

Cognitive, neuropsychiatric and imaging comparisons between early-onset and late-onset Alzheimer's disease participants from LEADS and ADNI3

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Abstract

Background: The overarching goal of the Longitudinal Early-onset Alzheimer Disease study (LEADS) is to optimally characterize early-onset AD (EOAD) and establish an EOAD clinical trials network. Here we report the baseline demographic and imaging biomarker comparisons of the LEADS cohort to late-onset AD (LOAD) subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI3).

Method: 123 amyloid-positive EOAD, 47 amyloid-negative EOnonAD, 60 cognitively normal young controls were compared to 130 amyloid-positive LOAD, 110 amyloid-negative LOnonAD and 286 amyloid-negative cognitively normal older controls. To account for the effect of cognitive aging between EO and LO populations, each cognitive measure was Z-transformed. Cortical and hippocampal atrophy were quantified using W-scores adjusted for age, sex and total intracranial volume. Z-scores and W-scores were compared using t-test or Wilcoxon rank test as appropriate. All p-values were corrected for multiple comparisons using the false discovery rate correction.

Result: EOAD showed greater pathology burden and greater cortical atrophy (AD signature) relative to LOAD. EOAD also showed greater cognitive impairment across all cognitive tests. EOAD showed greater functional impairment, more depression but less neuropsychiatric behaviors overall compared to LOAD (Table 1 and Figure 1, all $p < 0.05$). Repeating the analyses stratified by cognitive stage (MCI/dementia) or CDR global rating (0.5/1) did not result in any major differences.

EOnonAD differed from LOnonAD by also showing greater impairment on all cognitive and functional measures. There were no significant differences in amyloid and tau

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burden, or atrophy W-scores between these groups. EOnonAD were more depressed and showed more functional impairment compared to LOnonAD (Table 2 and Figure 2, all $p < 0.05$). Repeating the analyses split by cognitive stage (MCI/dementia) or CDR global rating (0.5/1) did not result in any major differences.

Conclusion: Consistent with our preexisting hypotheses, EOAD and EOnonAD perform much worse relative to their LO counterparts. EOAD also show greater pathological burden as expected. The reported analyses were done in chronological rather than disease time (time since disease onset). Benchmarking individuals along the disease spectrum might prove to be a better strategy especially when conducting analyses on rate of disease progression.

