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Tau PET shows both direct and atrophy-mediated effects on cognition: 4-way decomposition of the effects of tau PET and atrophy on cognitive performance

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Abstract

Background: Evidence suggests that tau pathology predicts subsequent neurodegeneration and that atrophy is associated with cognitive impairment. However, *in vivo* studies have shown that structural measures only partially mediate tau-cognition relationships, with direct effects of tau on cognition remaining. The objective of current study is to decompose the overall effect of tau on domain-specific cognitive performance, in the presence of atrophy as a mediator with which tau may interact.

Method: 705 participants with flortaucipir (FTP)-PET were selected from Alzheimer's Disease Neuroimaging Initiative—3 (Table 1). MRI scans closest to FTP were used to measure cortical thickness and volume in *a priori* regions (Desikan atlas, FreeSurfer v7.1) associated with memory, executive function, language, and visuospatial cognitive domains. Using a causal mediation framework, tau accumulation measured with FTP-PET in a temporal meta-region was the primary exposure, cognitive domain scores were the primary outcomes and regional structural measures were the hypothesized mediators. Statistical models incorporating exposure—mediator interactions (4-way decomposition) were used to identify natural direct and indirect effects.

Result: Across the entire cohort (age 74.26 (7.82), 58% cognitively unimpaired, 30.8% MCI, 11.2% Demented), regional morphometry in medial temporal lobe (MTL) subregions selected *a priori* for their relationship with memory function mediated the effect of tau on all cognitive domains (Table 2). Hippocampal volume had the largest total indirect effect (mediating the effect of tau) across all domains (37% (95% confidence intervals (CI): 28%, 47%) for memory, 28% (CI: 18%, 38%) for executive function, 37% (CI: 24%, 50%) for language, and 29% (CI: 10%, 49%) for the visuospatial domain). Similar mediating effects were observed for entorhinal cortical thickness and to a lesser extent parahippocampal cortical thickness. In contrast, the morphology of regions selected *a priori* based on functional neuroanatomical associations with executive function, language or visuospatial domains did not mediate tau-cognition relationships.

Conclusion: Our results suggest that the effect of MTL atrophy on tau-cognition associations may extend beyond memory function and be an important mechanism

by which tau accumulation affects multiple cognitive domains. Follow-up longitudinal studies will help to characterize the temporal dynamics of atrophy-mediated associations between tau and cognition.

Table 1: Demographic, morphometric, and neuropsychological evaluation measures of ADNI-3 participants at baseline visit.

