Alireza Atri[8], Gregory S. Day[9], Ranjan Duara[10], Neill R. Graff-Radford[9], Ian M. Grant[11], Lawrence S. Honig[12], Erik C. B. Johnson[13], David T. Jones[6], Joseph C. Masdeu[14], Mario F. Mendez[15], Erik Musiek[16], Chiadi U. Onyike[17], Meghan Riddle[18], Emily Rogalski[19], Stephen Salloway[18], Sharon Sha[20], R. Scott Turner[21], Thomas S. Wingo[22], David A. Wolk[23], Kyle Womack[16], Maria C. Carrillo[24], Gil D. Rabinovici[7], Bradford C. Dickerson[1], Liana G. Apostolova[4,5,25†], Dustin B. Hammers[4†] and the LEADS Consortium

Abstract

Background The clinical presentations of early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease are distinct, with EOAD having a more aggressive disease course with greater heterogeneity. Recent publications from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) described EOAD as predominantly amnestic, though this phenotypic description was based solely on clinical judgment. To better understand the phenotypic range of EOAD presentation, we applied a neuropsychological data-driven method to subtype the LEADS cohort.

Methods Neuropsychological test performance from 169 amyloid-positive EOAD participants were analyzed. Education-corrected normative comparisons were made using a sample of 98 cognitively normal participants. Comparing the relative levels of impairment between each cognitive domain, we applied a cut-off of 1 *SD* below all other domain scores to indicate a phenotype of "predominant" impairment in a given cognitive domain. Individuals were otherwise considered to have multidomain impairment. Whole-cortex general linear modeling of cortical atrophy was applied as an MRI-based validation of these distinct clinical phenotypes.

Results We identified 6 phenotypic subtypes of EOAD: Dysexecutive Predominant (22% of sample), Amnestic Predominant (11%), Language Predominant (11%), Visuospatial Predominant (15%), Mixed Amnestic/Dysexecutive Predominant (11%), and Multidomain (30%). These phenotypes did not differ by age, sex, or years of education. The APOE ε4 genotype was enriched in the Amnestic Predominant group, who were also rated as least impaired. Cortical thickness analysis validated these clinical phenotypes with dissociations in atrophy patterns observed between the Dysexecutive and Amnestic Predominant groups. In contrast to the heterogeneity observed from our neuropsychological

†Liana G. Apostolova and Dustin B. Hammers contributed equally to this work as senior author.

*Correspondence:
Deepti Putcha
dputcha@mgh.harvard.edu
Full list of author information is available at the end of the article

data-driven approach, diagnostic classifications for this same sample based solely on clinical judgment indicated that 82% of individuals were amnestic-predominant, 9% were non-amnestic, 4% met criteria for Posterior Cortical Atrophy, and 5% met criteria for Primary Progressive Aphasia.

Conclusion A neuropsychological data-driven method to phenotype EOAD individuals uncovered a more detailed understanding of the presenting heterogeneity in this atypical AD sample compared to clinical judgment alone. Clinicians and patients may over-report memory dysfunction at the expense of non-memory symptoms. These findings have important implications for diagnostic accuracy and treatment considerations.

Keywords Alzheimer's disease, Early-onset, Neuropsychology, Phenotypes, Variants, Cognition, Clinical

Background

Sporadic early-onset Alzheimer's disease (EOAD) is a clinical syndrome defined by symptom onset younger than age 65. It is the most common cause of early-onset dementia. However, EOAD is not simply late-onset Alzheimer's disease (LOAD) manifesting at a younger age. EOAD is often misdiagnosed due to its atypical presentation, resulting in a 1.6-year average delay in diagnosis compared to older-onset AD patients [1]. Patients with EOAD tend to have a more aggressive disease course [2, 3], and are more heterogeneous in terms of the types of clinical features evident at presentation, which may contribute to diagnostic challenges. Previous studies have identified a variety of clinical presentations of EOAD, including a memory-impaired phenotype [4], a language-impaired phenotype known as logopenic variant primary progressive aphasia (lvPPA) [5], a visuospatial-impaired phenotype known as posterior cortical atrophy (PCA) [6, 7], and a behavioral/dysexecutive variant [8, 9]. Further examination of the dysexecutive phenotype with FDG-PET hypometabolism patterns also suggested several subtypes [10], supporting the use of data-driven approaches to understanding phenotypic heterogeneity within AD. A recent large cohort study from our group (e.g., the Longitudinal Early-onset Alzheimer Disease Study; LEADS) reported amnestic predominance (81% of participants) in a large EOAD sample [11], utilizing a diagnostic approach that relied on clinical judgment to classify individuals into four categories: amnestic, non-amnestic, PCA, and PPA.

In addition to clinical presentation, patterns of cortical atrophy also differ between EOAD and LOAD [12]. Studies of cortical thickness in EOAD show greater neocortical atrophy in the posterior lateral temporal, lateral and medial parietal, frontal, and occipital cortex, with less atrophy in the medial temporal lobe (MTL) [13, 14]. Some studies also report preserved MTL thickness and hippocampal volumes compared to healthy older participants [15]. A recent publication from LEADS identified the EOAD signature of cortical atrophy, which included regions of the medial and lateral parietal cortices as well as the posterior lateral temporal cortex, with lesser involvement of the lateral prefrontal cortex and fusiform gyrus [12]. Notably, the authors highlighted the absence of prominent atrophy in the anterior medial and ventral temporal cortices, as is commonly observed in LOAD. These observable differences in MRI-based cortical atrophy patterns between EOAD and LOAD may improve diagnosis of younger patients who may present with a myriad of clinical symptoms and signs attributable to symptomatic AD.

The goals of the current study lie at the convergence of these clinical and neuroimaging observations regarding clinical heterogeneity within EOAD. We aim to complement the current state-of-the-art clinical phenotyping approach using the standard consensus diagnostic process ("clinical judgment") from LEADS by rigorously examining neuropsychological test performance within the LEADS cohort. Using a data-driven approach comparing the severity of impairment across cognitive domains, we hypothesize that we will identify a greater range of phenotypic heterogeneity compared to clinical judgment alone. Further, we expect to observe dissociations in the patterns of cortical atrophy associated with each clinical phenotype.

Methods

Enrolled participants were part of the 18-site multicenter LEADS (www.leads-study.org) cohort [16] comprised of 264 participants with EOAD and 98 cognitively normal (CN) participants. For the purposes of this study, we excluded participants who did not have complete neuropsychological test data that underwent quality control procedures. This resulted in a final sample of 169 EOAD participants (Table 1). Participants were 40–64-years-old at enrollment, fluent in English, in good general health, without other neurological or psychiatric disorders, and had a knowledgeable informant. Because LEADS focuses on sporadic early-onset dementia, impaired individuals with genetic mutations in Amyloid Precursor Protein (*APP*), Presenilin-1 (*PSEN1*) or Presenilin-2 (*PSEN2*), Microtubule Associated Protein Tau (*MAPT*), Chromosome 9

Table 1 Clinical characteristics of Early-onset Alzheimer's Disease (EOAD) and Cognitively Normal (CN) participants

Demographic	EOAD ($n=169$)	CN ($n=98$)
Age	58 ± 3.9	56.3 ± 6.1
Sex (% female)	49.7	57.0
Education (years)	15.5 ± 2.4	16.6 ± 2.3
Race (% White)	94.1	89.5
APOE e4 (% at least one allele)	58.4%	42%
CDR Global	CDR 0 ($n=3$) CDR 0.5 ($n=112$) CDR 1 ($n=54$)	CDR 0
CDR-SB	3.5 ± 1.7	0.02 ± 0.1
MMSE	23.0 ± 4.2	29.2 ± 2.6

CDR Clinical Dementia Rating, *CDR-SB* CDR Sum-of-Boxes, *MMSE* Mini-Mental State Examination, *APOE* apolipoprotein E

Open Reading Frame 72 (*C9ORF72*), or Progranulin (*GRN*) were excluded [17]. Diagnoses within LEADS were made via clinician consensus discussion, though this protocol did not provide standardized guidance [16]. Across sites, this process involved expert clinicians agreeing on a clinical diagnosis using participant- and informant- reports of symptom history and office-based exam findings. In this study we are referring to diagnosis made via this method as "clinical judgment." Cognitively impaired participants had a global Clinical Dementia Rating® (CDR) of 0, 0.5, or 1 at the time of enrollment. CN participants were had a global CDR of 0, were free of cognitive deficits on neuropsychological testing, had low cerebral amyloid based on quantitative analysis of PiB PET data (FLR DVR < 1.2), and had a Mini-Mental State Examination (MMSE; Folstein et al., 1975) score ≥ 24. CN participants were an average of 56.3-years-old ± 6.1 years, had an average of 16.6 ± 2.3 years of education, and were 57% female. Our EOAD sample was comprised of a highly educated (15.5 ± 2.4 years of education), mostly White (94.1%) participant group that was evenly split between males and females (49.7% female) and younger than 65-years (58.9 ± 3.9 years). Most participants were *APOE ε4* carriers (58.4%). All participants were evaluated in the early symptomatic stage of AD (3 cognitively impaired participants were rated with a global CDR of 0, 112 participants were rated with a global CDR of 0.5, and 54 participants were rated with a global CDR of 1). The 3 participants who were rated with a global CDR of 0 represented focal syndromes (primary language or visuospatial deficits) and as such had little global functional impairment at this stage that is measurable on the standard CDR. As a whole group, the average MMSE score was mildly impaired (23 ± 4.2 points).

