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Original Article

Characterizing and validating 12-month reliable cognitive change in Early-Onset Alzheimer's Disease for use in clinical trials

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ABSTRACT

Background: As literature suggests that Early-Onset Alzheimer's Disease (EOAD) and late-onset AD may differ in important ways, need exists for randomized clinical trials for treatments tailored to EOAD. Accurately measuring reliable cognitive change in individual patients with EOAD will have great value for these trials.

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Objectives: The current study sought to characterize and validate 12-month reliable change from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) neuropsychological battery.
Design: Standardized regression-based (SRB) prediction equations were developed from age-matched cognitively intact participants within LEADS, and applied to clinically impaired participants from LEADS.
Setting: Participants were recruited from outpatient academic medical centers.
Participants: Participants were enrolled in LEADS and diagnosed with amyloid-positive EOAD (n = 189) and amyloid-negative early-onset cognitive impairment not related to AD (EOnonAD; n = 43).
Measurement: 12-month reliable change (Z-scores) was compared between groups across cognitive domain composites, and distributions of individual participant trajectories were examined. Prediction of Z-scores by common AD biomarkers was also considered.
Results: Both EOAD and EOnonAD displayed significantly lower 12-month follow-up scores than were predicted based on SRB equations, with declines more pronounced for EOAD across several domains. AD biomarkers of cerebral β-amyloid, tau, and EOAD-specific atrophy were predictive of 12-month change scores.
Conclusions: The current results support including EOAD patients in longitudinal clinical trials, and generate evidence of validation for using 12-month reliable cognitive change as a clinical outcome metric in clinical trials in EOAD cohorts like LEADS. Doing so will enhance the success of EOAD trials and permit a better understanding of individual responses to treatment.

1. Introduction

Early-Onset Alzheimer's Disease (EOAD) is a relatively rare condition, beginning before the age of 65 and affecting approximately 5 % of all cases of Alzheimer's Disease (AD) [1]. Building upon early work on EOAD from mostly smaller samples and single-site cohorts [2–4], the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS, *NIA R56057195, NIA U016057195*) [5] was initiated in 2018 to provide deeper understanding of sporadic EOAD. Beginning with 18 sites across the United States, LEADS sought to become the most comprehensive repository of clinical, biomarker, and pathologic data on participants diagnosed with sporadic AD between ages 40–64 in the country. Recent findings from LEADS have revealed that sporadic EOAD manifests differently clinically and pathologically from traditional "Late-onset AD" (LOAD). Specifically, EOAD possesses an atrophy signature having greater involvement in inferior and superior parietal lobule, posterior cingulate, and mid- and caudal-lateral temporal cortices than LOAD, and less hippocampal and anterior temporal involvement [6]. Tau deposition in EOAD has been shown to be both advanced [7,8] and associated with white-matter hyperintensity burden [9], while *Apolipoprotein* (*APOE*) *ε4* rates were lower than those commonly observed in LOAD [10,11]. Clinically, EOAD participants display elevated rates of neuropsychiatric symptoms [12] and possess a unique baseline cognitive profile compared to LOAD; specifically, patients with EOAD tend to display greater impairments in executive functioning, processing speed, and visuospatial skills than those with LOAD, while displaying less impairments in immediate and delayed memory abilities [13]. LEADS has subsequently expanded internationally, aiming to develop a more globally representative cohort of participants with sporadic EOAD.

Although recent advancements in disease-modifying treatments for LOAD are promising [14,15], the aforementioned results from LEADS suggest that EOAD and LOAD differ in important ways [13]. The creation of pharmacological and behavioral interventions tailored specifically to EOAD participants is therefore needed. A critical goal of LEADS has been the development of clinical, functional, and biomarker outcomes for use in randomized clinical trials [5]. Longitudinal cognitive change is one such marker that will be essential to the conduct of clinical trials in EOAD. Therefore, tools to accurately measure cognitive change and predict cognitive decline over time in individual patients with EOAD will have great value. Sources of statistical and methodological bias exist when measuring change between two testing sessions, however, including practice effects, regression to the mean, testing variance, and normal variation in performance [16]. This means that the assessment of change is more complex than simply taking the difference between two scores, and that in some circumstances observed differences between scores may be large but not *meaningful*. Consequently, *reliable change methods* have been created and validated to statistically aid the determination of meaningfulness of observed cognitive changes in the context of these forms of bias (see [17] for review). One such model, developed by McSweeny and colleagues [18], uses linear regression to predict the Time 2 (T_2) performance of an individual based on their Time 1 (T_1) performance, along with other relevant predictors like demographic and test characteristics (e.g., age, education, retest interval). This predicted T_2 score can subsequently be compared to the observed T_2 score to characterize meaningful change – or *change beyond expectation* (see Calculation of Change Scores in the Methods for further explanation). These prediction algorithms are traditionally developed in one sample, and then applied to the specific performance characteristics of separate samples. This standardized regression-based (SRB) approach has over time predicted cognitive change with the highest accuracy [16], and when applied to LOAD samples, has increased the sensitivity of identifying individuals vulnerable to declining cognitive trajectories [19].

The purpose of the current project is therefore to characterize and estimate meaningful cognitive change *beyond expectation* in participants with early-onset dementia, and to validate the methods used to enhance incorporation of this cognitive metric in clinical trials for EOAD in the LEADS cohort. Using participants with β-amyloid-positive EOAD and early-onset β-amyloid-negative cognitive impairment not due to AD (or "Early-Onset non-AD", EOnonAD), the current study sought to quantify and compare 12-month reliable cognitive change both between and within diagnoses in LEADS, as well as to examine the distribution of individual participants declining *beyond expectation* or remaining stable within each sample. This follow-up interval coincides with the 12- to 18-month timeframes commonly utilized in pharmacological trials. For validation purposes, determination of how well this marker of change is predicted by common AD biomarkers (hippocampal volume, β-amyloid and tau deposition, and the EOAD atrophy signature) was also undertaken. It was hypothesized that 12-month reliable cognitive change would be worse in EOAD participants relative to those with EOnonAD, even after controlling for baseline cognitive severity. Additionally, AD biomarkers were expected to be highly predictive of this change. Although prediction equations exist for most measures in the LEADS neuropsychological battery [20,21], the average age of participants in these development samples is 72.4–73.9 years old, which is approximately 15 years older on average than the EOAD sample in the LEADS cohort (58.6 years [13]) and almost a decade older than the age-cutoff for EOAD. Given age's influence on cognitive performance and change over time [22,23], it was therefore necessary to first develop prediction algorithms from age-matched cognitively normal (CN) participants in the LEADS study.

Should our hypotheses be supported, they will provide evidence of validity for a valuable method to predict meaningful cognitive change beyond expectation in early-onset dementia, as well as characterization and validation of a cognitive outcome for use in future clinical trials

in EOAD. This tool can subsequently be used to select for treatment individual patients with EOAD who are susceptible to such declines. Therefore, by permitting the enrichment of intervention studies, this tool could be critical for the success of future trials in EOAD.