Figure 1. EOAD vs LOAD

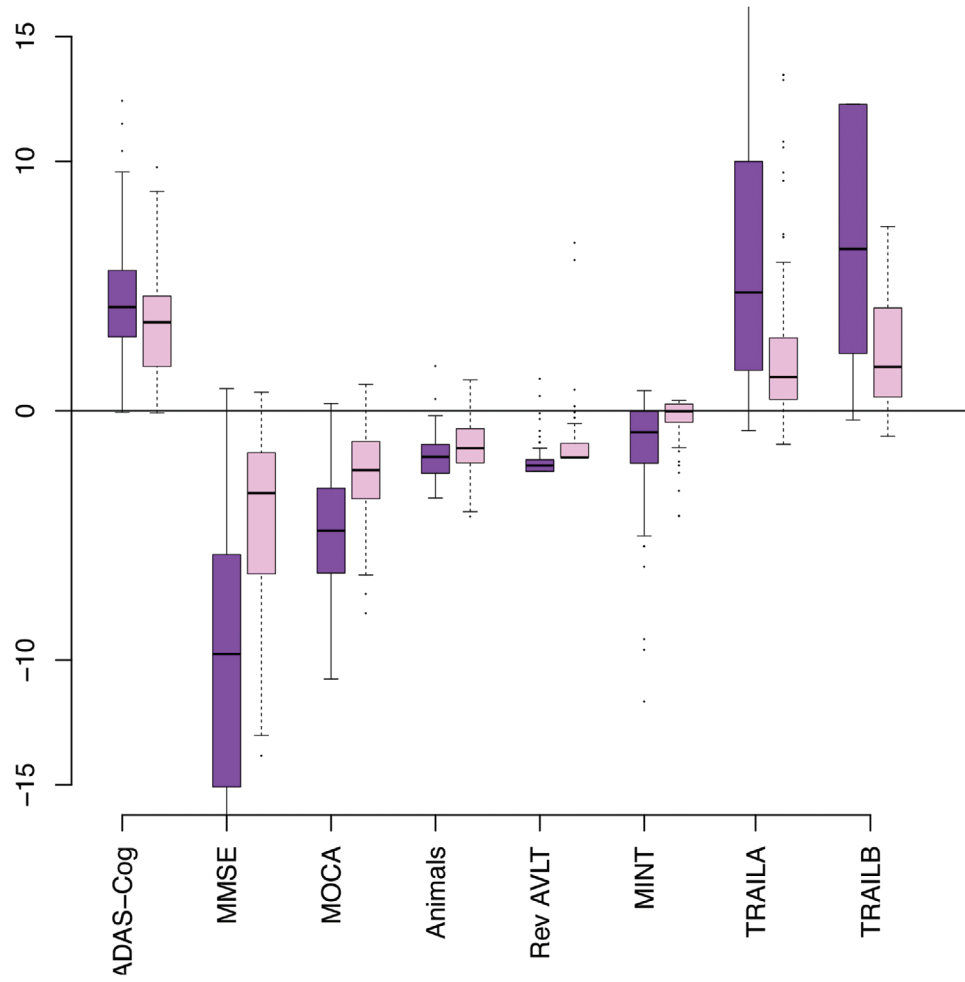


FIGURE 1

Figure 2. EOnonAD vs LOnonAD

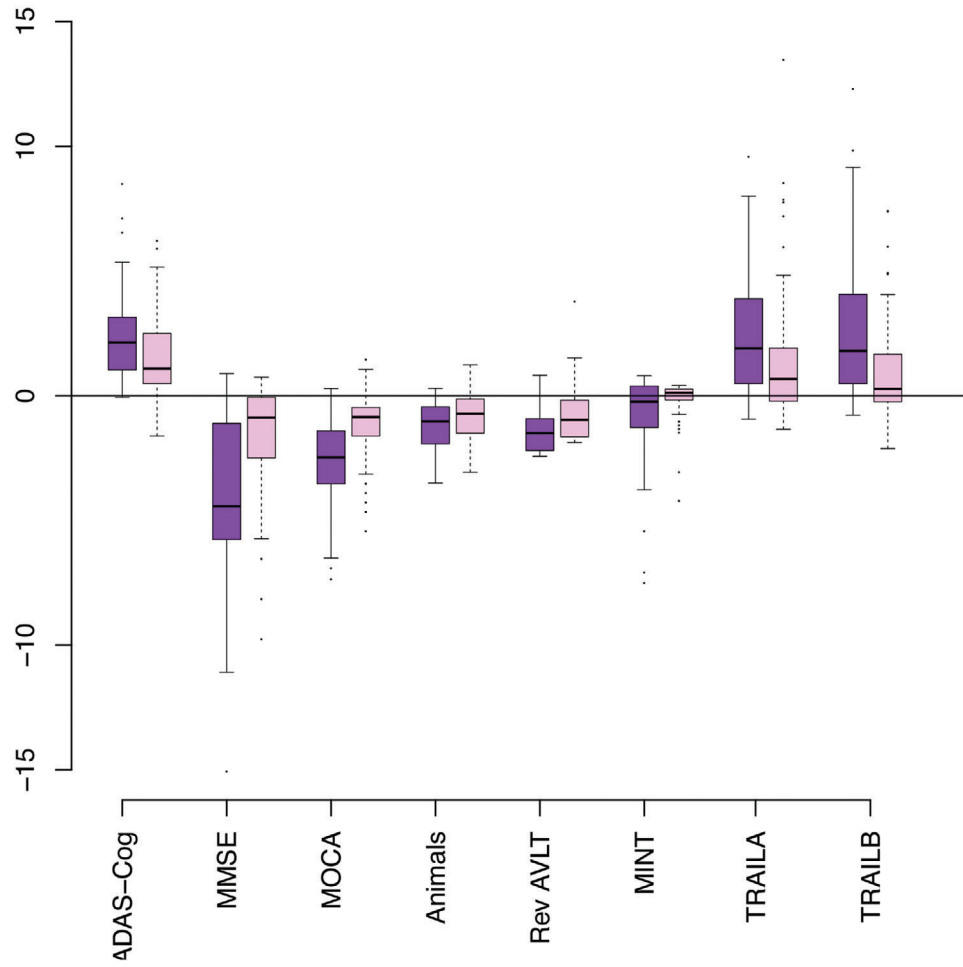


FIGURE 2

TABLE 1

Table 1. EOAD vs LOAD

	LEADS EOAD (N = 123)	ADNI LOAD (N = 130)	Standardized LEADS	Standardized ADNI	p-value
Age (years), Mean (SD)	58.89 (3.81)	77.34 (6.82)	--	--	<0.0001
Age at Onset, (years), Mean (SD)	55.63 (4.20)	76.48 (6.29)	--	--	<0.0001
Disease Duration, (years), Mean (SD)	3.21 (2.08)	0.85 (2.49)	--	--	<0.0001
Education (years), Mean (SD)	15.53 (2.45)	15.86 (2.51)	--	--	0.3148
Sex, females, N (%)	66 (53.66%)	58 (44.62%)	--	--	0.1763
FBB mean SUVR, Mean (SD)	1.56 (0.16)	1.50 (0.18)	--	--	0.0056
FTP metaROI SUVR, Mean (SD)	2.06 (0.44)	1.52 (0.33)	--	--	<0.0001
Hippocampus, W- score	-1.40 (0.90)	-1.18 (0.19)	--	--	0.1531
Entorhinal, W- score	-1.59 (1.52)	-1.59 (1.80)	--	--	0.9929
AD Signature, W- score	-2.42 (1.62)	-0.98 (1.19)	--	--	<0.0001
CDRGlobal 0.5/1, %	61%/39%	72%/28%	--	--	0.076
ADAS-Cog, Mean (SD)	33.64 (9.79)	26.96 (8.30)	4.42 (2.42)	3.46 (2.01)	0.0010*
MMSE, Mean (SD)	21.70 (4.65)	23.67 (5.28)	-10.16 (6.18)	-4.38 (4.27)	<0.0001*
MOCA, Mean (SD)	16.02 (5.77)	19.53 (4.63)	-4.80 (2.45)	-2.56	<0.0001*
Animal fluency, Mean (SD)	12.02 (5.30)	14.76 (5.65)	-1.84 (0.87)	-1.35 (1.11)	0.0002*
RevAVLT DR, Mean (SD)	1.80 (2.61)	2.23 (5.02)	-2.01 (0.61)	-1.37 (1.13)	<0.0001*
MINT, Mean (SD)	26.75 (5.27)	27.00 (6.00)	-1.38 (2.19)	-0.32 (0.87)	<0.0001*
Trails A, Mean (SD)	70.09 (43.55)	49.95 (27.18)	6.45 (6.18)	2.24 (3.05)	<0.0001*
Trails B, Mean (SD)	196.0 (94.74)	152.0 (83.20)	7.04 (4.78)	2.60 (2.69)	<0.0001*
FAQ, Mean (SD)	14.34 (7.59)	8.54 (7.60)	--	--	<0.0001
GDS, Mean (SD)	4.00 (2.50)	2.00 (2.00)	--	--	0.0070
NPI, Mean (SD)	3.12 (2.24)	5.76 (7.04)	--	--	0.0002