Institutional Review Board approval was obtained through a central review board overseen by Indiana University. Written informed consent was obtained from study participants or authorized representatives. LEADS participants received a standard clinical assessment including medical and family history, concurrent medication, and medical/neurological examinations as well as a comprehensive clinical assessment [11, 16].

Neuropsychological assessment and score analysis

Participants received the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS) 3.0 [18], NACC Frontotemporal Lobar Degeneration (FTLD) module, and LEADS-specific neuropsychological measures (MMSE, Rey Auditory Verbal Learning Test (RAVLT) [19], Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) [20], Digit Symbol Test from Wechsler Adult Intelligence Scale-Revised [21], and Tablet-Based Cognitive Assessment Tool (TabCAT) [22]. Test data were combined into the following domain composites: Executive Functioning, Speed/Attention, Episodic Memory, Language, and Visuospatial. The Executive Functioning domain included the UDS3 Trail Making Test Part B, UDS3 Digit Span Backward, UDS3 Phonemic Verbal Fluency, WAIS-R Digit Symbol Test, as well as TabCat Flanker and Match. The Speed/Attention domain included the UDS3 Trail Making Test Part A and UDS3 Digit Span Forward. The Episodic Memory domain included the RAVLT Delayed Recall, UDS3 Craft Story Memory Test- Delayed Paraphrase Recall, UDS3 Benson Figure Delayed Recall. The Language domain included the UDS3 Sentence Repetition and Word-Picture Matching, UDS3 Animal Fluency, and the UDS3 Multi-Lingual Naming Test. Lastly, the Visuospatial domain included the UDS3 Benson Figure Copy and TabCat Line Orientation and Line Length.

Residuals were calculated by controlling for education for each test score at baseline to compute cognitive domain-specific z-scores while controlling for the effect of education. Using the residuals of the CN group, each variable was centered by taking the median absolute difference (MAD) (or mean absolute difference [MeanAD] if needed), as follows: $\text{MAD} = \text{median}\ |xi - \bar{x}|$. Median was implemented because normality of individual composites was found to be violated using Shapiro–Wilk test. The MAD was subtracted for each variable and standardized using a robust scale estimate suitable for non-normal data to calculate the robust z-scores: $\text{z-score} = (X - \text{Median})/(1.486 * \text{MAD})$. Because of this use of the MAD, values for the robust z-scores in the

CN group may be slightly different than 0.0. If MAD was equal to zero, the MeanAD was used in the scale estimate to calculate the robust z-scores: z-score = (X − Median)/(1.253314 * MeanAD). The robust z-scores were grouped by cognitive domains into averages for each participant.

In order to determine if an individual participant demonstrated a "predominant" level of impairment in any given cognitive domain, we set a threshold of 1 standard deviation (*SD*) or greater impairment compared to all other cognitive domain scores (Fig. 1). For example, to be classified as "Amnestic Predominant", an individual's score on the "Episodic Memory" domain z-score must be 1*SD* or greater below their performance on all other cognitive domains composites. Because the domain of Speed/Attention is arguably a component of Executive Functioning, and because these composite domain scores were highly co-linear, we utilized scores in either domain to indicate the level of impairment in the Executive Function z-score category reported in this study. As in, if a participant had z-scores > 1*SD* lower on either the Executive Functioning or Speed/Attention domains than the Episodic Memory, Language, and Visuospatial domains, then that participant would be classified as "Dysexecutive Predominant". If z-scores on the Episodic Memory composite and the Executive Function composite were within 1*SD* of each other and both were greater than or equal to 1*SD* below all other domains, participants were classified as "Mixed Amnestic/Dysexecutive". Lastly, if z-scores across all cognitive composite domains were within 1*SD* of each other, the participant was classified as "Multidomain." Notably, characterizing an individual with a "predominant" impairment in a given cognitive domain does not indicate that they had intact performance in other cognitive domains. Our motivation for classifying participants in this manner is to examine an individual's cognitive profile from a neuropsychological actuarial approach which clinicians can then use to inform their diagnostic process in a complementary fashion. No participants demonstrated performance on either language or visuospatial composite scores that were within 1*SD* of scores in another domain and 1*SD* below all the other domain composite scores. The threshold of 1SD was set based on clinical neuropsychological practice guidelines suggesting that this threshold of discrepancy indicates a meaningful clinical difference among test scores on an individual's cognitive profile [23].

Neuroimaging

LEADS participants completed structural MRI and ^{18}F-Florbetaben (FBB) PET neuroimaging at baseline (see [16, 24] for detailed PET acquisition and processing protocols). Briefly, FBB-PET data were acquired 90 to 110 min post-injection of ~8 mCi of FBB (four 5-min frames). A composite neocortical FBB standardized uptake value ratio ($SUVR_{90\text{-}110}$) was calculated using the whole cerebellum as a reference region and converted to Centiloid (CL) units [25] using the ADNI formula [26].

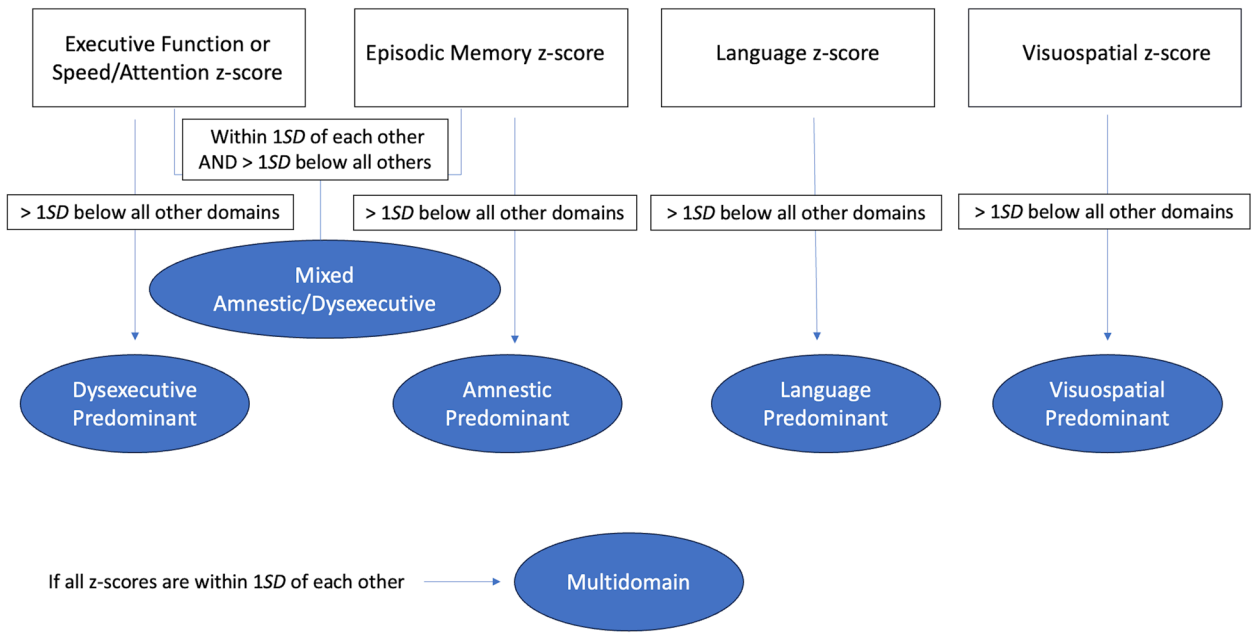

Fig. 1 Schematic of phenotypic classifications based on neuropsychological data. The top row delineates the cognitive composite z-scores (Executive Function, Episodic Memory, Language, and Visuospatial). *SD* = standard deviation

FBB PET data were available for 165 EOAD participants, all of whom were amyloid-positive (Aβ+) by visual read by expert reader and image quantification [24].