2. Method

2.1. Participants

A total of 310 LEADS participants were included in the study: 189 participants with amyloid-positive EOAD, 43 participants with amyloid-negative EOnonAD, and 78 CN participants. All participants possessed baseline and 12-month follow-up data that passed quality-control checks as of April 2024. Inclusion criteria for LEADS is as follows: being between 40 and 64 years of age at diagnosis of cognitive impairment, being in adequate general health and absent other psychiatric or neurological disorder, possessing knowledgeable informant, and being fluent in English [5]. Exclusion criteria were implemented to decrease the likelihood of familial forms of EOAD in the cohort, including: the presence of known pathogenic mutations in *Presenilin-1 (PSEN1), Presenilin-2* (*PSEN2), Amyloid Precursor Protein (APP), Chromosome 9 Open Reading Frame 72* (*C9ORF72*), *Microtubule Associated Protein Tau* (*MAPT*), or *Granulin Precursor aka Progranulin* (*GRN*) genes, and the presence of multiple first-degree relatives with EOAD – unless the aforementioned pathogenic mutations were absent. Diagnostic classification was made by local sites upon enrollment using formal consensus reviews with AD experts – including cognitive neurologists, geriatric psychiatrists, and neuropsychologists – using a combination of clinical, cognitive, genetic, fluid, and imaging biomarkers. Etiological classification of EOAD versus EOnonAD was made based on the presence or absence of cerebral β-amyloid pathology at baseline using amyloid-positron emission tomography (PET). Participants with cognitive impairment (EOAD or EOnonAD) were required to have Clinical Dementia Rating (CDR®) [24] scale global scores $\leq$1.0 at the time of enrollment, and CN participants had Mini-Mental Status Examination (MMSE) [25] scores $\geq$24 and a CDR global score of 0. Written informed consent was obtained from study participants or their legally authorized representatives, and Indiana University School of Medicine oversaw single-Institutional Review Board approvals.

2.2. Procedure

Details about LEADS protocol have been documented elsewhere [5]. All participants underwent standardized cognitive assessment at baseline, including measures from the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS) 3.0 [26]: Craft Story 21 Memory Test (Immediate and Delayed; [27]), Benson Complex Figure Recall Test (Immediate and Delayed; [28]), Trail Making Test Parts A and B (TMT-A and TMT-B; [29]), Montreal Cognitive Assessment (MOCA; [30]), Animal (Semantic) Fluency [31], Multilingual Naming Test (MINT; [32]), Vegetable (Semantic) Fluency [26], Letter (Phonemic; F & L) Fluency [26], and Number Span Test (Forward and Backward; [26]). The LEADS battery additionally included the Rey Auditory Verbal Learning Test (RAVLT; Total and Delayed; [33]) and the Alzheimer's Disease Assessment Scale-Cog (ADAS-Cog; [34]). The CDR and MMSE were administered for classification purposes. Description of these measures can be found from respective test developers, given their common usage among clinical neuropsychologists and cognitive neurologists.

The LEADS cognitive battery was re-assessed approximately 12 months after baseline, with the same test version being used at each administration. Additionally, brain imaging was undertaken using magnetic resonance imaging (MRI), and PET for β-amyloid (^{18}F-Florbetaben) and tau (^{18}F-Flortaucipir). The interested reader is invited to review details about LEADS imaging procedures in Touroutoglou et al. [6]. and Cho et al. [7]., respectively. Briefly, for structural measurements, MRI data were acquired with 3.0 Tesla scanners using a sagittal three-dimensional accelerated MPRAGE/IRSPGR T1-weighted sequence. The usual parameters for this sequence varied slightly by vendor and system type, but were as follows: TR=2300 ms, TE=2.98 ms, flip angle=9°, field of view=240 × 256 mm, in-plane voxel size=1 mm isotropic, 208 sagittal slices, and 2x acceleration [6]. Following quality control checks, MPRAGE data was normalized and processed using FreeSurfer v6.0. In the current study, MRI measures were converted into w-scores after adjustment for age and sex, for both baseline bilateral hippocampal volume (additionally corrected for intracranial volume), and the EOAD atrophy signature derived from Touroutoglou and colleagues [6]. Specifically, composite EOAD atrophy signature was generated from bilateral cortical thickness values from the following regions of interest (ROI): inferior parietal, precuneus, caudal lateral temporal, posterior cingulate, superior parietal, mid-lateral temporal, middle frontal gyrus, superior frontal gyrus, and the fusiform gyrus.

For amyloid and tau PET imaging, ^{18}F-Florbetaben PET (amyloid tracer) had an acquisition time of 90 to 110 min post-injection of ~8 mCi of ligand (four 5-min frames). ^{18}F-Flortaucipir PET (tau tracer) was acquired and had an acquisition time of 75 to 105 min post-injection of ~10 mCi of ligand (six 5-min frames; [7]. Image acquisition and reconstruction parameters, as well as quality control and image standardization, aligned with Alzheimer's Disease Neuroimaging Initiative (ADNI)−3 PET procedures [35], and PET data acquired at each site were uploaded to the Laboratory of Neuroimaging at the University of Southern California. Currently, amyloid burden was measured via a global composite centiloid value corrected for whole cerebellum uptake, and tau burden was defined by a meta-ROI standardized uptake value ratio (SUVR) corrected for inferior cerebellar gray matter.

2.3. Analyses

2.3.1. Demographic performance analyses

Independent samples t tests were used for the comparison of continuous demographic (e.g., age and education), testing (i.e., retest interval), and baseline cognitive performance variables between CN, EOAD, and EOnonAD groups. *Two-way chi square analyses* were conducted between diagnostic groups to compare categorical demographic variables (e.g., sex, racial/ethnicity).

2.3.2. Calculation of development sample SRBs

Linear multivariable regression analyses were used to create prediction equations for 12-month cognitive performances from the development sample of CN participants within LEADS (n = 78) based on McSweeny et al. [18]; however, for better statistical rigor, the current study used multiple hierarchical regression analyses instead of step-wise [36]. A unique prediction equation was derived for each of the measures in the LEADS cognitive battery. Similar to the well-established methodology [21,37–39], baseline (T_1) score, 12-month retest interval, and demographic variables (age, education, sex, and racial/ethnic diversity status) were regressed hierarchically on the respective 12-month (T_2) score. Specifically, Step 1 included T_1 score, Step 2 added 12-month retest interval, and Step 3 added demographic variables. Such a hierarchical arrangement was used to ensure that prediction equations could be obtained in the event that steps 2 or 3 were non-significant. For example, in incremental models T_1 RAVLT Delayed Recall, retest interval, and demographic variables were regressed on T_2 RAVLT Delayed Recall performance. Age was represented as years old at T_1, and education as the number of years of formal education. The retest interval was represented as days from T_1 to T_2. Sex was coded as *male*=1 and *female*=2, and racial/ethnic diversity was coded as *Caucasian/Non-Hispanic*=1 and *Non-Caucasian/Hispanic*=2. Based on previous literature [40], all scores in the repeated cognitive battery were represented as raw scores.