* p-value was calculated based on standardized Z-scores

TABLE 2

Table 2. EOnonAD vs LOnonAD

	LEADS EOnonAD (N = 47)	ADNI LOnonAD (N = 110)	Standardized LEADS	Standardized ADNI	p-value
Age (years), Mean (SD)	56.94 (6.65)	76.81 (6.23)	--	--	<0.0001
Age at Onset, (years), Mean (SD)	54.17 (6.32)	75.86 (5.67)	--	--	<0.0001
Disease Duration, (years), Mean (SD)	3.32 (1.70)	0.95 (2.55)	--	--	<0.0001
Education (years), Mean (SD)	15.60 (2.59)	16.45 (2.75)	--	--	0.1281
Sex, females, N (%)	34 (72.34)	75 (68.18)	--	--	0.6510
FBB mean SUVR, Mean (SD)	0.99 (0.06)	1.01 (0.08)	--	--	0.1344
FTP metaROI SUVR, Mean (SD)	1.22 (0.30)	1.21 (0.16)	--	--	0.8707
Hippocampus, W- score	-0.75 (1.14)	-0.56 (1.41)	--	--	0.5241
Entorhinal, W- score	-0.85(2.0)	-0.85 (2.03)	--	--	0.9869
AD Signature, W- score	-0.83 (1.81)	-0.39 (1.25)	--	--	0.1162
CDRGlobal 0.5/1, %	93%/7%	92%/8%	--	--	0.2052
ADAS-Cog, Mean (SD)	26.30 (6.80)	18.78 (6.43)	2.40 (1.87)	1.48 (1.56)	0.0048*
MMSE, Mean (SD)	26.04 (3.04)	27.42 (2.75)	-4.38 (4.04)	-1.35 (2.22)	<0.0001*
MOCA, Mean (SD)	21.13 (4.31)	23.15 (3.60)	-2.63 (1.83)	-1.18 (1.38)	<0.0001*
Animal fluency, Mean (SD)	15.62 (5.85)	17.92 (5.15)	-1.25 (0.96)	-0.74 (1.01)	0.0089*
RevAVLT DR, Mean (SD)	4.23 (3.48)	4.58 (4.26)	-1.45 (0.81)	-0.84 (0.96)	0.0007*
MINT, Mean (SD)	27.85 (4.74)	28.57 (5.29)	-0.92 (1.97)	-0.09 (0.77)	0.0007*
Trails A, Mean (SD)	45.00 (28.45)	40.59 (20.30)	2.89 (4.04)	1.19 (2.28)	0.0034*
Trails B, Mean (SD)	110.2 (60.28)	103.4 (63.21)	2.71 (3.04)	1.03 (2.04)	0.0007*
GDS, Mean (SD)	3.00 (3.00)	1.00 (2.00)	--	--	0.0004
FAQ, Mean (SD)	7.62 (5.86)	4.00 (5.55)	--	--	0.0037
NPI, Mean (SD)	4.28 (3.07)	4.62 (6.85)	--	--	0.7452

* p-value was calculated based on standardized Z-scores