MRI data were acquired with 3.0 Tesla scanners using a sagittal 3D accelerated MPRAGE/IRSPGR T1-weighted sequence. The typical parameters for this sequence were the following, although these varied slightly by vendor and system type: Repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, flip angle = 9°, slice thickness = 1 mm, field of view = 240 × 256 mm, 208 sagittal slices, and 2 × acceleration. All MRI data were visually inspected for gross artifacts (e.g., subject motion) and evaluated on image quality prior to data processing [27]. Each participant's structural MRI data underwent intensity normalization, skull stripping, and automated segmentation of cerebral white matter to locate the gray matter/white matter boundary via FreeSurfer v6.0. Defects in the surface topology were corrected [28], and the gray/white boundary was deformed outward using an algorithm designed to obtain an explicit representation of the pial surface. Cortical thickness was calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface [29]. Whole-brain maps of cortical thickness were registered to template surface space (fsaverage) and smoothed geodesically with full-width-half-maximum (FWHM) of 15 mm. MRI data for three EOAD participants were not available or did not pass quality control, and an additional two participants failed data processing in FreeSurfer, resulting in a final sample of 164 EOAD participants for statistical analysis.

Statistical analysis

Descriptive statistical analysis on clinical characteristics and neuropsychological data was conducted on the whole sample, as well as on each of the phenotypic variants derived from our data-driven approach. Means and standard deviations were calculated on our variables of interest, including age, sex, education, race, *APOE ε4* carrier status (percentage of participants with at least one allele), CDR Global and Sum-of-Box scores, and the MMSE. Differences between the phenotypic variants were evaluated using one-way analysis of variance and two-sample t-tests. Chi-square (χ2) tests were conducted to determine group differences on nominal variables such as CDR and *APOE ε4* carrier status. Statistical significance was set at $p < 0.05$ uncorrected due to the limited number of comparisons conducted.

To identify the spatial topography of cortical atrophy in the whole sample as well as in each EOAD phenotypic variant group, we converted each participant's vertex-wise estimates of cortical thickness to *W*-scores [12, 30]. *W*-scores are analogous to *Z*-scores adjusted for specific covariates, which in this study were participants' age, sex, and years of education. Separately for each vertex, we first performed a multiple linear regression analysis using cortical thickness data obtained from CN participants (mean age = 56.93 ± 5.90, 38 men/64 women), which resulted in beta coefficient values for age, sex, and years of education as well as individual values of residuals. Using these parameters, we then computed *W*-scores for each vertex and patient with the following formula:

$$W_{ij} = \frac{T_{ij} - \widehat{T}_{ij}}{SD_i}$$

where T_{ij}= the observed cortical thickness at vertex i and for participant j, $\widehat{T}_{ij}$= the predicted cortical thickness at vertex i and for participant j based on age and sex of the participant and β coefficients obtained from Aβ- controls, and SD_i= the standard deviation of the individual residuals obtained from CN participants at vertex i. Because *W*-scores in this study were calculated using cortical thickness, more negative values indicate greater cortical atrophy relative to what would be expected solely based on age, sex, and level of education of each participant. Mean cortical atrophy for each EOAD phenotypic variant was calculated by averaging vertex-wise *W*-score maps from all participants belonging to the group.

Results

Clinical and Neuropsychological characteristics of 6 distinct EOAD phenotypic variants

Using our data-driven approach of contrasting neuropsychological test performance across cognitive domains (Executive Function, Speed/Attention, Memory, Language, and Visuospatial), we identified 6 distinct phenotypic variants (Fig. 2A): "Amnestic Predominant" (11.2% of the total sample), "Dysexecutive Predominant" (21.9%), "Language Predominant" (10.7%), "Visuospatial Predominant" (15%), "Mixed Amnestic/Dysexecutive" (11.2%), and "Multidomain" (29.6%). Demographic variables (age, sex, education, race) were similar across participants (all $p > 0.05$; Table 2). *APOE ε4* allele carriers were particularly enriched in the Amnestic Predominant variant (89%; $\chi2 = 16.8$, $p < 0.005$). The Visuospatial Predominant variant was the least enriched with the *APOE ε4* allele (33.3%). We did not observe a statistical difference on global clinical severity ratings (CDR) across phenotypic variants (χ2, $p > 0.05$), as most participants were rated at the very mild stage of illness (most were CDR 0.5). We did, however, observe differences on the CDR sum-of-boxes score (CDR-SB) between phenotypic variants ($F = 2.87$, $p = 0.02$). Specifically, the Amnestic Predominant variants were rated as milder in functional impairment (lower CDR-SB) compared to the

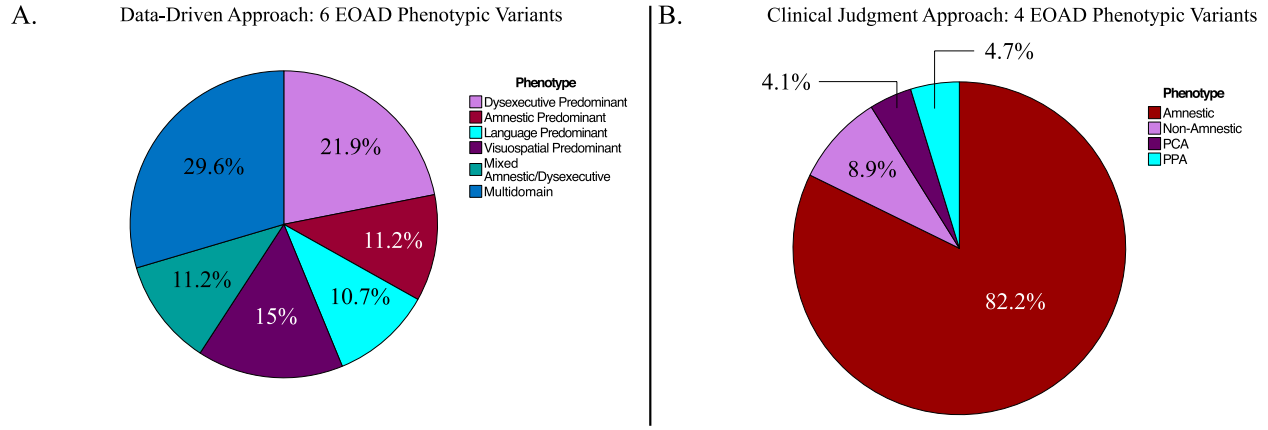

Fig. 2 Phenotypic variants of EOAD. A comparison of EOAD phenotypic variants derived from (**A**) a neuropsychological data-driven approach and (**B**) a clinical judgment based approach. Percent of the total sample is graphed by phenotypic classification in both approaches. PCA = Posterior Cortical Atrophy. PPA = Primary Progressive Aphasia

Table 2 Clinical characteristics of 6 data-driven phenotypic variants. Significant differences were observed between variants on APOE e4 carrier status, CDR status, and MMSE scores