2.3.3. Calculation of change scores

To examine reliable change, the specific SRB prediction algorithms were subsequently applied to the current baseline and 12-month follow-up performances of participants in LEADS. An individual normalized deviation of change (or *Z*-score) was thus calculated for each participant. This *Z*-score reflected the difference between the Observed 12-month follow-up score (T_2) and the Predicted 12-month follow-up score (T_2'), normalized by the *standard error of the estimate* (SE_{est}) of the regression ($Z = [T_2 - T_2']/ SE_{est}$) [18]. While some debate exists in the literature about the proper standard error estimator to use in reliable change methods [41], we have previously shown that the SE_{est} is equivalent to other estimators [42]. Using this equation, positive *Z*-scores reflect performance at follow-up being higher than predicted, and negative *Z*-scores reflect performance at follow-up being lower than predicted. Of note, for ease of interpretation, the directionality of *Z*-scores for tasks where higher scores denote worse performance was reversed (e.g., TMT-A, TMT-B, and ADAS-Cog); as such, positive *Z*-scores reflected better performance at follow-up and negative *Z*-scores reflected worse performance. Finally, these *Z*-scores can be separated – or trichotomized – into three ranges and classified as "decline", "stable", or "improve". When using a confidence interval of stability of 90 % (standard for McSweeny's method [18]), *Z*-scores >1.645 represent "improvement" (or positive change beyond expectation), *Z*-scores <−1.645 represent "decline" (or negative change beyond expectation), and *Z*-scores between ±1.645 represent "stable" (or an anticipated level of change). A normal distribution of the *Z*-scores would thus result in 5 % of participants declining, 90 % remaining stable, and 5 % improving.

2.3.4. Characterization of 12-month change in early-onset dementia

To characterize 12-month change, *Z*-scores for each of the 16 cognitive variables of interest in the LEADS battery were first compared to expectation of no change ($Z = 0$) for the EOAD and EOnonAD groups based on the assumption of a normal distribution of *Z*-scores using *one-sample t tests*; of note, these *one-sample t tests* are statistically the same as comparing Observed and Predicted 12-month follow-up scores using *paired t tests*, and inform us whether the observed score significantly deviates from the model-based prediction. Then, seven *Z*-score cognitive composites were calculated for each group by taking the average of the individual *Z*-scores within a cognitive domain, with similar *one-sample t tests* being used to denote composite change over time. Cognitive composites included the following domains: Episodic Immediate Memory, Episodic Delayed Memory, Language, Attention/ Processing Speed, Executive Functioning, and Visuospatial skills (see **Supplementary Table S1** for listing of specific variables per domain, based on cognitive composites calculated in prior LEADS analyses [43]).

Third, the resultant composite *Z*-scores were compared between EOAD and EOnonAD groups using *multiple analysis of covariance* (*MANCOVA*), after accounting for *APOE* ε4 status and cognitive severity at baseline (i.e., MMSE). Following significant omnibus testing, post-hoc *analyses of covariance* (*ANCOVA*) were conducted for each composite. Further, trichotomization was conducted on the composite *Z*-scores to identify participants from each diagnostic group as significantly "declined", "remained stable", and "improved" on individual domains. Finally, examining the ability of traditional AD biomarkers to estimate 12-month cognitive change for each (un-trichotomized) composite *Z*-score was undertaken using *hierarchical linear regression*, with Step 1 including relevant demographic variables (age, sex, racial/ethnic diversity, *APOE* ε4 status), Step 2 including bilateral hippocampal volume, Step 3 including β-amyloid centiloid value, Step 4 including tau meta-ROI SUVR, and Step 5 including the bilateral EOAD atrophy signature. These latter analyses were conducted separately for EOAD and EOnonAD groups, given the potential circularity of β-amyloid as a result of its being the classification tool between EOAD and EOnonAD.

Measures of effect size were expressed throughout as absolute values for *Cohen's* d values (*t tests*), η^2 (*ANCOVA/MANCOVA*), and r^2 (regression). To protect against multiple comparisons, the use of multi-variate procedures and application of the *Holm's sequential Bonferroni* method of family-wise adjustment [44] of the two-tailed alpha level were undertaken for all primary analyses.

3. Results

3.1. Demographic analyses

Table 1 reflects demographic characteristics of participants from the LEADS sample. CN participants were younger, had higher levels of education, performed better on the MMSE, and possessed greater proportions of racial/ethnic diversity and women than clinical impairment groups (*ps*=0.001–0.04). They also displayed less amyloid and tau burden, hippocampal atrophy, and greater cortical thickness in ROIs associated with the EOAD atrophy signature than the EOAD group (*ps*<0.001). No differences were observed in retest interval or *APOE* ε4 carrier status (ps=0.23–0.99). Between the impaired groups, no differences were evident for age, education, sex, racial/ethnic diversity, nor hippocampal atrophy (*ps*=0.25–0.99). The EOAD group was more impaired than the EOnonAD group on the MMSE, had greater amyloid and tau burden, greater atrophy in the EOAD signature ROIs, and higher rates of *APOE* ε4 carrier status (*ps*=0.001–0.04). As indicated above, *APOE* ε4 status and MMSE were used as covariates in *MANCOVA* analyses.

3.2. Calculation of development sample SRBs

Results of the prediction of the LEADS cognitive battery T_2 scores based on the current sample of 78 CN participants are presented in Table 2. For each individual measure, the final model's adjusted r^2, SE_{est}, constant, and unstandardized beta weights for relevant variables are listed. Across 15 of the 16 measures, T_2 performance was best predicted by the model including baseline performance, retest interval, and demographics (*ps*=0.001–0.03); the only exception was Craft Story Immediate Recall, where T_2 performance was best predicted by the model including baseline performance only (*p*<.001 for Step 1).

3.3. Characterization of 12-month change in early-onset dementia

As can be observed in Table 3, when using *one-sample t* tests to compare *Z*-scores for each cognitive measure to an expected *Z*-score of zero based on the normal distribution of *Z*-scores, significance was observed for all 16 variables for the EOAD group (ps<0.001, *ds*=0.69–3.74). For EOnonAD, significant Z-scores were observed for 15 of 16 measures administered (ps=0.001–0.04, *ds*=0.33–1.02); significant change was not observed for Number Span Backward (*p*=.11, d = 0.25). For both groups, all *Z*-scores observed were negative. As a reminder, a negative *Z*-score indicates that the Observed 12-month score was lower than the Predicted 12-month score and suggests a reliable "decline" over one year, whereas a positive *Z*-score indicates that Observed 12-month score was higher than Predicted 12-month score, suggesting a reliable "improvement" over one year.