Variable	All participants (N=705)	Aβ- CN participants (N=281)	Aβ+ CN participants (N=128)	Aβ+ Impaired participants (N=173)	All Aβ+ participants (N=301)
Age	74.26 (7.82)	72.59 (7.06)	74.74 (7.51)	75.85 (8.16)	75.38 (7.90)
Sex (% Female)	51.77%	57.30%	60.94%	47.40%	53.16%
APOE4 Carrier Status (% Carrier)	38.16%	23.13%	53.91%	64.74%	60.13%
Diagnosis (Normal/MCI/Dementia)	409/217/79			0/106/67	128/106/67
Metatemporal Tau (SUVR)	1.28 (0.27)	1.18 (0.09)	1.24 (0.15)	1.53 (0.41)	1.41 (0.36)
Memory Composite	0.62 (0.81)	1.02 (0.55)	1.01 (0.61)	-0.2 (0.74)	0.31 (0.91)
Executive Function Composite	0.71 (1.08)	1.19 (0.8)	1.01 (0.83)	-0.17 (1.18)	0.33 (1.20)
Language Composite	0.56 (0.93)	0.94 (0.72)	0.88 (0.75)	-0.09 (1.03)	0.32 (1.04)
Visuospatial Composite	0.00 (0.82)	0.22 (0.61)	0.11 (0.72)	-0.37 (1.01)	-0.17 (0.93)
Total Gray Matter Volume (mm3)	592452 (56340.71)	603073.9 (55669.15)	594320.7 (52277.57)	575236.9 (57635.07)	583352.3 (56131.59)
Mean Thickness	2.36 (0.10)	2.38 (0.08)	2.37 (0.09)	2.32 (0.11)	2.34 (0.11)
Memory Domain					
Hippocampal Volume (mm3)	3681.22 (545.38)	3884.43 (451.43)	3791.77 (375.83)	3328.07 (553.48)	3525.26 (536.81)
Parahippocampal Thickness	2.60 (0.24)	2.65 (0.21)	2.61 (0.21)	2.52 (0.26)	2.56 (0.25)
Entorhinal Cortex Thickness	3.10 (0.38)	3.23 (0.26)	3.18 (0.24)	2.87 (0.45)	3.00 (0.41)
Fusiform Gyrus thickness	2.63 (0.14)	2.66 (0.11)	2.65 (0.13)	2.57 (0.18)	2.60 (0.16)
Executive Function Domain					
White Matter Hyperintensity Volumes	4529.43 (6098.92)	3102.12 (3642.18)	4571.38 (5304.43)	6135.55 (8345.83)	5470.39 (7241.93)
Caudal Middle Frontal Thickness	2.41 (0.13)	2.43 (0.11)	2.42 (0.12)	2.36 (0.15)	2.39 (0.14)
Rostral Middle Frontal Thickness	2.26 (0.12)	2.27 (0.11)	2.28 (0.11)	2.24 (0.13)	2.26 (0.13)
Superior Middle Frontal Thickness	2.52 (0.12)	2.54 (0.11)	2.53 (0.11)	2.48 (0.14)	2.50 (0.13)
Lateral orbitofrontal thickness	2.51 (0.12)	2.52 (0.11)	2.51 (0.11)	2.49 (0.14)	2.50 (0.13)
Medial orbitofrontal thickness	4.68 (0.28)	4.72 (0.25)	4.71 (0.25)	4.60 (0.3)	4.65 (0.29)
Pars Triangularis thickness	2.33 (0.11)	2.33 (0.10)	2.34 (0.10)	2.31 (0.12)	2.31 (0.11)
Language Domain					
Left Temporal pole thickness	3.42 (0.34)	3.48 (0.27)	3.49 (0.31)	3.30 (0.39)	3.38 (0.37)
Left Pars Triangularis thickness	2.33 (0.13)	2.37 (0.12)	2.34 (0.12)	2.31 (0.13)	2.32 (0.13)
Left Pars Opercularis thickness	2.47 (0.12)	2.48 (0.11)	2.48 (0.11)	2.43 (0.14)	2.45 (0.13)
Left Pars Orbitalis thickness	2.57 (0.18)	2.57(0.17)	2.59(0.18)	2.54 (0.19)	2.56 (0.18)
Visuospatial Domain					
Superior Temporal Gyrus thickness	2.59 (0.16)	2.64 (0.14)	2.61 (0.14)	2.50 (0.17)	2.55 (0.17)
Inferior Parietal Thickness	2.31 (0.12)	2.34 (0.11)	2.33 (0.11)	2.25 (0.14)	2.28 (0.13)
Inferior Temporal Thickness	2.65(0.15)	2.68 (0.12)	2.67 (0.12)	2.59 (0.18)	2.62 (0.16)
Pars Opercularis thickness	2.46 (0.11)	2.48 (0.10)	2.47 (0.09)	2.43 (0.12)	2.45 (0.11)
Pars Orbitalis Thickness	2.56 (0.15)	2.57 (0.14)	2.57 (0.14)	2.54 (0.16)	2.55 (0.15)
Lingual Gyrus	2.00 (0.13)	2.00 (0.12)	2.02 (0.13)	1.97 (0.13)	1.99 (0.13)
Lateral Occipital Thickness	2.14 (0.12)	2.15 (0.11)	2.15 (0.13)	2.11 (0.14)	2.13 (0.14)
Pericalcerine Thickness	1.66 (0.15)	1.66 (0.14)	1.68 (0.15)	1.65 (0.16)	1.66 (0.15)

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Table 2: Percent attributable in a 4-way decomposition analysis of three structural brain regions on four different cognitive domains in the ADNI data set.