Demographic	Dysexecutive Predominant ($n=37$)	Amnestic Predominant ($n=19$)	Language Predominant ($n=18$)	Visuospatial Predominant ($n=26$)	Mixed Amnestic/ Dysexecutive ($n=19$)	Multidomain ($n=50$)	*ANOVA* p -value
% of Sample	22%	11%	11%	15%	11%	30%	
Age	59.5 ± 3.2	59.4 ± 4.8	58.9 ± 3.5	57.2 ± 3.5	59.5 ± 3.5	58.9 ± 4.4	n.s
Sex (% female)	40.5	63.2	44.4	42.3	47.4	58.0	n.s
Education (years)	15.5 ± 2.4	15.7 ± 1.9	15.4 ± 2.5	15.5 ± 1.8	15.6 ± 2.8	15.5 ± 2.6	n.s
Race (% White)	91.9	89.5	94.4	92.3	94.7	98.0	n.s
APOE ε4 (% at least one allele)	56.7	88.9	47.1	33.3	77.8	57.4	$p=0.002$
Disease Duration (years)	3.3 ± 2.0	3.8 ± 1.6	4.3 ± 3.4	3.5 ± 1.8	2.8 ± 1.9	2.1 ± 1.9	n.s
CDR Global	CDR 0.5 ($n=22$) CDR 1 ($n=15$)	CDR 0 ($n=1$) CDR 0.5 ($n=16$) CDR 1 ($n=2$)	CDR 0.5 ($n=11$) CDR 1 ($n=7$)	CDR 0.5 ($n=15$) CDR 1 ($n=11$)	CDR 0 ($n=1$) CDR 0.5 ($n=15$) CDR 1 ($n=3$)	CDR 0 ($n=1$) CDR 0.5 ($n=33$) CDR 1 ($n=16$)	n.s
CDR-SB	3.7 ± 1.5	2.7 ± 1.1	4.0 ± 1.6	4.1 ± 1.5	2.9 ± 1.8	3.3 ± 2.0	$p=0.02$
MMSE	22.7 ± 4.1	25.5 ± 2.7	21.8 ± 4.5	20.6 ± 4.3	24.3 ± 3.3	23.5 ± 4.4	$p=0.001$

CDR Clinical Dementia Rating, *SB* Sum-of-Boxes, *MMSE* Mini-Mental State Examination, *n.s.* non-significant at the level of $p>0.05$

Dysexecutive Predominant ($t=2.8$, $p=0.004$), the Language Predominant ($t=2.9$, $p=0.003$), the Visuospatial Predominant ($t=3.6$, $p=0.0004$) variants. The Amnestic Predominant, the Mixed Amnestic/Dysexecutive, and the Multidomain groups were comparable on the CDR-SB ($p>0.05$). Similarly, we observed a difference across phenotypic variants on the MMSE, a crude global cognitive screening measure ($F=4.1$, $p=0.001$). We observed that the Amnestic Predominant group scored higher on the MMSE compared to the Dysexecutive Predominant ($t=2.8$, $p=0.004$), the Language Predominant. ($t=3.1$, $p=0.002$), the Visuospatial Predominant ($t=4.4$, $p=0.00003$), and the Multidomain ($t=1.9$, $p=0.03$) groups while scoring comparably to the Mixed Amnestic/Dysexecutive variant ($p>0.05$).

The 6 distinct EOAD phenotypic variants observed based on objective neuropsychological data (data-driven approach) did not entirely overlap with the 4 phenotypic variants classified by clinician judgment alone (Fig. 2B). These included Amnestic (82.2% of this total sample), Non-Amnestic (8.9%), PCA (4.1%) and PPA (4.7%). Out of the 82.2% of participants diagnosed clinically as

"Amnestic", 13% were classified based on our data-driven approach as Amnestic Predominant, 21% as Dysexecutive Predominant, 10.7% as Language Predominant, 14.4% as Visuospatial Predominant, 11.5% as Mixed Amnestic/Dysexecutive, and 29.5% as Multidomain (Fig. 3). Out of the 8.9% of participants classified by clinical judgment as "Non-Amnestic," 40% were classified as "Dysexecutive Predominant" based on our neuropsychological data-driven approach, 13.3% as Language Predominant, 20% as Visuospatial Predominant, 6.7% as Mixed Amnestic/Dysexecutive, and 20% as Multidomain. Furthermore, a greater number of participants demonstrated a primary deficit in language or visuospatial domains than those meeting the strict clinical criteria of PPA and PCA, respectively. Specifically, of the 7 participants diagnosed with PCA by clinical judgment, 1 was classified as Dysexecutive Predominant, 1 was Amnestic Predominant, 1 was Language Predominant, 2 were Visuospatial Predominant and 2 were multidomain based on our neuropsychological data-driven approach. Similarly, of the 8 participants diagnosed with PPA by clinical judgment, 1 was classified as Dysexecutive Predominant, 1 was Visuospatial Predominant, 2 were Mixed Amnestic/Dysexecutive, and 4 were Multidomain. None of these PPA participants met criteria for a Language Predominant impairment based on their neurological test scores.

Each of the 6 phenotypic variants derived from our neuropsychological data-driven approach, by definition, demonstrated a 1*SD* or greater impairment difference from all other cognitive domains (Fig. 4). However, in the case of the Dysexecutive, Language, Visuospatial, Mixed Amnestic/Dysexecutive, and Multidomain phenotypic variants, other cognitive domains were also normatively impaired, defined as greater than or equal to 1*SD* below the normative mean derived from education-matched cognitively normal participants. We excluded 6 participants from Fig. 4 to optimize visualization of these composite performance scores. See Supplementary Materials Table 1 for a summary of complete neuropsychological domain composite values. The Amnestic Predominant variant alone was characterized by circumscribed episodic memory impairment with normative preservation in all other cognitive domains. The neuropsychological profiles for each EOAD phenotype based on clinical judgment (Supplemental Materials Fig. 1) show greater multidomain impairment in each of the 4 EOAD diagnostic categories.

MRI-based validation of EOAD phenotypic variants

Using cortical thickness measurements in our EOAD participant group compared to age- and education-matched CN participants, we mapped cortical atrophy "signatures" of the subset of participants who had high-quality MRI data (n = 164), as a whole group as well as within each of the 6 clinical phenotypic variants derived from our neuropsychological data-driven approach (Fig. 5). The pattern of cortical atrophy observed in the whole EOAD group is the same as a previously published "cortical atrophy signature" of EOAD from the LEADS cohort [12], though the participant cohorts were not identical. For the phenotypic variants, we observed the most circumscribed atrophy pattern primarily in the medial and lateral temporoparietal cortices in the Amnestic Predominant group, which was consistent with the strikingly specific memory deficits observed on neuropsychological test data

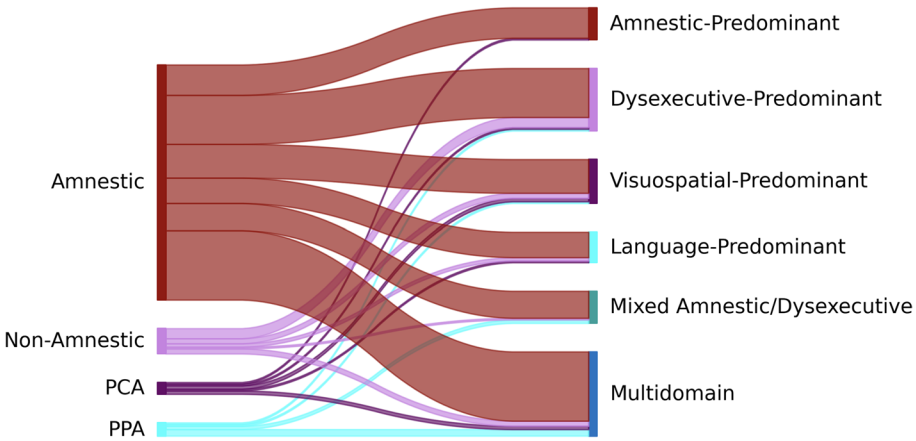

Fig. 3 Schematic depiction of EOAD diagnostic classifications by method. The left side of the figure lists the four diagnostic variants of EOAD based on clinical judgment and the right side lists the six data-drive phenotypic variants of EOAD. The colors within this schematic are linked to the diagnoses made by clinical judgment, and can be used to visually link what proportion of each diagnosis made by clinical judgment comprises each of the six neuropsychological data-driven phenotypic variants. PCA = Posterior Cortical Atrophy. PPA = Primary Progressive Aphasia