When evaluating the deviation from expectation for composite *Z*-scores for each group separately, all seven composites were significantly smaller than zero for both the EOAD (ps<0.001, *ds*=0.95–3.97) and EOnonAD (ps=0.001–0.02, *ds*=0.38–1.07) groups. *Z*-scores for composites of Global Cognition and Visuospatial skills were particularly small, with ADAS-Cog displaying the smallest *Z*-scores (e.g., −7.22 in EOAD) for an individual measure in each group. Additionally, when comparing composite *Z*-scores for each cognitive domain between the diagnostic groups using *MANCOVA* controlling for *APOE* ε4 status and MMSE, a significant omnibus difference was present (*Wilk's Lambda*=0.738, *p*<.001, η^2=0.262). Specifically, post-hoc *ANCOVA* indicated that group differences existed for Immediate Memory, Delayed Memory, Global Cognition, Executive Functioning, and Attention/Processing Speed (*ps*=0.001–0.04, η^2s=0.028–0.243). In each cir-

Table 1
Demographic characteristics of the CN, EOAD, and EOnonAD groups in LEADS.

	CN	EOAD	EOnonAD	Post Hoc Comparisons (*p* value)		
				EOAD vs CN	EOnonAD vs CN	EOAD vs EOnonAD
N	78	189	43			
Age in years	56.14 (5.9)	58.62 (4.1)	58.21 (5.7)	<0.0001	.07	.30
Sex - % Female	61.8 %	52.4 %	34.3 %	.06	.02	.26
Racial/Ethnic Diversity %	29.2 %	7.5 %	14.3 %	<0.001	.03	.60
Education in years	16.55 (2.2)	15.41 (2.3)	15.51 (2.4)	<0.0001	.06	.99
Retest Interval in days	477.74 (141.8)	477.86 (153.5)	452.33 (120.8)	.99	.99	.91
Mini-Mental State Exam	29.18 (1.0)	22.14 (4.8)	25.86 (4.8)	<0.0001	<0.0001	<0.0001
APOE ε4 %	44.9 %	53.1 %	35.7 %	.23	.33	.045
Amyloid Centiloid	9.95 (13.2)	95.27 (27.2)	5.85 (10.3)	<0.001	.99	<0.001
Tau SUVR	1.15 (0.1)	2.08 (0.5)	1.18 (0.2)	<0.001	.99	<0.001
Bilateral Hippocampal Volume w-score	−0.59 (1.3)	−1.49 (1.2)	−1.15 (1.3)	<0.001	.06	.31
Bilateral EOAD Atrophy Signature w-score	−0.15 (0.9)	−2.86 (1.8)	−0.29 (1.5)	<0.001	.46	<0.001
CDR Global (0.5 [%] / 1.0 [%])	0 % / 0 %	68.8 % / 31.2 %	88.4 % / 11.6 %	–	–	.009

Note: CN = Cognitive Normal, EOAD = Early-Onset Alzheimer's Disease, EOnonAD = Early-Onset non-Alzheimer's Disease, APOE ε4 = rate of Apolipoprotein ε4 carriers, Amyloid Centiloid = standardized centiloid value from amyloid-PET, Tau SUVR = standardized uptake value ratio from tau-PET, Bilateral Hippocampal Volume w-score = w-score values (adjusting for age, sex, and intracranial volume) for bilateral hippocampal volumes, Bilateral EOAD Atrophy Signature w-score = w-score values (adjusting for age and sex) for a composite of bilateral cortical thickness for regions of interest from (6), CDR Global = Clinical Dementia Rating scale – global score (range of 0, 0.5, 1.0, 2.0, 3.0). Values represent mean and *SD* unless otherwise noted. EOAD vs. CN, EOnonAD vs. CN, and EOAD vs. EOnonAD represent *p* values from the post-hoc *t-tests* comparing the respective groups following significant *Analysis of Variance* analysis.

Table 2
Regression equations for Predicted 12-month scores from LEADS Cognitively Normal (CN) sample (n = 78).

	Observed Baseline Score	Observed 12-month Score	Coefficients							r^2	SE_{est}
			Constant	Baseline Coefficient	Retest Interval	Age	Education	Sex	Racial/ Ethnic Diversity		
Immediate Memory Composite											
RAVLT Total Recall	48.23 (8.6)	50.21 (8.9)	55.833	.569	−0.009	−0.335	−0.245	−1.011	−3.420	.427	6.769
Craft Story Total Recall	22.27 (6.7)	22.51 (5.3)	15.043	.143	–	–	–	–	–	.054	2.885
Delayed Memory Composite											
RAVLT Delayed Recall	9.91 (3.3)	10.06 (3.5)	8.763	.594	−0.007	−0.054	.093	.745	−0.763	.411	2.665
Craft Story Delayed Recall	20.35 (6.6)	20.82 (5.3)	17.248	.201	−0.002	−0.043	−0.027	1.304	−1.406	.145	2.902
Benson Figure Delayed Recall	12.13 (2.5)	12.53 (2.4)	6.246	.438	.001	−0.043	.162	.045	−0.048	.229	2.136
Global Cognition Composite											
ADAS-Cog Total	15.01 (2.2)	14.79 (1.5)	9.381	.231	.000	.041	−0.023	−0.139	.063	.100	1.421
MOCA Total	27.08 (2.4)	27.42 (2.2)	11.709	.470	.000	−0.028	.303	.312	−0.999	.509	1.596
Language Composite											
MINT Total	29.94 (2.4)	30.17 (2.1)	7.483	.778	−0.001	−0.013	.005	.262	−0.104	.758	1.041
Animal Fluency	23.06 (5.9)	23.32 (5.4)	3.404	.745	−0.002	.019	.162	−0.924	1.115	.604	3.402
Vegetable Fluency	15.88 (4.5)	15.64 (4.5)	−0.797	.573	−0.002	.047	.128	1.257	1.229	.334	3.654
Phonemic Fluency	28.37 (10.2)	30.79 (8.2)	−4.501	.410	−0.002	.029	.976	4.045	.054	.286	6.912
Attention/ Processing Speed Composite											
TMT-A	26.03 (8.2)	25.49 (10.5)	6.493	.571	.017	.155	−0.451	−4.532	1.680	.244	9.133
Number Span Forward	6.95 (1.2)	7.05 (1.5)	4.948	.795	.000	−0.018	−0.049	−0.474	−0.714	.519	1.048
Executive Functioning Composite											
TMT-B	59.78 (23.1)	61.67 (27.7)	41.870	.676	−0.008	.052	−1.185	−8.229	10.343	.463	20.298
Number Span Backward	5.28 (1.4)	5.29 (1.3)	2.669	.589	.001	−0.005	−0.015	−0.041	−0.452	.483	.935
Visuospatial Composite											
Benson Figure Copy	15.56 (1.0)	15.49 (1.1)	9.502	.330	.001	−0.031	.121	.185	−0.047	.125	1.074

Note: RAVLT = Rey Auditory Verbal Learning Test, Craft Story = Craft Story 21 Memory Test, ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognition subscale, MOCA = Montreal Cognitive Assessment, MINT = Multilingual Naming Test, TMT-*A* = Trail Making Test Part A, TMT-*B* = Trail Making Test Part B. Observed Baseline and 12-month scores are in raw score *Mean* (*SD*). Retest interval is in days, age and education are in years, sex is coded as *male* = 1 and *female* = 2, and racial/ethnic diversity is coded as *Caucasian/Non-Hispanic* = 1 and *Non-Caucasian/Hispanic* = 2. r^2 = adjusted squared value of Pearson's correlation coefficient for Baseline and 12-month scores, SE_{est} = Standard error of the estimate.

cumstance, the composite *Z*-scores for the EOAD group were significantly more negative (reflecting greater declines) than EOnonAD.

