

Neuropsychological and Plasma Biomarker Signatures of Alzheimer's Disease: a Catalan Multicenter Study

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BACKGROUND

Blood-based biomarkers (BBMs) have emerged as accurate and minimally invasive tools for the diagnosis of Alzheimer's disease (AD). However, their relationship with neuropsychological performance across real-world settings remains unexplored. Alzheimer's disease (AD) and suspected non-neurodegenerative cognitive impairment (SND) frequently present with overlapping clinical profiles, challenging differential diagnosis.

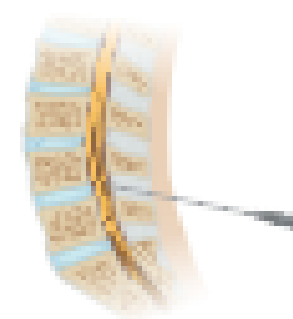
By leveraging data from six memory clinics across **Catalonia** (Spain), we aimed to characterize and compare the neuropsychological profiles of AD and SND, and to explore their associations with plasma p-tau217 and neurofilament light chain (NfL) concentrations.



METHODS

We included 177 individuals who were classified into three groups according their clinical and CSF profile: AD (n=92), suspected non-neurodegenerative cognitive impairment (SND; n=40), and cognitively unimpaired controls (CU; n=45).

* PROCEDURES


Lumbar puncture
CSF Aβ₄₂
CSF t-tau CSF p-tau


Blood sample
Plasma p-tau₂₁₇
Plasma NfL


Neuropsychological assessment
Covering the 5 major cognitive domains

* STATISTICAL ANALYSES

- Baseline neuropsychological performance between AD and SND was compared using ANCOVAs adjusting for age and education
- Linear regression models were performed to examine the associations between plasma biomarkers and cognitive performance
- Each neuropsychological measure was used as the dependent variable in separate models, with plasma p-tau217 and NfL as independent variables
- All models were adjusted for age and years of education

RESULTS

There were no differences in age, sex or years of education among the patient groups. Biomarker levels were more altered in the AD group when compared to SND. Demographics, clinical and biomarker data are shown in Table 1.

Compared to SND, the AD group showed poorer performance on verbal learning and encoding tasks, as well as in measures assessing free and cued delayed recall and visual memory (all p<0.01). Additionally, significant differences were found in favor of the SND group in visuospatial (F[1,130]=4.3,p<0.05) and visuospatial (F[1,130]=4.9,p<0.05) functions [Figure 1].

In SND and AD participants, while NfL did not show significant associations, plasma p-tau217 was negatively associated with learning and memory measures (β =-2.08 to -0.61, all p<0.05), auditory comprehension tasks (β =-4.78, p<0.05), visuospatial function (β =-3.65,p<0.01), and visual attention/processing speed (β =-2.26, <0.05) [Figure 2].