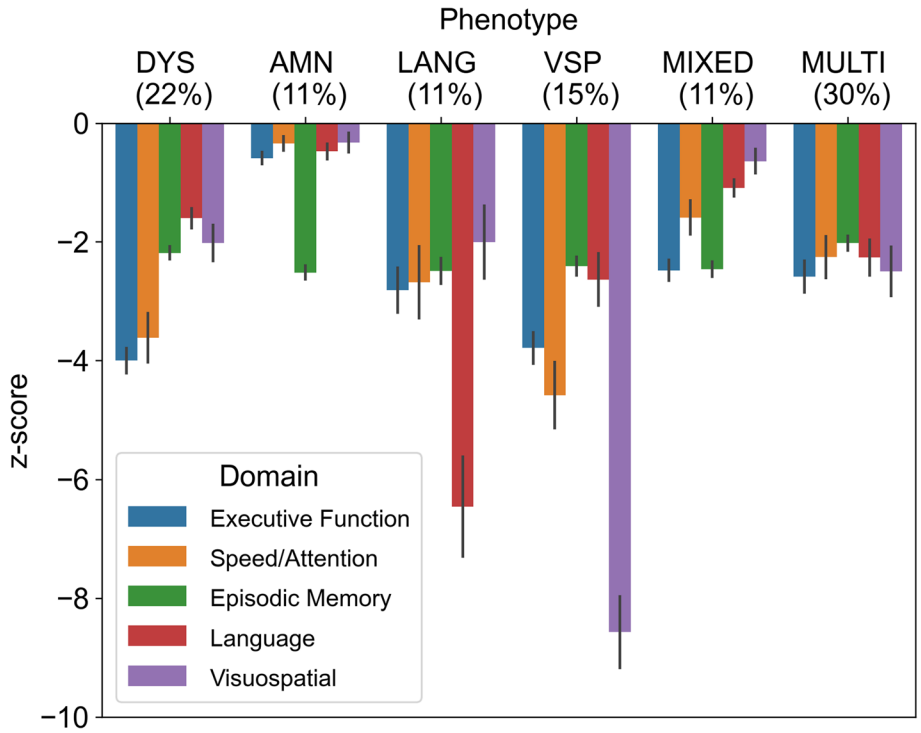

Fig. 4 Neuropsychological profile of 6 distinct EOAD phenotypic variants. Normalized data (z-scores) are shown in each cognitive domain for each distinct EOAD phenotypic variant (DYS = Dysexecutive Predominant, AMN = Amnestic Predominant, LANG = Language Predominant, VSP = Visuospatial Predominant, MIXED = Mixed Amnestic/Dysexecutive, and MULTI = Multidomain). For visualization purposes, data were excluded from six extreme outlier datapoints defined as greater than 3 standard deviations from the mean (5 individuals labeled as Language Predominant and 1 labeled as Visuospatial Predominant). Full reporting of means and standard deviations inclusive of these individuals is included in the Supplementary Materials

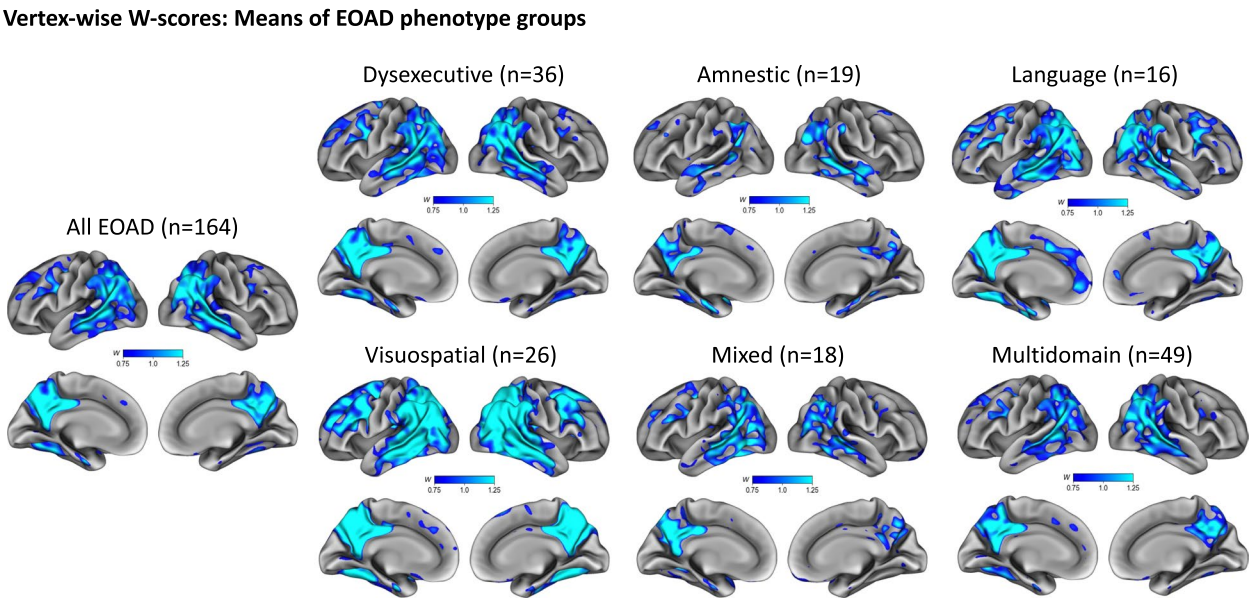

Fig. 5 Spatial topography of cortical atrophy in 6 distinct neuropsychological data-driven EOAD phenotypic variants based on neuropsychological test profiles. Colored vertices on the cortical surface maps indicate areas where EOAD participants, on average, showed greater atrophy than cognitively normal control participants at a vertex-wise threshold of $W < -0.75$

(Fig. 3). In contrast, the Dysexecutive, Language, and Visuospatial Predominant variants demonstrated a high degree of atrophy in lateral posterior parietal and lateral temporoparietal cortex with relative sparing of bilateral anterior medial temporal cortex compared to other cortical regions. Notably, all phenotypic variants demonstrated a high degree of cortical atrophy in bilateral medial parietal cortices and angular gyri which is reported across the AD phenotypic spectrum. We also conducted a brain-behavior correlation analysis wherein we conducted whole cortex vertex-wise correlations between cognitive domain composite z-scores and cortical atrophy (Supplementary Materials Fig. 2). From this, we show that the topography of these correlations is generally consistent with the pattern of atrophy shown in Fig. 5, providing converging evidence that the regions that are atrophic in a given domain-specific impairment group (e.g., dysexecutive-predominant) are the regions in which cortical atrophy is related to those cognitive domains (e.g., executive function) across the entire EOAD sample.

We also mapped cortical atrophy patterns of these same EOAD participants classified by the 4 phenotypic variants derived from the clinical judgment approach (Fig. 6). We found these atrophy patterns similar to the atrophy patterns that we observed using our neuropsychological test performance-based approach. Specifically, the atrophy pattern in the Amnestic clinical judgment phenotype looked very similar to the Amnestic Predominant neuropsychological data-driven phenotype, with prominent MTL and lateral temporoparietal atrophy and very little dorsolateral prefrontal cortex (DLPFC) atrophy. Additionally, the Non-amnestic clinical judgment phenotype was similar to our Dysexecutive Predominant phenotype, with greater atrophy observed in the DLPFC and less prominent atrophy in the MTL. However, the atrophy maps for the clinical judgment-based phenotypes of PCA and PPA did not entirely align with our neuropsychological data-driven phenotypes for Visuospatial Predominant