3.4. Individual distributions of stability versus decline

Further, we considered the distributions of individual participants that either "declined", remained "stable", or "improved" relative to composite *Z*-score predictions over the interval between Baseline and 12-month cognitive test administrations. As a reminder, using a Z-score of 1.645, one would expect 5 % of participants to show "decline," 90 % to remain "stable," and 5 % to "improve" if the samples were normally distributed. As can be seen in Fig. 1, the distributions for the CN group were displayed as a coherence check, and indicated that majority of CN participants were stable across neuropsychological domains (ranging from 93.6 % to 100 %). For the EOAD group, "declining" was predominant across composite domains (54.4 % to 92.0 %). Finally, 60.5 % to 76.7 % of EOnonAD participants remained "stable" across domains of Delayed Memory, Language, Executive Functioning,

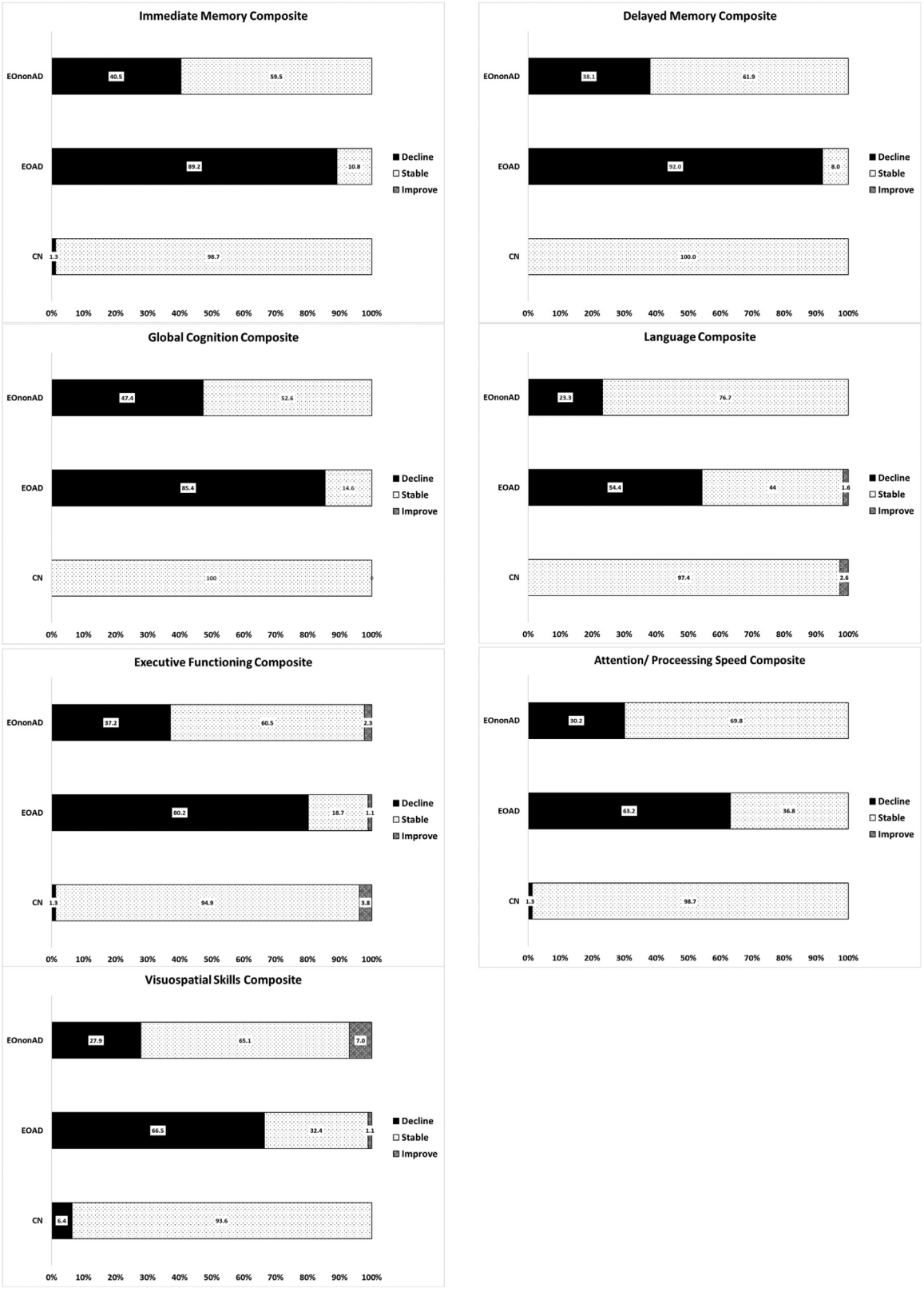

Fig. 1. Distribution of cognitive composites performance over 12-months after *Z*-score trichotomization. The values listed in each panel denote the percentages of individual participants per group that either *declined beyond expectation*, remained stable, or *improved beyond expectation*.

Table 3
Observed neuropsychological performances over time for the EOAD and EOnonAD groups.

