Cross-modal Neuroimaging Correlation And Its Relation To Cognitive Impairment In Alzheimer's Disease

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BACKGROUND

The visualization of β-Amyloid plaques and tau neurofibrillary tangles using positron emission tomography (PET) has opened opportunities to study various disease mechanisms of Alzheimer's Disease (AD)[1]

Cortical atrophy, measured through magnetic resonance imaging (MRI) as cortical thickness[4], strongly correlates with the accumulation of tau at the single-patient level[2],and tau burden strongly correlates with the severity of hypometabolism[6] and clinical symptoms[3]

Tau burden and cortical atrophy coupling has been shown to significantly mediate the association between β-Amyloid and cognition[3], but the correlation between these three imaging modalities and cognitive impairment is not well understood.

Goal: To investigate the spatial coupling between structural MRI, amyloid PET, and tau PET and examine its clinical relevance in a heterogenous cohort of AD.

Hypothesis: The spatial pattern of neurodegeneration would more closely match the topography of tau PET than that of amyloid PET. We further hypothesized that the tau-atrophy coupling would be associated with the severity of each patient's cognitive impairment.

MATERIALS AND METHODS

Participants: 58 amyloid-positive individuals with atypical AD (Centiloid values > 25) recruited from the Massachusetts Alzheimer's Disease Research Center (MADRC). Sample characteristics shown in **Table 1.**

Cognitive assessment: Clinical Dementia Rating (CDR) Sum-of-Boxes (CDR-SB) and CDR Global scores were used to quantify levels of cognitive impairment.

Neuroimaging: Tau burden measured with ^{18}F-Flortaucipir PET, amyloid with ^{11}C-Pittsburgh Compound-B or ^{18}F-Florbetaben PET, and atrophy with MRI. Amyloid burden quantified as Centiloid (**Table 1**)

Statistical Analysis:

- Each biomarker was summarized for the same set of 68 cortical regions of interest (ROIs) using automated parcellations with FreeSurfer. Regional neuroimaging data were Z-scored. Z-scores for individuals within an ROI were calculated as Z= (observed values – mean of reference data set)/standard deviation of reference data set. We then calculated within-participant Spearman rank correlations between an individual's Z-scores across all ROIs to measure the strength of the association between a pair of imaging modalities as in Whitwell et al (2018). Repealed measures of ANOVA compared the magnitude of Tau Atrophy correlation to the magnitude of Amyloid Atrophy correlation.
- To assess the relationship between these couplings and clinical severity we used simple regression analysis to assess the relationship between these couplings and clinical severity as quantified by Clinical Dementia Rating Sum-of-Boxes (CDR-SB).