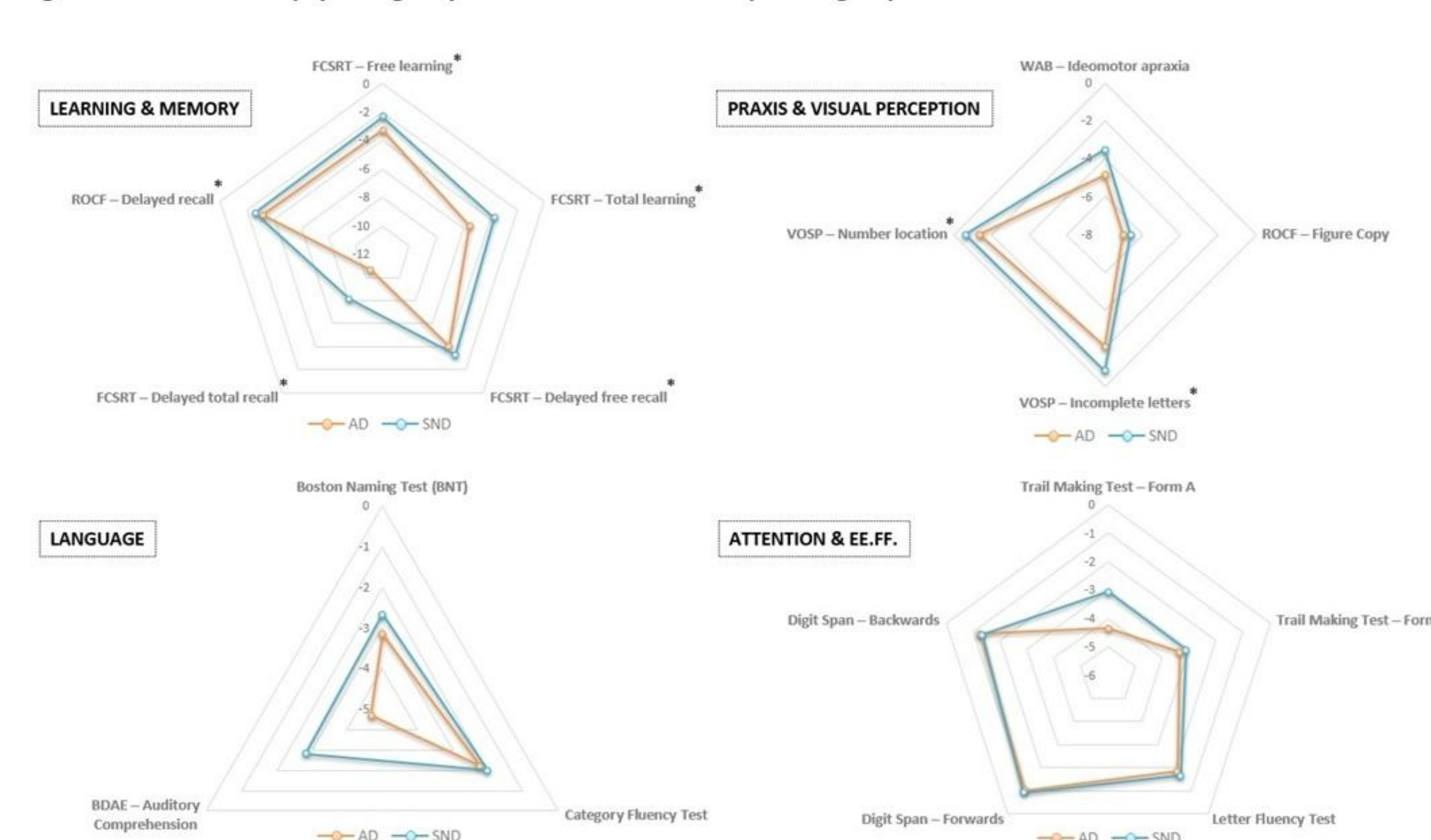
Table 1. Demographics, clinical data and biomarker levels of the study groups

	SND n=40	AD n=92	CU n=45
Demographics & clinical data			
Age at baseline	71.26±6.56 ³	72.16±5.07 ³	60.75±10.46
Sex (% women)	47.5%	55.4%	66.7%
Years of education	10.05±4.15	10.27±4.41	11.96±3.91
Age at onset	69.32±6.71	70.11±5.34	-
Time to diagnosis (years)	-1.98±1.97	-2.05±1.57	-
GDS (% stage 3)	87.5%	75%	0%
MMSE score	25.39±3.55 ^{2,3}	23.53±3.56 ^{1,3}	28.8±1.42 ^{1,2}
Biomarkers levels			
CSF Aβ ₁₋₄₂	1025.07±409.95 ³	476.65±176.60 ^{1,3}	970.33±275.82 ²
CSF t-tau	382.85±498.28 ²	641.73±366.73 ^{1,3}	243.17±111.49 ²
CSF p-tau	44.75±22.84 ²	109.46±71.69 ^{1,3}	51.29±18.25 ²
Plasma p-tau ₂₁₇	0.21±0.16 ²	0.75±0.47 ^{1,3}	0.12±0.21 ²
Plasma NfL	18.31±9.51 ²	25.41±13.91 ^{1,3}	11.51±3.07 ²

Data are presented as means ± standard deviation. Key: GDS, Global Deterioration Scale; CSF, cerebrospinal fluid; Aβ₁₋₄₂, Amyloid-beta 42; t-Tau, total tau; p-tau, phosphorylated tau; NfL, Neurofilament Light chain.

¹Significantly different from SND ²Significantly different from AD ³Significantly different from CU

Figure 1. Baseline neuropsychological performance between the patient groups



Key: Radar plots display mean performance (Z-converted scores obtained from the CU group) across key cognitive domains between the patient groups. Time-dependent scores (e.g., Trail Making Test, BNT Time, ROCF Time) were inverted so that lower scores uniformly indicate worse performance across all metrics. Key: Plots show the significant results from linear regression models. FCSRT; Free and Cued Selective Reminding Test; ROCF, Western Aphasia Battery; Rey-Osterrieth Complex Figure; BDAE, Boston Diagnostic Aphasia Examination; VOSP, Visual Object and Space Perception battery.