	EOAD				EOnonAD			
	Baseline	Observed 12-month	Predicted 12-month	*Z-Score*	Baseline	Observed 12-month	Predicted 12-month	*Z-Score*
N	**189**				**43**			
Immediate Memory Composite	–	–	–	−3.34 (1.2)**	–	–	–	−1.80 (1.7) **
RAVLT Total Recall	22.48 (10.8)	16.26 (12.36)	35.68 (6.2)	−2.82 (1.3) **	36.69 (13.8)	31.74 (17.4)	44.09 (8.1)	−1.71 (1.8) **
Craft Story Immediate Recall	7.90 (5.5)	6.06 (5.6)	15.95 (0.6)	−3.90 (1.4) **	14.14 (7.8)	14.53 (8.9)	16.65 (0.7)	−1.97 (2.0) **
Delayed Memory Composite	–	–	–	−2.88 (0.7) **	–	–	–	−1.39 (1.4) **
RAVLT Delayed Recall	1.80 (2.6)	1.05 (2.4)	5.06 (2.1)	−1.53 (0.7) **	5.50 (4.5)	14.74 (4.8)	7.36 (3.0)	−0.94 (1.3) **
Craft Story Delayed Recall	4.34 (5.2)	3.06 (4.8)	14.57 (1.2)	−4.16 (1.1) **	10.91 (7.9)	11.84 (8.9)	15.57 (1.4)	−2.11 (2.1) **
Benson Figure Delayed Recall	2.82 (3.4)	1.70 (3.0)	7.95 (1.6)	−2.91 (1.1) **	8.53 (5.0)	7.81 (5.3)	10.46 (2.3)	−1.24 (2.0) **
Global Cognition Composite	–	–	–	−6.18 (4.0) **	–	–	–	−2.09 (3.0) **
ADAS-Cog	23.76 (7.0)	27.05 (9.9)	16.78 (1.6)	−7.22 (6.5) **	20.08 (5.9)	19.93 (6.9)	15.92 (1.4)	−2.82 (4.1) **
MOCA	15.74 (6.0)	12.94 (6.9)	21.54 (3.0)	−5.44 (3.0) **	21.85 (5.4)	22.15 (5.8)	24.40 (2.6)	−1.45 (2.6) **
Language Composite	–	–	–	−2.32 (2.4) **	–	–	–	−1.19 (2.4) **
MINT	25.60 (7.1)	21.59 (9.8)	26.52 (5.5)	−4.67 (7.8) **	27.77 (5.5)	25.72 (9.7)	28.21 (4.2)	−2.39 (7.2) *
Animal Fluency	11.87 (5.7)	8.92 (6.6)	14.72 (4.4)	−1.70 (1.4) **	15.49 (7.0)	14.30 (8.3)	17.59 (5.6)	−0.97 (1.4) **
Vegetable Fluency Fluency	7.18 (4.1)	5.12 (4.5)	10.33 (2.6)	−1.43 (0.9) **	10.16 (4.5)	9.70 (5.3)	12.00 (2.8)	−0.63 (1.1) **
Phonemic Fluency	18.88 (11.0)	14.86 (10.8)	25.21 (5.9)	−1.50 (1.2) **	20.14 (9.2)	20.02 (12.11)	25.48 (5.0)	−0.79 (1.3) **
Attention/ Processing Speed Composite	–	–	–	−3.14 (2.4) **	–	–	–	−1.55 (2.5) **
TMT-A	75.97 (48.4)	101.20 (52.9)	55.12 (27.5)	−4.99 (4.0) **	49.51 (40.6)	60.98 (50.3)	39.93 (23.6)	−2.30 (3.9) **
Number Span Forward	5.27 (1.7)	4.46 (2.3)	5.83 (1.4)	−1.31 (1.9) **	6.02 (1.5)	5.63 (2.5)	6.46 (1.2)	−0.79 (2.1) *
Executive Functioning Composite	–	–	–	−2.52 (1.5) **	–	–	–	−1.25 (2.0) **
TMT-B	233.32 (93.7)	252.14 (82.6)	179.38 (63.2)	−3.55 (2.2) **	135.47 (94.9)	156.44 (101.15)	114.34 (63.1)	−2.07 (2.9) **
Number Span Backward	3.29 (1.6)	2.61 (1.8)	4.01 (0.9)	−1.49 (1.5) **	4.02 (1.9)	4.00 (2.2)	4.40 (1.1)	−0.43 (1.7)
Visuospatial Composite	–	–	–	−5.48 (5.0) **	–	–	–	−1.89 (4.9) *
Benson Copy	11.39 (5.3)	8.12 (6.4)	14.02 (1.8)	−5.48 (5.0) **	13.12 (4.8)	12.53 (5.9)	14.57 (1.6)	−1.89 (4.9) *

Note: EOAD = Early-Onset Alzheimer's Disease, EOnonAD = Early-Onset non-Alzheimer's Disease, Observed Baseline = Observed score at Baseline visit, Observed 12-month = Observed score at 12-month visit, Predicted 12-month = Predicted score at 12-month visit, *Z*-Score = (Observed 12-month – Predicted 12-month) / Standard Error of the Estimate (SE_{est}), RAVLT = Rey Auditory Verbal Learning Test, Craft Story = Craft Story 21 Memory Test, ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognition subscale, MOCA = Montreal Cognitive Assessment, MINT = Multilingual Naming Test, TMT-*A* = Trail Making Test Part A, TMT-*B* = Trail Making Test Part B. All values are *Mean* (*SD*). Positive *Z*-Scores reflect better Observed 12-month performance than Predicted 12-month for all measures.

* Denotes *Z*-score different than zero, $p<.05$.

** Denotes *Z*-score different than zero, $p<.001$.

Attention/Processing Speed, with relatively equal numbers of participants "declining" and remaining "stable" for Immediate Memory and Global Cognition. Overall, for both impairment groups the impairment distributions deviated significantly from expectation (*p*s<0.001) across cognitive domains – and very few participants improved.

3.5. Prediction of 12-month change with ad biomarkers

Finally, the ability of AD biomarkers to predict 12-month cognitive change for each composite *Z*-score was undertaken using *hierarchical linear regression*. For the EOAD group, examination of r^2 values in Table 4 (and **Supplementary Table S2** for an expanded display of statistical results) indicates that hippocampal volume (Step 2) did not incrementally predict 12-month change across any cognitive composite (*p*s=0.06–0.87). Conversely, β-amyloid burden (Step 3) predicted 12-month change for Immediate Memory, Global Cognition, Attention/Processing Speed, and Executive Functioning (*p*s=0.006–0.046), and tau disposition (Step 4) significantly predicted 12-month change across all seven cognitive composites (*p*s=0.001–0.02). Further, the EOAD atrophy signature (Step 5) significantly predicted 12-month change for Immediate Memory, Global Cognition, Attention/Processing Speed, Executive Functioning, and Visuospatial Skills (*p*s=0.001–0.004). For the EOnonAD group, hippocampal volume (Step 2) did not incrementally predict 12-month change across any composite (*p*s=0.24–0.93). In contrast, β-amyloid burden (Step 3) predicted 12-month change in four of seven composites (*p*s=0.001–0.049), tau deposition (Step 4) predicted change in five composites (*p*s=0.003–0.04), and EOAD atrophy signature (Step 5) predicted change in two composites (*p*s=0.01–0.02).

4. Discussion

By calculating aged-matched SRB prediction equations (Table 2) for the LEADS cognitive battery, the current study has developed and validated a tool – 12-month reliable cognitive change – to enhance clinical intervention trials in early-onset dementia. As the LEADS battery incorporates all neuropsychological measures used in the UDS, these prediction equations also serve to extend those created by Kiselica and colleagues [21] to younger populations. When applying these prediction algorithms to the cognitively impaired groups in LEADS, the result is a metric of change that accounts for practice effects, regression to the mean, and individual variance common in repeated testing scenarios. This *change beyond expectation* is therefore a more reliable estimate of change over time relative to the simple difference in scores between T_1 and T_2 [45], as the latter may speak to a statistical difference between scores whereas the former considers a difference between performances using a normative standard [16]. The fact that this method permits the examination of change at the level of the individual [41] means that such a clinical metric could be particularly useful as either an outcome or selection variable for intervention trials in EOAD. Fig. 1 highlights this point, as the values listed in each panel of the figure denote the percentages of individual participants per group that either *declined beyond expectation*, remained stable, or *improved beyond expectation* for a particular domain. Although Table 3 indicates widespread and severe 12-month declines across groups for all domains, review of Fig. 1 reveals that approximately 1/3 of EOAD participants were stable on domains of language, attention/processing speed, and visuospatial skills over that time period. Even for domains where individual impairment was more

Table 4
Hierarchical regression results of Alzheimer's biomarkers predicting 12-month change.

