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CLINICAL MANIFESTATIONS

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NEUROPSYCHOLOGY

Longitudinal cognitive trajectories in sporadic early-onset Alzheimer's Disease: Findings from LEADS

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Abstract

Background: Early Onset Alzheimer's Disease (EOAD) is a rare condition that manifests prior to the age of 65, and affects approximately 5% of patients with Alzheimer's disease. The Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) is the largest prospectively-evaluated cohort of participants with sporadic EOAD in the United States, initiated to better understand the features of this condition. The current analyses sought to examine longitudinal cognitive trajectories of patients with EOAD over time.

Method: Data from 100 participants with amyloid-positive EOAD, 30 participants with amyloid-negative cognitive impairment (EOnonAD), and 65 cognitively normal age-matched participants were compared. All had at least three study visits. Cognitive trajectories across a comprehensive cognitive battery across 24-56 months were examined using mixed-effects modeling, including the years of onset x diagnostic group interaction controlling for years since onset, education, sex, and the random effect of each participant.

Result: Across all measures, clinical groups generally displayed declines over time, with performances for the EOAD group tending to approach the lower limit of performance ranges (**Figure 1**). Relatedly, significantly greater slopes of decline were seen over time for the EOAD group than the CN group across all cognitive domains evaluated (ps<.001; **Table 1**). When comparing between clinical groups, greater declines were also evident for the EOAD group relative to the EOnonAD group for a screener of global cognition, and for specific measures of attention, verbal fluency, processing speed, language, and delayed story recall (ps .001 to .049; **Table 2**). No differences

in trajectory were observed between clinical groups for unstructured verbal memory, visual memory, or visuospatial skills (ps>.05; **Tables 1 and 2**).

Conclusion: In addition to worse cognition at baseline, sporadic EOAD participants displayed pronounced declines in cognition over 24-56 months across all domains evaluated. Relative to the EOnonAD group, cognitive trajectories appear to be worse predominantly for executive and attentional processes, with variability across episodic memory tasks. This suggests that EOAD pathology is not solely directed at memory functioning. Future research will focus on comparing cognitive trajectories of EOAD and late-onset AD, in an effort to understand similarities and differences in the types and rates of cognitive trajectories.

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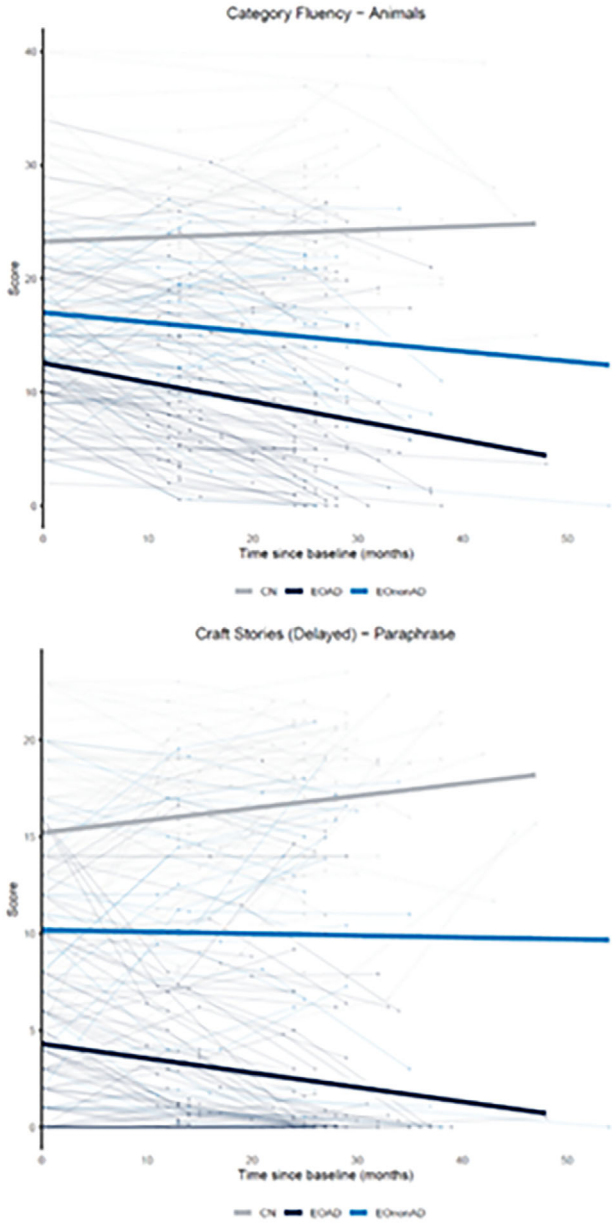

Figure 1. Cognitive performance over time for the cognitively normal (CN), amyloid-positive Early-Onset Alzheimer's Disease (EOAD), and amyloid-negative Early-Onset non-Alzheimer's Disease (EOnonAD) groups.