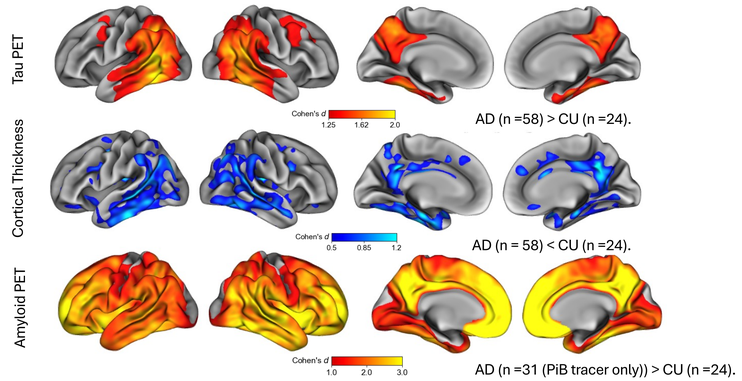
RESULTS

Table 1. Sample Characteristics

	AD	aEOAD	lvPPA	PCA	Total	Omnibus p
N	3 (5.2)	21 (36.2)	16 (27.6)	18 (31.0)	58	
Age (years)	68.80 (6.43)	58.62 (4.59)	65.70 (8.74)[1]	68.34 (8.10)[1]	64.12 (8.20)	<0.01
Education (years)	17.33 (1.15)	16.71 (2.37)	15.56 (2.85)	16.94 (1.86)	16.50 (2.36)	0.14
Sex, Female	2 (66.7%)	12 (57.1%)	11 (68.8%)	11 (61.1%)	36 (62.1%)	0.553
Non-Hispanic White	3 (100.0%)	21 (100.0%)	16 (100.0%)	17 (94.4%)	57 (98.3%)	<0.001
CDR Sum of Boxes	3.83 (3.62)	4.26 (1.30)	2.34 (1.52)[1]	3.78 (1.74)	3.56 (1.78)	0.298
CDR Global						0.235
0	0 (0.0%)	0 (0.0%)	3 (18.8%)	0 (0.0%)	3 (5.2%)	
0.5	2 (66.7%)	12 (57.1%)	10 (62.5%)	12 (66.7%)	36 (62.1%)	
1	1 (33.3%)	9 (42.9%)	3 (18.8%)	6 (33.3%)	19 (32.8%)	
Centiloid	110.76 (44.43)	96.77 (25.09)	109.16 (26.03)	101.89 (29.13)	102.50 (27.38)	0.52

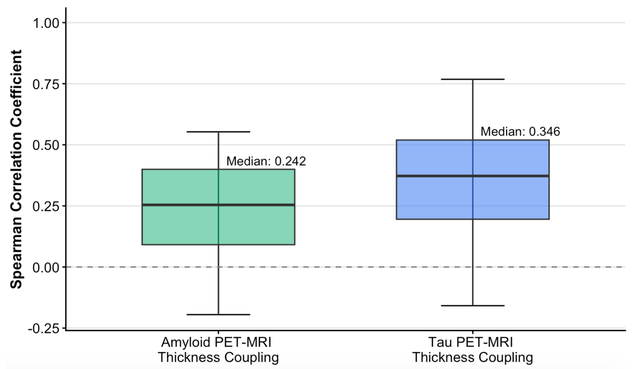
Values represent mean (SD) for numeric variables; n (%) for ordinal and nominal variables. [1]Significantly different from aEOAD. AD = Alzheimer's disease, aEOAD = amnestic early onset AD, lvPPA = logopenic variant primary progressive aphasia, PCA = posterior cortical atrophy.

Fig. 1. Whole-cortex maps of multimodal AD-related imaging biomarkers.



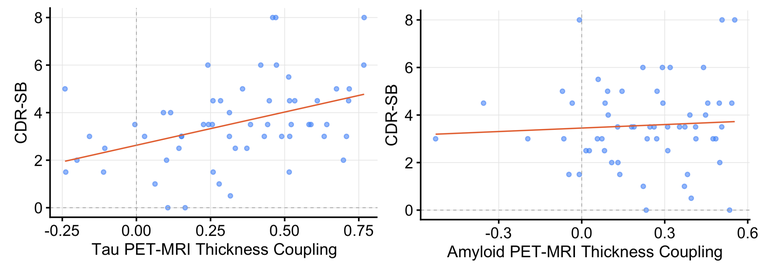
Group-level effect size (Cohen's *d*) maps show signal abnormalities in AD patients relative to controls of cortical thickness, FTP PET, and PiB PET.

Fig. 2. Within-Participant Correlations: PET Pathology vs MRI thickness



As predicted, we observed that the spatial coupling between tau and atrophy was stronger (M = 0.35, SD = 0.26) than the coupling between amyloid and atrophy (M = 0.24, SD = 0.26), $F(1,57) = 8.14$, $p < .001$.

Fig. 3. Relationships Between Cross-modal Coupling and Clinical Severity



We also observed a relationship between the tau-atrophy coupling and clinical severity ($F(1,56) = 11.73$, $p < .001$), such that stronger tau-atrophy coupling was associated with greater clinical impairment (r = .42, $p < .01$). No such relationship was observed with amyloid-atrophy coupling ($p < .65$).

CONCLUSIONS

Using an individual-level design, this study sheds light on variability of the correlations between imaging modalities in atypical AD. Our findings support the close concordance between patterns of atrophy and tau deposition in atypical AD, consistent with other studies.

We demonstrated that the atrophy and tau coupling is predictive of the clinical impairment, highlighting the relevance of the tau-atrophy coupling as a tool to predict individual AD patient's cognitive impairment.
Ongoing work includes analysis of longitudinal data to examine whether Tau-atrophy coupling can predict future cognitive decline.

REFERENCES & ACKNOWLEDGMENTS

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