	Incremental r^2 change, p value				
Early-Onset Alzheimer's Disease (n = 189)	Immediate Memory	Delayed Memory	Global Cognition	Attention/ Processing Speed	Executive Functioning
Step 1: Demographic Variables	–	–	–	–	–
Step 2: Hippocampal Volume	r^2 = 0.004, p=.42	r^2 = 0.020, p=.09	r^2 = 0.026, p=.06	r^2 = 0.017, p=.09	r^2 = 0.003, p=.50
Step 3: Amyloid Centiloid	r^2 = 0.051, p=.004	r^2 = 0.022, p=.07	r^2 = 0.045, p=.01	r^2 = 0.041, p=.006	r^2 = 0.031, p=.03
Step 4: Tau SUVR	r^2 = 0.117, p<.001	r^2 = 0.107, p<.001	r^2 = 0.168, p<.001	r^2 = 0.042, p=.004	r^2 = 0.077, p<.001
Step 5: EOAD Atrophy Signature	r^2 = 0.072, p<.001	r^2 = 0.013, p=.14	r^2 = 0.106, p<.001	r^2 = 0.041, p=.004	r^2 = 0.065, p<.001
	Incremental r^2 change, p value				
Early-Onset not Alzheimer's Disease (n = 43)	Immediate Memory	Delayed Memory	Global Cognition	Attention/ Processing Speed	Executive Functioning
Step 1: Demographic Variables	–	–	–	–	–
Step 2: Hippocampal Volume	r^2 = 0.014, p=.46	r^2 = 0.037, p=.24	r^2 = 0.009, p=.61	r^2 = 0.006, p=.63	r^2 = 0.000, p=.89
Step 3: Amyloid Centiloid	r^2 = 0.172, p=.007	r^2 = 0.066, p=.11	r^2 = 0.035, p=.32	r^2 = 0.146, p=.02	r^2 = 0.073, p=.08
Step 4: Tau SUVR	r^2 = 0.127, p=.01	r^2 = 0.076, p=.08	r^2 = 0.175, p=.02	r^2 = 0.136, p=.01	r^2 = 0.096, p=.04
Step 5: EOAD Atrophy Signature	r^2 = 0.085, p=.02	r^2 = 0.138, p=.01	r^2 = 0.000, p=.94	r^2 = 0.017, p=.35	r^2 = 0.042, p=.15

Note: Demographic Variables = age, education, sex, racial/ethnic diversity, and *Apolipoprotein ε4* status; Hippocampal Volume = w-score of bilateral hippocampal volume adjusting for intracranial volume, age, and sex; Amyloid Centiloid = standardized centiloid value from amyloid-PET; Tau SUVR = Tau Meta-Region of Interest Standardized Uptake Value Ratio from tau-PET; EOAD Atrophy Signature = w-score of bilateral composite cortical thickness of the regions of interested implicated in EOAD adjusting for age and sex (6).

universal (immediate and delayed memory, global cognition, and executive functioning), there were still 10–20 % of EOAD participants that did not decline over time. The effect is more pronounced for EOnonAD participants, for although the total EOnonAD sample displayed consistent declines when applying cutoffs typically used in clinical practice (negative *Z*-scores of 1.19–2.09), consistently 1/2 to 2/3rd of individual EOnonAD participants remained stable across cognitive domains over 12-months.

For intervention trials seeking to examine a pharmaceutical agent's capacity to reduce cognitive declines over time – as is commonly done in recent AD disease modifying treatment studies – selection of participants displaying declines will be important to draw reliable conclusions about the drug's efficacy. When reviewing recent work by Duff and Sevigny-Resetco looking at SRBs for measures in the UDS battery in LOAD [46] and comparing this to the current results, declines observed in EOAD appear to be greater over 12–18 months than those observed in LOAD. For example, Duff & Sevigny-Resetco found *Z*-scores of −3.35, −1.41, and −1.75 for the MOCA, Craft Memory Delayed Memory, and TMT-B tasks, respectively, whereas in Table 3 of the current study *Z*-scores for the EOAD group were −5.44, −4.16, and −3.55 for the same measures. To ensure that this comparison is not biased by differences in the prediction equations as a result of characteristics of the respective development samples, review of the raw scores for these measures tell a similar story. Specifically, $T_2 - T_1$ declines for Duff & Sevigny-Resetco were 1.92 points on the MOCA, 0.79 points on Craft Memory Delayed Memory, and 2.01 second on TMT-B for LOAD, versus 2.80 points on the MOCA, 1.3 points on Craft Memory Delayed Memory, and 18.82 second on TMT-B for EOAD currently. Relatedly, the "minimal clinically important difference" is a metric that determines the smallest magnitude of a change necessary for patients to perceive as declining/improving [47]. This 2.80-point raw-score-decline on the MOCA over 12-months for the EOAD group exceeds the declines of 0.89, 1.26, and 2.32 points on the MMSE necessary to indicate a clinically meaningful decline in cognitively normal, MCI, and "mild AD dementia" patients, respectively [48]. Together, these results suggest that use of EOAD cohorts in clinical trials may possess a distinct advantage to LOAD cohorts in that declines are more readily observable over traditional timelines for intervention trials in AD (12–18 months).

Additionally, an outcome measure for such trials needs to be sensitive to changes in cognition across either one or more domains, but not so sensitive that declines are washed out due to "floor effects". First, as previously indicated in Table 3, the composite *Z*-scores were consistently large and negative across domains for both EOAD and EOnonAD groups, indicating that 12-month reliable change metrics maintain good sensitivity to detect impairments in a variety of domains. This is important because unlike in LOAD where the initial cognitive manifestations are primarily in memory [49], we have previously shown that EOAD presents in a more diffuse cognitive profile – with particular impact on non-amnestic domains [13]. Therefore outcome measures in EOAD trials will need to detect change in both amnestic and non-amnestic domains. Second, outcome measures should not be highly susceptible to floor effects, or the psychometric inability of a measure to detect scores lower than that observed at baseline. Previously, we documented raw score longitudinal change in cognition in EOAD between baseline and up to 42 months [50], observing that memory measures like RAVLT and Benson Delayed Recall had little room to decline beyond the low baseline scores (1.79 and 2.85 points, respectively). Those results discouraged the use of memory tests as outcome measures for EOAD trials [50], given their inability to detect decline beyond baseline. In contrast to raw scores, individual and composite *Z*-scores for memory measures appear to be capable of registering significant 12-month change in EOAD, specifically because of the SRB emphasis on *change beyond expectation* relative to control samples. These metrics are therefore less restricted by the distance from baseline scores to the floor for a measure, but instead can be sensitive towards identifying treatment effects even for low baseline performance. Even more encouragingly, the ADAS-Cog shows robust 12-month effects in EOAD and is already widely used as an outcome measure in AD clinical trials, supporting its use in trials targeting EOAD. Together, this provides strong support for SRB-based 12-month reliable cognitive change as an outcome measure in EOAD trials.

