Nature and magnitude of cognitive dysfunction associated with early tau VOI from tau PET in preclinical Alzheimer's disease

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Background

- In preclinical Alzheimer's disease (AD), early tau accumulation appears necessary for cognitive impairment.
- The early tau VOI metric is proposed to provide a PET marker for identification of individuals with elevated temporal but not global tau, and to correspond with the tau staging proposed by Braak[1,2].
- The utility of the early tau VOI can be determined by examination of the extent to which it is associated with indices of cognition, such as the Cogstate Brief Battery (CBB), which has demonstrated utility and sensitivity to detecting AD-related cognitive impairment, particularly when considered as domain-specific composite scores[3,4]

Aim:

1. To explore relationships between early tau VOI and cognition in amyloid-β+ cognitively unimpaired older adults.
2. To examine differences in cognitive performance between individuals classified as positive/negative according to established criteria for the early tau VOI.

Method

Sample:

- Data were drawn from the baseline visit of the A4 study for participants who had available tau PET and CBB data. See Table 1 for demographics. All participants were classified as Aβ+ on the basis of 18-F Florbetapir amyloid PET.

Measures:

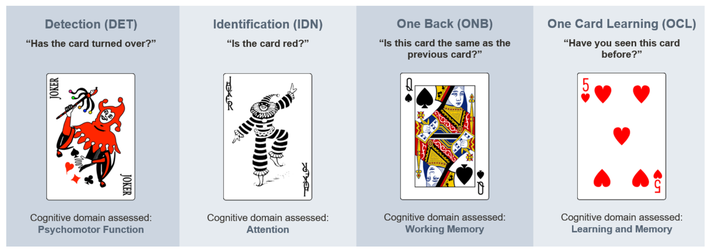
Tau PET: 18-F Flortaucipir tau PET

- Early tau VOI comprised an average SUVr from the entorhinal, parahippocampal, fusiform, and inferior temporal regions[1]
- Participants were classified as tau positive based on the cut score of SUVr >1.1052[1]

Cognition:

- Figure 1 summarizes the CBB tests and the cognitive domains measured by each test.
- Individual test scores were standardized to z-scores using age-matched normative data and then averaged to derive Psychomotor/Attention (PSA) and Learning/Working Memory (LWM) composite scores.

Figure 1: Cogstate Brief Battery



Results

Table 1: Sample Demographics

	A+T- (n=311)	A+T+ (n=52)
Age	71.9 (4.7)	72.9 (5.3)
% (n) Female	57.9 (180)	59.6 (31)
% (n) APOE4 Carrier	54.3 (169)	75.0 (39)
Years of Education	16.2 (2.9)	16.2 (2.9)
Race: White	92.0 (286)	92.3 (48)

Table 2: Summary of Correlations and Between Group Differences for Early Tau VOI and each of the Cognitive Composites

	Correlation with Early Tau VOI SUVr	A+T- (n=311)	A+T+ (n=52)	Wilcoxon Rank Sum Test *p*-value
LWM	*Spearman's ρ* = -0.17, *p* = .001	-0.07 (0.80)	-0.42 (0.71)	.003
PSA	Spearman's ρ = -0.06, *p* = .225	-0.02 (0.81)	-0.18 (0.84)	.130

Figure 2: Correlation of LWM with Early Tau VOI SUVr

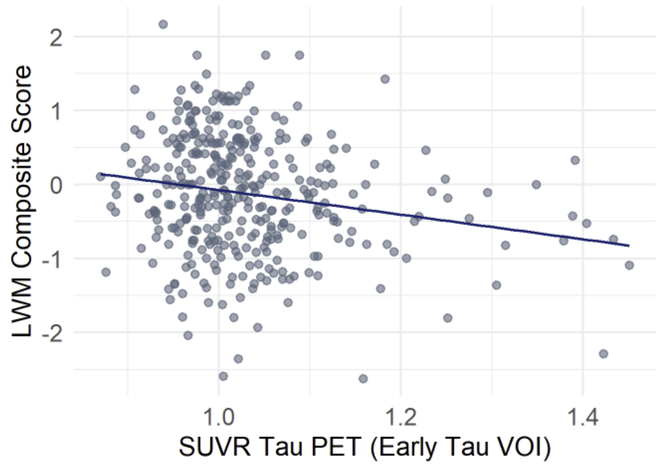
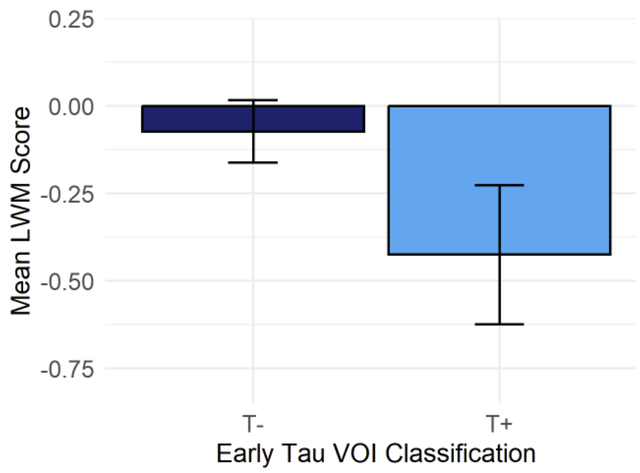


Figure 3: Mean (95% CI) LWM Performance by Early Tau VOI Status



Results

Analyses:

- Spearman correlations between early tau VOI SUVr and each of the CBB composites.
- Comparison of performance on each of the CBB composite scores between early tau VOI positive and negative participants using Wilcoxon Rank Sum test.
- Comparison of performance on each of the CBB composites against age adjusted normative means for both the early tau VOI positive and negative participants.

Results:

- SUVr for the early tau VOI was associated significantly with the LWM composite (Spearman's ρ = -0.17, p = .001, Table 2, Figure 2), but not the PSA composite (Table 2).
- On the LWM, the tau positive group (z = -0.42 [95% CI = -0.62, -0.23]) performed significantly worse than the tau negative group (z = -0.07 [95% CI = -0.16, 0.02], p <.001, Table 2).There was no significant difference between tau group on the PSA composite (Table 2).
- Compared to age-adjusted normative data the tau positive group performed significantly worse on the LWM composite (Figure 3). Performance of the tau negative group did not differ significantly from age-matched normative data for LWM (Figure 3).
- There was no significant difference between either early tau VOI group and age-adjusted normative data for the PSA composite.

Conclusion

- In preclinical AD, accumulation of tau in the regions comprising the early tau VOI is associated with subtle learning and working memory dysfunction but not with psychomotor speed or attentional functions.
- The specificity of this relationship indicates that the impact of tau accumulation of this region is specific to cognitive abilities that typically rely on medial temporal lobe function.
- The results of this study further support the use of the early tau VOI as an indicator of early-stage AD.

References

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3. White et al. Sensitivity of Individual and Composite Test Scores from the Cogstate Brief Battery to Mild Cognitive Impairment and Dementia Due to Alzheimer's Disease. J Alzheimers Dis. 2023;96(4):1781-1799. doi: 10.3233/JAD-230352. PMID: 38007647.
4. Lim et al. Relationships Between Performance on the Cogstate Brief Battery, Neurodegeneration, and Aβ Accumulation in Cognitively Normal Older Adults and Adults with MCI, Arch Clin Neuropsychol. 2015; 30(1), 49–58, doi:10.1093/arclin/acu068

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