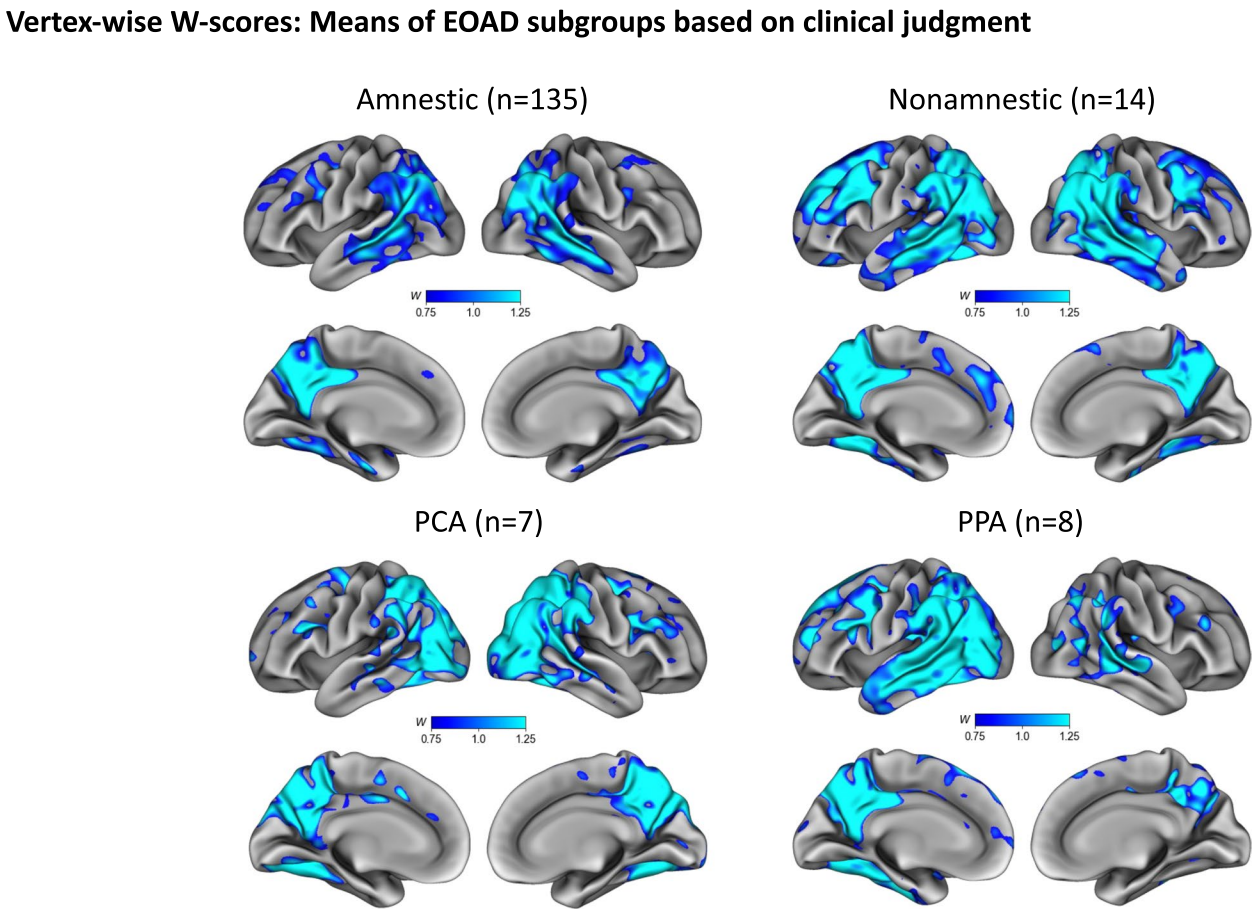

Fig. 6 Spatial topography of cortical atrophy in 4 EOAD phenotypes based on clinical judgment. Colored vertices on the cortical surface maps indicate areas where EOAD participants, on average, showed greater atrophy than cognitively normal control participants at a vertex-wise threshold of $W < 0.75$

and Language Predominant variants, respectively. The PCA map indicated more circumscribed lateral occipitoparietal atrophy than our Visuospatial Predominant map, which included greater lateral frontal atrophy. Lastly, the PPA map revealed an atrophy pattern that was more left-lateralized, while our Language Predominant map displayed bilateral atrophy in the same regions.

Discussion

We examined the neuropsychological profiles of EOAD participants to determine if we would observe greater phenotypic heterogeneity using this neuropsychological data-driven approach than can be ascertained based on clinical judgment alone, in the service of better characterizing this population to improve diagnosis and individualized treatment planning. Comparing test performance across cognitive domains, we identified 6 distinct phenotypic variants of EOAD: Dysexecutive Predominant, Amnestic Predominant, Language Predominant, Visuospatial Predominant, Mixed Amnestic/Dysexecutive, and Multidomain. These results add a dimension to the 4 clinical phenotypes—i.e., Amnestic, Non-Amnestic, PCA, and PPA—commonly derived from clinician judgment and consensus discussion [11]. We found that 82% of our EOAD sample were classified as "Amnestic" based on clinical judgment identifying those individuals with memory impairment (regardless of the level of impairment in other domains). Upon further examination of the cognitive profiles of this sample, our neuropsychological data-driven approach classified 11% of the EOAD sample as "Amnestic Predominant," indicating that the memory domain was not only impaired, but was the predominant domain of impairment compared to all other cognitive domains. Based on our phenotyping approach, another 11% were classified as being "Mixed Amnestic/Dysexecutive", and an additional 30% were classified as "Multidomain," which includes memory impairment along with comparable deficits in non-memory domains. We conclude that EOAD participants who were classified by clinical judgment as Amnestic in our study may in fact have memory impairment that is driven by primary executive dysfunction, slowed processing speed, or perceptual deficits in the language or visuospatial domains rather than relatively pure memory impairment, as we found in our Amnestic Predominant sample. Using the neuropsychological data-driven approach, our observations are more similar to those of other groups who have observed rates of non-amnestic EOAD variants between 30 and 64% [31, 32], with a large number of participants presenting with language and visuospatial dysfunction. However, these studies are relatively smaller in scope, calling on the need to study EOAD phenotypic heterogeneity in much larger samples with complementary approaches. Taken together, our observations in this study suggest that individuals who present with a primary deficit in a given cognitive domain may in fact be impaired across other cognitive domains as well. Additionally, neuropsychological tests thought to represent a given cognitive domain may actually depend on multiple cognitive domains for normal performance (e.g., "memory" tests typically depend on language or visuospatial function as well as executive function and processing speed). Across phenotyping methodologies and studies, however, there is consensus that atypical (i.e., non-amnestic) presentations are more prevalent in EOAD compared to late-onset AD [32, 33].

When examining demographic or clinical features that vary across our 6 phenotypic variants, we discovered that individuals classified as Amnestic Predominant were milder in illness severity based on the CDR-SB, and performed the highest compared to the other variants on a global screening measure of cognition (MMSE) as well as overall neuropsychological test performance. While the Language Predominant and Visuospatial Predominant phenotypes may have started out earlier in the course of illness with circumscribed cognitive impairment in language and visuospatial domains, respectively, they developed significant multidomain impairment by the time of inclusion in this study. This finding highlights the need to identify these atypical variants of AD at pre-symptomatic or the earliest stages of single-domain impairment and include them at earlier stages in large-scale studies such as this one. Additionally, though basic demographic variables of age, sex, and education were not statistically significant among our 6 phenotypic variants, there is a possible trend of a higher proportion of females in our Amnestic-predominant phenotype compared to the others; this will need to be studied in greater depth in a larger sample.

With respect to genotype, we found that EOAD participants who were classified as either Amnestic Predominant or Mixed Amnestic/Dysexecutive variant were more likely to have at least one *APOE* ε4 allele than non-amnestic variants. The greatest difference between the 6 neuropsychological data-driven phenotypes was observed between the Amnestic Predominant variant, of which 89% of individuals had at least one ε4 allele, and the Visuospatial Predominant variant, of which only 33% had at least ε4 allele. In between, 57% of our Dysexecutive Predominant group had at least one ε4 allele, which is consistent with prior work reporting that 54% of their dysexecutive AD cohort also had at least one ε4 allele [9]. While the association between the presence of an ε4 allele and MTL-based amnestic presentations has been made in late-onset AD [34, 35], this study offers evidence of a difference in ε4 carrier status among differing

phenotypic variants of EOAD. These results are compelling in light of prior work supporting the hypothesis that the presence of an ε4 allele is associated with a different neuroanatomical profile compared to individuals without an ε4 allele in both LOAD [35] and EOAD participants [36].