Examining Table 3 more closely, it can be observed that 12-month declines were most pronounced for measures of global cognition and visuospatial skills, followed by domains of immediate memory and attention/processing speed. The magnitude of declines in the former two domains are likely explained at least in part psychometrically, as the calculation of *Z*-scores incorporates the standard error term for each measure in the domain; because cognitively normal participants tend to perform strongly on these particular tasks, the standard error values are quite small (see Table 2), and mistakes by cognitively-impaired groups are magnified resulting in large negative *Z*-scores (beyond those typically observed in clinical settings; e.g., *Z*s=−6.18 to −5.48). Additionally, a portion of the EOAD sample presented with a clinical phenotype of Posterior Cortical Atrophy, which could in part lead to a bimodal distribution of the Visuospatial domain. However, the findings for immediate memory and attention/processing speed are consistent with documentation of non-amnestic predominance of deficits in EOAD at baseline [43], as well as the frequency of non-amnestic clinical phenotypes observed in EOAD (e.g., logopenic variant primary progressive aphasia, posterior cortical atrophy, or frontal-variant AD) [1,51,52]. While Tort-Merino

and colleagues recently observed similarly large declines in measures of learning and attention/executive functioning in a sample of EOAD participants from Spain, they found rates of decline for memory measures to be just as large [53]. As MRI findings from Touroutoglou et al. [6]. revealed that the most pronounced atrophy signals for EOAD are in regions associated with attentional/visuoexecutive processing – and not in hippocampal/medial temporal lobe regions associated with memory dysfunction – the pattern of neurodegeneration in EOAD therefore supports these current findings.

Support for these 12-month change scores can also be provided from our group comparisons and predictors of decline. For example, results revealed that the EOAD participants displayed greater 12-month declines relative to expectation than EOnonAD participants for composites of Immediate and Delayed Memory, Global Cognition, Attention/Processing Speed, and Executive Functioning, even after accounting for *APOE ε4* status and baseline MMSE score. These results support our hypotheses and are consistent with previous findings showing widespread worse performances at baseline for EOAD participants relative to those with EOnonAD [43], and speak to the commonly-observed trend that those with lower scores at baseline on particular domains tend to be more susceptible to cognitive declines, and less susceptible to benefitting from previous exposure (the "rich get richer effect" [54–56]). Similarly, the presence of cerebral β-amyloid accumulation in EOAD participants appears to lead to worse cognitive outcomes across several cognitive domains. This is likely a result of β-amyloid oligomers triggering neuronal death from pro-inflammatory, metabolic reprogramming related to a host of downstream pathways, including oxytosis/ferroptosis, mitochondrial dysfunction, and autophagy/lysosomal dysfunction [57–59].

Also consistent with hypotheses, Table 4 revealed that 12-month cognitive change in the LEADS battery was consistently predicted by common AD biomarkers. Specifically, global β-amyloid and tau accumulation was predictive of declines across the majority of cognitive domain composites in EOAD participants, with tau deposition having a slightly higher magnitude of effect than β-amyloid burden. This is likely associated with tau deposition occurring later in the pathological sequela of AD [60], and thus being more temporally synchronous with the manifestation of cognitive change. While the EOAD atrophy signature – a composite of bilateral cortical thickness in ROIs implicated in EOAD – was predictive of 12-month change across five of seven cognitive domains, bilateral hippocampal volume was not predictive of declines in any cognitive domain. This is consistent with literature suggesting that memory dysfunction in EOAD is more related to widespread memory networks and executive dysfunction, instead of hippocampal atrophy as observed in LOAD [61]. These results also provide convergent validation of the EOAD atrophy signature using longitudinal data. The prediction results for EOnonAD were surprising, however, as they also revealed that global amyloid and tau accumulation successfully predicted 12-month decline across domains of immediate memory, global cognition, and language; this is despite EOnonAD patients by definition not having a high enough amyloid burden to warrant a diagnosis of EOAD at baseline. These results likely highlight the heterogeneous etiologies contributing to EOnonAD, as well as the frequent occurrence of concomitant AD pathology in other forms of neurodegeneration [62,63]. As the sample size of the EOnonAD group was too small to permit supplementary analysis among clinical phenotypes of EOnonAD, future analyses should be repeated when larger samples of EOnonAD participants have been enrolled.

A few limitations should be listed for current analyses. First, as these SRB prediction equations were created for a specific set of cognitive measures and for individuals matching the age-range of the diagnosis of EOAD (aged 40–64), our findings may not generalize to other cognitive measures or older age populations. Second, these findings were observed for retest intervals of approximately 12-months based on the retest interval in LEADS, and therefore may not generalize to other retest intervals (e.g., 6 or 18 months) until examined in further studies [23]. Third, these SRB equations were developed in a cognitively intact sample, therefore a degree of extrapolation was required on the predictive models when applying them to clinical samples. Although there are limitations to this statistically, including for the potential for over-estimation at the extremes of the distribution (leading to higher expectations for improvement at T_2 and the subsequent appearance of under-performance for those impaired-at-baseline upon follow-up), this step is routine in the cognitive SRB literature [17] and necessary to provide an appropriate clinical benchmark for "expected change over time". Consequently, the impact of floor effects and their influence on extrapolation in EOAD requires further investigation, with future work considering curvilinear modeling of cognitive trajectories in LEADS. Fourth, the SRB-developmental sample was small (n = 78) relative to the previously-published prediction equations for these measures in older adults (n = 1341 for [21], and n = 386 for [20]). Although we felt that using this sample was more appropriate given the consistency of ages and diagnostic classification methods to the EOAD and EOnonAD groups, the relatively smaller sample size could have resulted in greater prediction variance (SE_{est}). Future work is warranted to validate these SRBs in an external sample. Relatedly, although the developmental sample was relatively heterogenous in terms of racial/ethnic diversity and sex, the cognitively impaired groups in LEADS were rather homogenous for these demographic variables, as well as for educational attainment. Repeated analysis is advised after LEADS is able to enroll a more broadly representative sample for its cognitively impaired groups. Fifth, the LEADS battery was created to be complementary to the NACC UDS neuropsychological battery; therefore, the Z-score composites were comprised of varying numbers of cognitive measures, with the domain of visuospatial skills only including one measure and the global cognition domain only including two measures. Finally, although reliable change methods account for a number of methodological sources of bias, *change beyond expectation* does not necessarily equate to clinical significance – as a statistically significant change that is too small to be of clinical relevance is possible.

Despite these limitations, the current results support the validation of using 12-month reliable cognitive change as a clinical metric in clinical trials in EOAD populations like LEADS. Given the compatibility of LEADS and NACC UDS batteries, these results similarly hold for younger populations in NACC, permitting the more accurate quantification of meaningful change beyond expectation over 12-months. Results similarly support that using EOAD cohorts in clinical trials may confer particular advantages to LOAD cohorts. The use of reliable and meaningful measurements of change as trial outcomes will enhance the success of EOAD trials and permit a better understanding of individual responses to treatment.

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Consent

All authors have read and provided consent to be associated with this manuscript.

Declaration of competing interest

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CRediT authorship contribution statement

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Supplementary materials

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