Distinct and Overlapping Cognitive Features in Early-Onset Alzheimer's Disease and Posterior Cortical Atrophy

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KEY TAKEAWAYS: 1. At the same level of severity, PCA and aEOAD are more cognitively similar than clinically assumed; visuospatial cognitive performance is the only discriminator. 2. Visuospatial cognitive testing is the most critical differentiating tool between these variants and should be standard in AD assessment protocols. 3. The absence of routine visuospatial assessment risks PCA misdiagnosis, carrying direct consequences for clinical practice and trials.

BACKGROUND & OBJECTIVE

- Posterior cortical atrophy (**PCA**) is defined as a **visuospatial-predominant** syndrome with relative sparing of executive, language, and episodic memory functions in early stages. [1]
- Amnestic Early-onset Alzheimer's disease (**aEOAD**), defined as symptom onset younger than age 65, is associated with **amnestic-predominant** deficits and relative sparing in other domains. [2,5]
- Secondary domains of impairment across AD syndromes are often observed at initial clinical presentation, obscuring phenotypic boundaries and complicating diagnosis.[3, 4, 5.]
- Despite distinct clinical diagnostic criteria, the degree of cognitive and neuroanatomical overlap between PCA and aEOAD has not been systematically characterized.

Objective: To characterize the overlapping and distinct profiles of cognitive impairment and cortical atrophy across PCA and aEOAD.

METHODS

Participants: The neuropsychological profiles of 79 participants who met criteria for either PCA (N= 42) or aEOAD (N= 37) largely at the early symptomatic stage of illness were compared (Table 2). 76 individuals were confirmed to be Aβ-positive, the remaining 3 were untested.

Cognitive Domain	Neuropsychological Tests
Attention and Processing Speed	• MAT Part A • Digit Span Forwards
Executive Function	• MAT Part B • COWA Letter Fluency • FAB Inhibitory Control • Digit Span Backwards
Visuospatial	• BCE Overlapping Figures • VOSP Number Location • NAB Visual Discrimination
Language	• COWA Animal Fluency • Auditory Naming Test w/ Phonemic Cues (50-item)
Memory	• OLMT recognition discriminability (d') • CVLT-II-SF recognition discriminability(d')

Table 1. *Neuropsychological tests within each cognitive domain.* *MAT = Mental Alternation Test, BCE = Boston Cognitive Examination, VOSP = Visual Object and Space Perception Battery, NAB= Neuropsychological Assessment Battery, COWA = Controlled Word Association Test, OLMT = Object-Location Memory Test, CVLT-II-SF = California Verbal Learning Test Second Edition Short Form, FAB = Frontal Assessment Battery*

Neuropsychological Assessment

- A comprehensive neuropsychological battery was administered (**Table 1**). Medians and interquartile ranges summarized within-group performance in each domain (**Figure 1**).
- Domain-level cognitive performance was compared between groups using Mann-Whitney U tests on norm-referenced z-scores (**Figure 1**).

Neuroimaging

- Cortical thickness was measured using FreeSurfer v7.1.1.
- Vertex-wise correlations with cognitive domain z-scores were examined using linear regression, with age and sex included as covariates.
- Analyses were conducted across the full cohort to capitalize on the full range of brain-behavior heterogeneity.

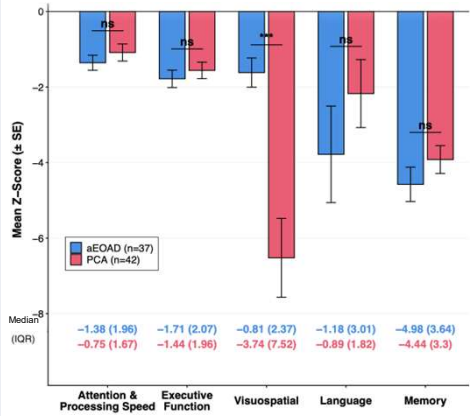
RESULTS

Table 2. ***Participant characteristics***

	aEOAD (n = 37)	PCA (n = 42)	p
Mean age, years (SD)	61.94 (6.15)	67.78 (8.16)	0.001*
Sex, male, n	15	19	0.847
Education (years), M (SD)	16.54 (2.16)	16.98 (2.25)	0.383
CDR Global = 0.5	N= 20	N= 20	0.246
CDR Global = 1	N= 17	N= 19	0.246
CDR Global = 2	N= 0	N= 3	0.246
MoCA Total Score, M (SD)	18.22 (5.65)	17.49 (6.31)	0.598