Table 1. Results of mixed-effects linear regression between cognitively normal (CN) and amyloid-positive Early-Onset Alzheimer's Disease (EOAD) groups.

	EOAD vs CN		
	B (se)	p-value	adjusted p-value
MOCA	-1.94 (0.22)	<0.0001	<0.0001
Craft Stories - immediate	-1.47 (0.25)	<0.0001	<0.0001
Craft Stories - delayed	-1.54 (0.24)	<0.0001	<0.0001
Benson Complex Figure - copy	-1.12 (0.2)	<0.0001	<0.0001
Benson Complex Figure - recall	-0.68 (0.17)	<0.0001	0.0001
Number Span Forward	-0.24 (0.08)	0.0032	0.0044
Number Span Backward	-0.33 (0.07)	<0.0001	<0.0001
Category Fluency - Animals	-1.65 (0.27)	<0.0001	<0.0001
Category Fluency - Vegetables	-0.97 (0.23)	<0.0001	<0.0001
TrailA	0.07 (0.09)	0.4252	0.4488
TrailB	-1.96 (0.36)	<0.0001	<0.0001
MINT	-1.37 (0.19)	<0.0001	<0.0001
Phonemic Fluency	-2.72 (0.44)	<0.0001	<0.0001
ADAS	0.78 (0.49)	0.1113	0.1321
AVLT	-0.8 (0.18)	<0.0001	<0.0001
Flanker	-0.14 (0.09)	0.1286	0.1437
LO	-0.19 (0.64)	0.7631	0.7631
LL	-1.1 (0.38)	0.0039	0.0049
Match (Digit Symbol)	-3.64 (0.62)	<0.0001	<0.0001

Reported are the beta parameter estimates, standard error (se), p-values and adjusted p-values using the false positive rate method for EOAD vs CN. These models adjust for years from onset, education, interaction between years of onset and diagnosis group, gender and the random beta of each subject. Only participants with Month 24 visit are included. A total of 195 participants had a Month 24 visit, which consists of 65 CN participants, 30 EOnonAD participants and 100 EOAD participants.

Table 2. Results of mixed-effects linear regression between cognitively normal (CN) and amyloid-negative Early-Onset non-Alzheimer's Disease (EOnonAD) groups.

	EOAD vs EOnonAD		
	B (se)	p-value	adjusted p-value
MOCA	-1.41 (0.38)	0.0002	0.0041
Craft Stories - immediate	-0.62 (0.32)	0.0510	0.0969
Craft Stories - delayed	-0.83 (0.29)	0.0051	0.0195
Benson Complex Figure - copy	-0.57 (0.35)	0.1041	0.1521
Benson Complex Figure - recall	0 (0.26)	0.9878	0.9878
Number Span Forward	-0.41 (0.11)	0.0004	0.0041
Number Span Backward	-0.35 (0.12)	0.0026	0.0163
Category Fluency - Animals	-0.87 (0.38)	0.0232	0.0489
Category Fluency - Vegetables	-0.85 (0.29)	0.0039	0.0184
TrailA	0.06 (0.12)	0.6425	0.8138
TrailB	-1.09 (0.61)	0.0732	0.1173
MINT	-0.82 (0.31)	0.0090	0.0245
Phonemic Fluency	-1.46 (0.64)	0.0226	0.0489
ADAS	0.39 (0.69)	0.5682	0.7711
AVLT	0.08 (0.22)	0.7288	0.8655
Flanker	0.01 (0.15)	0.9405	0.9878
LO	0.12 (0.96)	0.9036	0.9878
LL	-1 (0.56)	0.0741	0.1173
Match (Digit Symbol)	-2.7 (0.98)	0.0066	0.0209

Reported are the beta parameter estimates, standard error (se), p-values and adjusted p-values using the false positive rate method for EOAD (compared to EOnonAD). These models adjust for years from onset, education, interaction between years of onset and diagnosis group, gender and the random beta of each subject. Only participants with a Month 24 visit are included. A total of 195 participants had a Month 24 visit, which consists of 65 CN participants, 30 EOnonAD participants and 100 EOAD participants.