	Memory		Executive Function		Language		Visuospatial	
Hippocampus								
% CDE	0.65***	[0.55,0.74]	0.73***	[0.63,0.84]	0.64***	[0.52,0.77]	0.73***	[0.54,0.92]
% INTref	-0.02	[-0.06,0.03]	-0.01	[-0.05,0.02]	-0.02	[-0.05,0.02]	-0.02	[-0.09,0.04]
% INTmed	0.13***	[0.08,0.18]	0.10***	[0.04,0.16]	0.11**	[0.04,0.17]	0.17**	[0.04,0.30]
% PIE	0.24***	[0.18,0.31]	0.18***	[0.10,0.25]	0.27***	[0.17,0.36]	0.12	[-0.02,0.26]
% Mediated	0.37***	[0.28,0.47]	0.28***	[0.18,0.38]	0.37***	[0.24,0.50]	0.29**	[0.10,0.49]
% Interaction	0.11***	[0.05,0.17]	0.09**	[0.03,0.15]	0.09**	[0.02,0.16]	0.14*	[0.02,0.27]
% Eliminated	0.35***	[0.26,0.45]	0.27***	[0.16,0.37]	0.36***	[0.23,0.48]	0.27**	[0.08,0.46]
Entorhinal Cortex								
% CDE	0.74***	[0.65,0.83]	0.77***	[0.67,0.87]	0.68***	[0.55,0.80]	0.80***	[0.63,0.96]
% INTref	0.01	[-0.03,0.05]	0.01	[-0.03,0.04]	0.01	[-0.04,0.06]	0.01	[-0.04,0.07]
% INTmed	0.10***	[0.05,0.14]	0.08**	[0.03,0.14]	0.11***	[0.05,0.18]	0.12*	[0.02,0.23]
% PIE	0.16***	[0.10,0.21]	0.14***	[0.07,0.21]	0.20***	[0.11,0.28]	0.07	[-0.05,0.18]
% Mediated	0.25***	[0.17,0.33]	0.22***	[0.13,0.32]	0.31***	[0.19,0.43]	0.19*	[0.04,0.34]
% Interaction	0.10***	[0.05,0.16]	0.09**	[0.03,0.16]	0.13**	[0.04,0.21]	0.14*	[0.01,0.27]
% Eliminated	0.26***	[0.17,0.35]	0.23***	[0.13,0.33]	0.32***	[0.20,0.45]	0.20*	[0.04,0.37]
Parahippocampus								
% CDE	0.90***	[0.83,0.96]	0.92***	[0.85,0.99]	0.88***	[0.78,0.97]	0.86***	[0.73,0.99]
% INTref	0.04	[-0.00,0.08]	0.04	[-0.01,0.08]	0.05	[-0.00,0.11]	0.08	[-0.01,0.16]
% INTmed	0.04**	[0.01,0.07]	0.04*	[0.01,0.07]	0.06**	[0.01,0.10]	0.08*	[0.01,0.15]
% PIE	0.02*	[0.00,0.05]	0.00	[-0.02,0.03]	0.02	[-0.01,0.05]	-0.02	[-0.06,0.03]
% Mediated	0.06**	[0.02,0.11]	0.04	[-0.00,0.08]	0.07*	[0.02,0.13]	0.06	[-0.01,0.14]
% Interaction	0.08**	[0.02,0.14]	0.08*	[0.01,0.14]	0.11**	[0.03,0.19]	0.16*	[0.02,0.29]
% Eliminated	0.10**	[0.04,0.17]	0.08*	[0.01,0.15]	0.12**	[0.03,0.22]	0.14*	[0.01,0.27]
Observations	705		705		705		705	

95% confidence intervals in brackets
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$