* p < 0.05

CONCLUSIONS

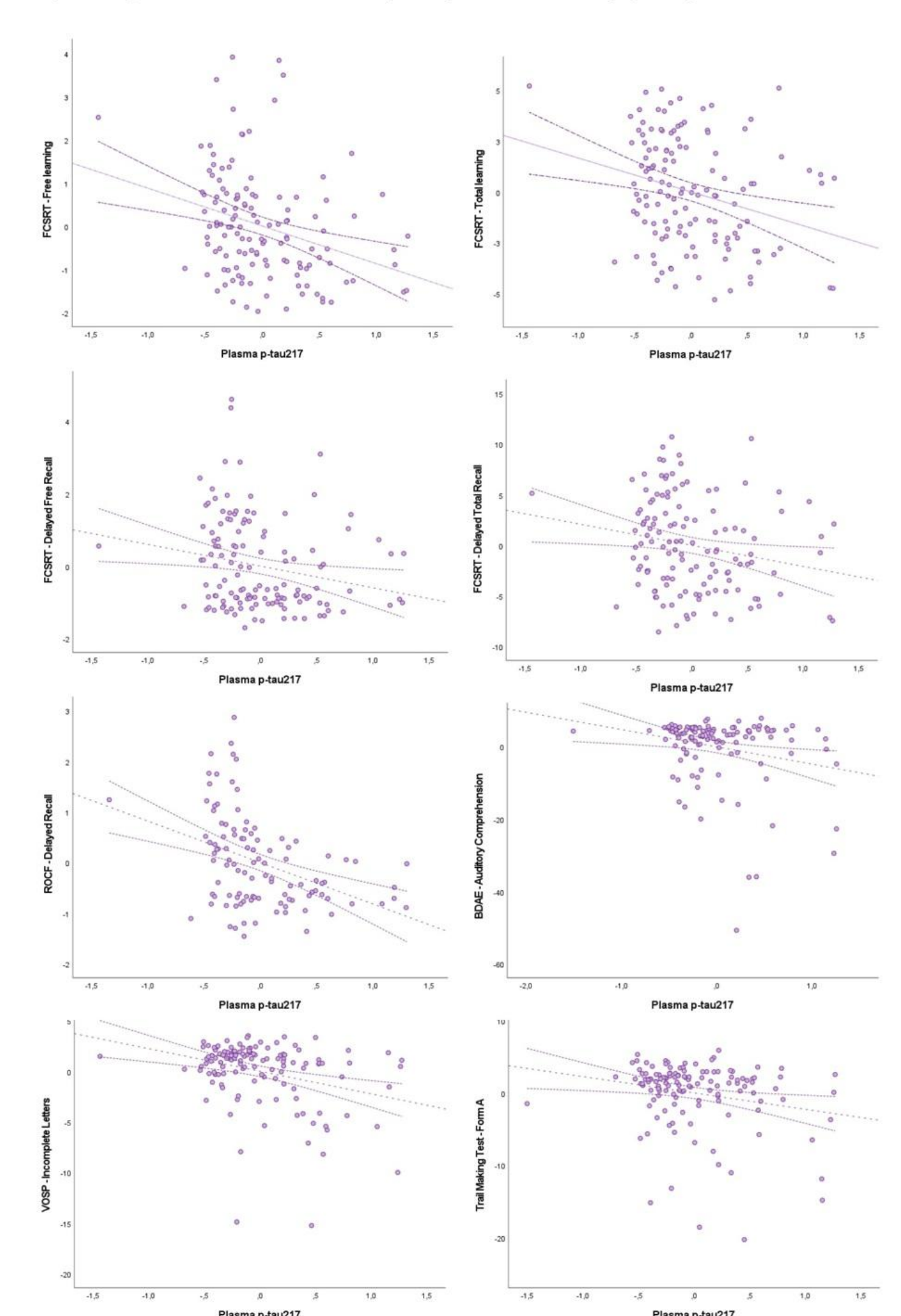
Patients with AD exhibited the characteristic profile of episodic memory impairment, along with poorer visuosperceptive and visuospatial performance compared to those with SND. Higher plasma p-tau217 levels were associated with worse performance across multiple cognitive domains. These findings underscore the value of neuropsychological assessments and plasma p-tau217 for capturing disease-related cognitive decline and enhancing differential diagnosis between AeD and SND in clinical practice.

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Figure 2. Significant associations between plasma p-tau217 and neuropsychological measures in AD and SND.



Key: Plots show the significant results from linear regression models. FCSRT; Free and Cued Selective Reminding Test; ROCF, Rey-Osterrieth Complex Figure; BDAE, Boston Diagnostic Aphasia Examination; VOSP, Visual Object and Space Perception battery.