When examining MRI-based cortical atrophy measurements of each of these 6 neuropsychological data-driven phenotypic variants, we found that each EOAD variant had overlapping yet distinct cortical atrophy "signatures," similar to what has been discovered with other clustering approaches [37]. All variants demonstrated a high degree of atrophy in bilateral medial parietal cortex and angular gyri, two posterior hubs of the default mode network known to be impacted across AD phenotypes [38, 39]. Each variant also demonstrated phenotype-specific atrophy patterns. Consistent with previously published work demonstrating that the Amnestic and Dysexecutive variants of AD may be related to disruption in distinct regions of the default mode network [33, 40], we found that the Amnestic Predominant variant had a more circumscribed atrophy profile that included the MTL and lateral temporoparietal cortex, while the Dysexecutive Predominant variant demonstrated greater atrophy of frontal and parietal regions with relative sparing of the MTL. The Language Predominant and Visuospatial Predominant variants demonstrated atrophy in the language and visuospatial networks as expected, though more widespread bilateral atrophy was also observed. Relative to the cortical atrophy signatures of the 4 clinical judgment-based EOAD phenotypes, there was a high degree of overlap between our "Amnestic Predominant" variant and the Amnestic clinical phenotype as well as between our "Dysexecutive Predominant" and the Non-Amnestic clinical phenotype. However, the PCA atrophy signature map indicated more circumscribed lateral occipitoparietal atrophy than our Visuospatial Predominant map, which included greater lateral frontal atrophy. Lastly, the PPA map revealed an atrophy pattern that was more left-lateralized, while the Language Predominant variant map displayed bilateral atrophy in the same regions. These discrepancies could be due to the fact that the consensus diagnostic criteria for PCA [6] and PPA [5] are much more stringent than cross-sectional neuropsychological profiles can reflect. For example, an individual is only classified as PCA if they demonstrate visuospatial impairment in the context of relatively intact cognition in other domains. In contrast, our Visuospatial Predominant variant also included individuals who, while demonstrating the most significant impairment in the visuospatial domain, also had a significant level of cognitive impairment in other domains (Fig. 3). Thus, the underlying atrophy patterns in our neuropsychological data-driven approach of these atypical presentations were not as constrained as the phenotypic atrophy signatures derived from a clinical judgment approach.

A major strength of this study was in the leveraging of a large multi-center dataset (LEADS) of participants with biomarker-confirmed EOAD. Studying the clinical heterogeneity of this disease through the lens of EOAD is useful because it affords us the opportunity to study the effects of underlying AD pathology in individuals with lower contributions of age-related comorbidities such as diabetes, obesity, heart disease, and other cerebrovascular factors [41]. However, this is not to say that the disease acts on the brains of younger and older adults in the same way. From our study of EOAD, our conclusions converge with conclusions from the existing literature that AD affects younger-onset individuals in different ways compared to LOAD in that individuals with EOAD are more phenotypically heterogeneous at presentation compared to LOAD.

Our study also had some limitations related to the lack of "process pure" cognitive test data—a limitation that is common to studying atypical clinical presentations of AD. Specifically, neuropsychological test performance in some domains (e.g., executive functions or memory) may have been impacted by primary perceptual processing impairment (e.g., visuospatial perception), thus potentially undermining cognitive performance in non-amnestic phenotypic variants. It is also a common phenomenon for the distributions of visuospatial and language domain scores to be skewed due to ceiling effects in cognitive normal individuals, resulting in extreme negative z-score values for impaired performance. Though we are reassured that 70% of the scores within the visuospatial domain and 78% of scores within the language domain fall within the typical normative range (± 3 *SD*), this feature of the data should be taken into consideration when interpreting the extent of impairment in these domains. Another concern is that our observed phenotypic heterogeneity may in fact be reflecting different stages of disease progression. Assessing disease stage in different clinical syndromes is quite challenging given the differences in sensitivity to impairment across cognitive tests. Reassuringly for this study sample, our participants were mostly at the earliest symptomatic stages (CDR 0.5); overall global CDR scores did not differ across data-driven phenotypic variants although CDR-SB scores showed some differences between groups. It is also reassuring that the phenotypic variants that resulted from our analysis did not differ in terms of disease duration. Future longitudinal studies assessing clinical change over time within an individual will be needed to determine the influence of disease stage the heterogeneity of EOAD phenotypes. It will also be important to analyze

which cognitive domain was impacted first when assessing heterogeneity; these data were not available for this study. Lastly, despite a relatively large overall sample size of 169 EOAD participants, some of the phenotypic variants had a relatively small sample size which could have undermined the signal observed in the cortical atrophy signatures we reported. It will be important to replicate this work in a larger dataset with greater racial and ethnic representation of the general population to determine the robustness of our observations.

Conclusions

By analyzing neuropsychological test data from the multicenter LEADS cohort, we identified 6 distinct phenotypic variants of EOAD: Dysexecutive Predominant, Amnestic Predominant, Language Predominant, Visuospatial Predominant, Mixed Amnestic/Dysexecutive, and Multidomain. Each variant presented with distinct yet overlapping patterns of cortical atrophy that represented vulnerability in the cortical regions subserving the predominant cognitive domain impacted. These results add a dimension to the 4 clinical phenotypes—i.e., Amnestic, Non-Amnestic, PCA, and PPA—commonly derived from clinician judgment and consensus discussion in this population [11]. Individuals with EOAD primarily tend to be classified by clinical judgment as amnestic, though our study suggests that so-called "memory" impairment in this population may in fact be driven by primary executive dysfunction, slowed processing speed, or perceptual deficits in the language or visuospatial domains, rather than relatively pure memory dysfunction. We conclude that a neuropsychological data-driven approach to understanding EOAD heterogeneity complements traditional approaches relying on clinical judgment. We hope that our novel approach to formally phenotyping individuals diagnosed with EOAD will lead to earlier and more accurate diagnosis of EOAD, as well as help to tailor individualized interventions targeting the optimization of cognitive and functional abilities in these patients depending on their clinical presentations.

Abbreviations

ADAS-Cog	Alzheimer's Disease Assessment Scale- Cognitive Subscale
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
C9ORF72	Chromosome 9 Open Reading Frame 72
CDR-SB	Clinical Dementia Rating Sum-of-Boxes
CDR	Clinical Dementia Rating
CN	Cognitively Normal
DLPFC	Dorsolateral Prefrontal Cortex
EOAD	Early-onset Alzheimer's disease
GRN	Progranulin
LEADS	Late-onset Alzheimer's disease
lvPPA	Logopenic variant Primary Progressive Aphasia
MAD	Mean Absolute Difference
MAPT	Microtubule Associated Protein Tau
MMSE	Mini-Mental State Examination
MTL	Medial Temporal Lobe
NACC FTLD	National Alzheimer's Coordinating Center's Frontotemporal Lobar Degeneration
PCA	Posterior Cortical Atrophy
PPA	Primary Progressive Aphasia
PSEN1	Presenilin-1
PSEN2	Presenilin-2
RAVLT	Rey Auditory Verbal Learning Test
SD	Standard Deviation
TabCAT	Tablet-Based Cognitive Assessment Tool
UDS	Unified Data Set

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-025-01689-8.

Supplementary Material 1.

Acknowledgements

The authors would like to thank the patients and families who participated in this research, without whose partnership this research would not have been possible.

LEADS Consortium author list

LEADS Consortium iuleads@iu.edu
Updated Sep 5 2024
Paul Aisen
Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, California, USA 92121
paisen@usc.edu
Laurel Beckett
Department of Public Health Sciences, University of California – Davis, Davis, California, USA 95616
labeckett@ucdavis.edu
Jeffrey Dage
Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
jdage@iu.edu
Ani Eloyan
Department of Biostatistics, Center for Statistical Sciences, Brown University, Providence, Rhode Island, USA 02912
ani_eloyan@brown.edu
Tatiana Foroud
Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
tforoud@iu.edu
Bernardino Ghetti
Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
bghetti@iupui.edu
Lea T. Grinberg
Department of Pathology, University of California – San Francisco, San Francisco, California, USA 94143
Department of Neurology, University of California – San Francisco, San Francisco, California, USA 94143
Lea.Grinberg@ucsf.edu
Dustin Hammers
Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
hammersd@iu.edu
Clifford R. Jack Jr.
Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA 55905
jack.clifford@mayo.edu
Kala Kirby
Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202

kalhall@iu.edu
Joel Kramer
Department of Neurology, University of California – San Francisco, San Francisco, California, USA 94143
Joel.Kramer@ucsf.edu
Robert Koeppe
Department of Radiology, University of Michigan, Ann Arbor, Michigan, USA 48109
koeppe@med.umich.edu
Walter A. Kukull
Department of Epidemiology, University of Washington, Seattle, Washington, USA 98105
kukull@uw.edu
Renaud La Joie
Department of Neurology, University of California – San Francisco, San Francisco, California, USA 94143
renaud.lajoie@ucsf.edu

Julien Lagarde
Department of Neurology, University of California – San Francisco, San Francisco, California, USA 94143
julien.lagarde@ucsf.edu

Melissa E. Murray
Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, USA 55905
Murray.Melissa@mayo.edu
Kathy Newell
Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
klnewell@iu.edu
Kelly Nudelman
Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
kholohan@iu.edu

Angelina Polsinelli
Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
apolsine@iu.edu

Rema Raman
Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, California, USA 92121
remar@usc.edu