*aEOAD = Amnestic Early-Onset Alzheimer's Disease; PCA = Posterior Cortical Atrophy; MoCA = Montreal Cognitive Assessment; MoCA maximum possible score is 30; CDR = Clinical Dementia Rating. CDR of 0.5 = very mild impairment, CDR of 1 = mild impairment, CDR of 2 = moderate impairment, CDR of 3 = severe impairment. Continuous variables were compared using Welch's t-test; categorical variables were compared using the chi-square test of independence. **p < .001*

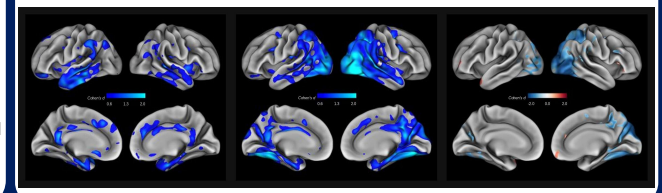
Figure 1. ***Cognitive Profiles in aEOAD and PCA***



- PCA demonstrated greater visuospatial impairment than aEOAD (p<.001), while performance across memory, executive function, and language domains **did not differ** between groups.
- The visuospatial dissociation, consistent with known posterior parieto-occipital involvement in PCA **(Figure 2),** reinforces visuospatial assessment as the only key domain distinguishing between these variants.

Figure 2. ***Cortical atrophy in aEOAD and PCA***

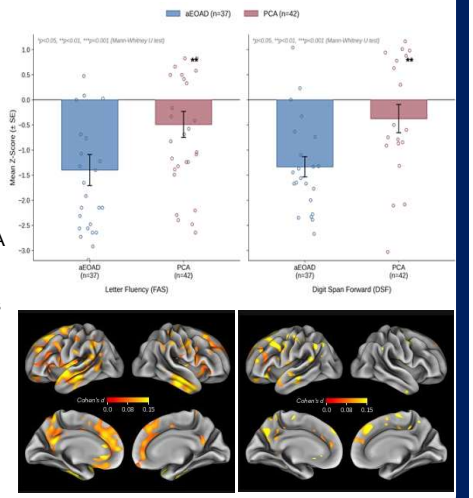
a. *aEOAD Atrophy* **b.** *PCA Atrophy* **c.** *aEOAD v. PCA*



RESULTS

Figure 3. ***Selective sparing of verbal attention and letter fluency in PCA***

- Subtest-level analyses revealed selective impairment in letter fluency and inhibitory control in aEOAD relative to PCA (p<.05), with performance on these tasks correlating with prefrontal cortical atrophy, which is typically spared in PCA.



CONCLUSIONS

- In addition to an expected predominant visuospatial deficit, PCA participants exhibited non-visuospatial impairment comparable to aEOAD at similar levels of clinical severity.
- Subtest-level analyses revealed specific impairment in aspects of executive functions in aEOAD relative to PCA that are associated with cortical thickness in the prefrontal cortex– an area less affected in PCA .
- **The broader equivalence across domains underscores the risk of misclassifying or under-detecting PCA** in settings where visuospatial testing is not routinely administered (e.g., clinical trials outcome measures).
- **Visuospatial assessment emerges as the most diagnostically discriminating domain between PCA and EOAD**, supporting targeted use of posterior cortical batteries in differential diagnosis.
- **Our results support calls for syndrome-specific neuropsychological protocols** in memory clinics, observational research cohorts, and clinical trials.

REFERENCES

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