Alexander Taurone
Department of Biostatistics, Center for Statistical Sciences, Brown University, Providence, Rhode Island, USA 02912
alexander_taurone@brown.edu

Maryanne Thangarajah
Department of Biostatistics, Center for Statistical Sciences, Brown University, Providence, Rhode Island, USA 02912
maryanne_thangarajah@brown.edu

Arthur Toga
Laboratory of Neuro Imaging, USC Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC, Los Angeles, California, USA 90033
toga@loni.usc.edu
Alexandra Touroutoglou
Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA 02129
atouroutoglou@mgh.harvard.edu
Prashanthi Vemuri
Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA 55905
Vemuri.Prashanthi@mayo.edu
Alireza Atri
Banner Sun Health Research Institute, Sun City, Arizona, USA 85351
alireza.atri@bannerhealth.com
David Clark
Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
clarkdg@iu.edu
Gregory S. Day
Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA 32224
day.gregory@mayo.edu
Ranjan Duara
Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami, Florida, USA 33140
ranjan.duara@msmc.com
Neill R. Graff-Radford
Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA 32224
graffradford.neill@mayo.edu
Ian Grant
Department of Psychiatry and Behavioral Sciences, Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA 60611
ian.grant@northwestern.edu
Lawrence S. Honig
Taub Institute and Department of Neurology, Columbia University Irving Medical Center, New York, New York, USA 10032
lh456@columbia.edu
Erik C.B. Johnson
Department of Neurology and Human Genetics, Emory University School of Medicine, Atlanta, Georgia, USA, 30307
erik.johnson@emory.edu
David T. Jones
Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA 55905
Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA 55905
jones.david@mayo.edu
Joseph C. Masdeu
Nantz National Alzheimer Center, Houston Methodist and Weill Cornell Medicine, Houston, Texas, USA 77030
jcmasdeu@houstonmethodist.org
Mario Mendez
Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, California, USA 90095
mfmendez@mednet.ucla.edu
Erik Musiek
Department of Neurology, Washington University in St. Louis, St. Louis, Missouri, USA 63130
musieke@wustl.edu
Chiadi U. Onyike
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA 21205
cuo@jhmi.edu
Meghan Riddle
Department of Neurology, Alpert Medical School, Brown University, Providence, Rhode Island, USA 02912
mriddle@kentri.org
Emily Rogalski
Healthy Aging & Alzheimer's Research Care Center, Department of Neurology, University of Chicago, Chicago, Illinois, USA, 60637
erogalski@uchicago.edu

Steven Salloway
Department of Neurology, Alpert Medical School, Brown University, Providence, Rhode Island, USA 02912
stephen_salloway@brown.edu
Sharon Sha
Department of Neurology & Neurological Sciences, Stanford University, Palo Alto, California, USA 94304
ssha1@stanford.edu
Raymond Scott Turner
Department of Neurology, Georgetown University, Washington D.C., USA 20057
raymond.turner@georgetown.edu
Thomas S. Wingo
Department of Neurology, UC Davis Alzheimer's Disease Research Center, University of California – Davis, Davis, California, USA, 95816
thomas.wingo@emory.edu
David A. Wolk
Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA 19104
david.wolk@pennmedicine.upenn.edu
Kyle Womack
Department of Neurology, Washington University in St. Louis, St. Louis, Missouri, USA 63130

kylew@wustl.edu
Maria C. Carrillo
Medical & Scientific Relations Division, Alzheimer's Association, Chicago, Illinois, USA 60603
mcarrillo@alz.org
Gil D. Rabinovici
Department of Neurology, University of California – San Francisco, San Francisco, California, USA 94143
gil.rabinovici@ucsf.edu
Bradford C. Dickerson
Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA 02129
brad.dickerson@mgh.harvard.edu
Liana G. Apostolova
Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA 46202
Department of Radiology and Imaging Sciences, Center for Neuroimaging, Indiana University School of Medicine Indianapolis, Indianapolis, Indiana, USA 46202
lapostol@iu.edu

Authors' contributions
D.P. and D.B.H conceptualized, analyzed, interpreted the data, and wrote the main manuscript. L.A. and B.D. contributed to interpretation and substantively revised the manuscript. Y.K., A.E., A.T., and M.T. contributed to the analysis. P.A., J.D., T.F., C.J., J.K., K.N., R.R., and P.V. were involved in the conceptualization and interpretation. A.T., A.A., G.D., R.D., N.G.R., I.G., L.H., R.J., J.M., M.M., E.M., C.O., M.R., E.R., S.S., SS., R.S.T., T.W., G.W., K.W., M.C., and G.D.R. contributed to the acquisition of the data. All authors have approved the submitted version and have agreed to be accountable for the author's own contributions and to ensure that questions related to eh accuracy or integrity of the work are appropriately investigated, resolved, and documented in the literature.

Funding
This study was generously supported by R56 AG057195, U01AG6057195, U24AG021886, Alzheimer's Association LEADS GENETICS-19–639372, Alzheimer's Association LDRFP-21–818464, Alzheimer's Association LDRFP-21–824473, and Alzheimer's Association LDRFP-21–828356. NACC is funded by the National Institute on Aging (NIA; U24 AG072122). National Alzheimer's Coordinating Center (NACC) data are contributed by the following NIA-funded Alzheimer's Disease Research Centers (ADRCs): P30 AG010133, P30 AG062422, P30 AG066462, P30 AG066507, P30 AG062421, P30 AG066506, P30 AG072977, P30 AG066444, P30 AG066515, P30 AG062677, P30 AG072980, P30 AG072979, and P30 AG066511 as well as R01 DC014296, R21 DC019567, R21 AG073744, K01 AG084820, K23 AG065450, P50 AG005134, and P30 AG062421, and by the Tommy Rickles Chair in Primary Progressive Aphasia Research. This research was carried out in part at the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hospital (MGH), using resources provided by the Center for Functional Neuroimaging Technologies, P41EB015896, a P41 Biotechnology Resource Grant supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health (NIH). This work also involved the use of instrumentation supported by the NIH Shared Instrumentation Grant Program and/or High-End Instrumentation Grant Program; specifically, grant number(s) S10RR021110, S10RR023043, and S10RR023401.

Data availability
All data will be made available upon request.

Declarations

Ethics approval and consent to participate
Institutional Review Board approval was obtained through a central review board overseen by Indiana University. Written informed consent was obtained from study participants or authorized representatives.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Frontotemporal Disorders Unit and Massachusetts Alzheimer's Disease Research Center, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, 149 13th St, Charlestown, Boston, MA 02129, USA. [2]Department of Biostatistics, Center for Statistical Sciences, Brown University, Providence, RI 02912, USA. [3]Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego 92093, USA. [4]Department of Neurology, Indiana University School of Medicine, Indianapolis, IN 46202, USA. [5]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN 46202, USA. [6]Department of Radiology, Mayo Clinic, Rochester, MN 55902, USA. [7]Department of Neurology, University of CA – San Francisco, San Francisco, CA 94143, USA. [8]Banner Sun Health Research Institute, Sun City, AZ 85351, USA. [9]Department of Neurology, Mayo Clinic in Florida, Jacksonville, FL 32224, USA. [10]Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center, Miami, FL 33140, USA. [11]Department of Psychiatry and Behavioral Sciences, Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA. [12]Taub Institute and Department of Neurology, Columbia University Irving Medical Center, New York, NY 10032, USA. [13]Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322, USA. [14]Nantz National Alzheimer Center, Houston Methodist and Weill Cornell Medicine, Houston, TX 77030, USA. [15]Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA. [16]Department of Neurology, Washington University in St. Louis, St. Louis, MO 63130, USA. [17]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21218, USA. [18]Department of Neurology, Alpert Medical School, Brown University, Providence, RI 02912, USA. [19]Department of Neurology, University of Chicago, Chicago, IL 60615, USA. [20]Department of Neurology & Neurological Sciences, Stanford University, Palo Alto, CA 94305, USA. [21]Department of Neurology, Georgetown University, Washington, DC 20057, USA. [22]Department of Neurology and Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA. [23]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA. [24]Medical & Scientific Relations Division, Alzheimer's Association, Chicago, IL 60631, USA. [25]Department of Radiology and Imaging Sciences, Center for Neuroimaging, Indiana University School of Medicine Indianapolis, Indianapolis, IN 46202, USA.

Received: 23 August 2024 Accepted: 31 January 2025
Published online: 06 February 2025

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