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for the Alzheimer's Disease Neuroimaging Initiative

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Background

The hypothalamus is an early site of tau accumulation^{1,2} and regulates essential homeostatic functions, including sleep, circadian rhythms, and stress responses.³ These processes become increasingly disrupted with aging and Alzheimer's disease (AD), highlighting the hypothalamus as a key region in disease pathophysiology.^{4,5,6}

Here, we examined regional differences in hypothalamic grey matter volume across cognitively normal (CN) older adults, individuals with mild cognitive impairment (MCI), and AD dementia, as well as associations with *in vivo* A β and tau PET burden, and cognitive performance.

Methods

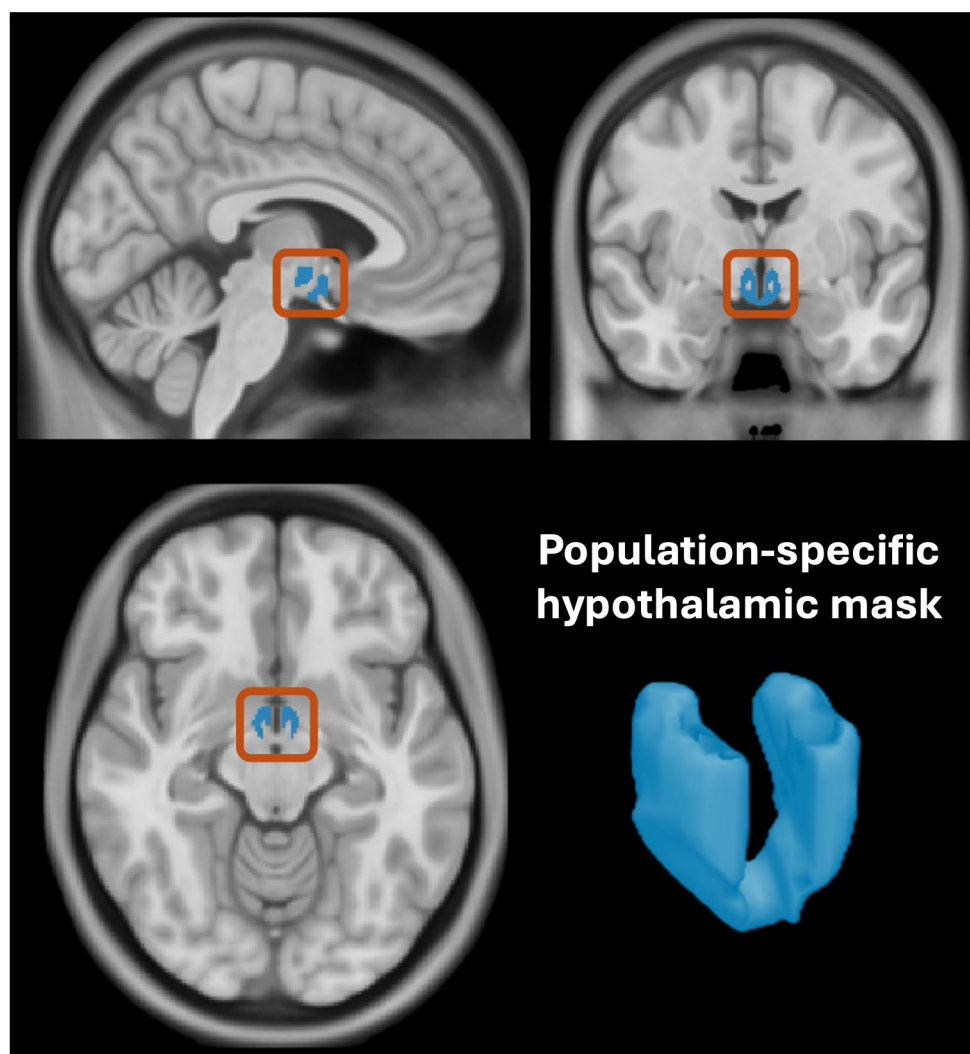
Participants. 462 participants from the ADNI3 cohort.

	CN		MCI	AD dementia
	208 A β -	105 A β +	98 A β +	51 A β +
Age (years)	70.5 $\pm$ 6.9	73.8 $\pm$ 7.3	74.6 $\pm$ 6.8	77.0 $\pm$ 8.3
Female (n, %)	122 (59%)	65 (62%)	41 (42%)	23 (45%)
Education (years)	17.0 $\pm$ 2.2	16.6 $\pm$ 2.3	16.2 $\pm$ 2.3	15.0 $\pm$ 2.4
<i>APOE</i> ϵ 4 carriers (n, %) [†]	49 (24%)	60 (58%)	58 (59%)	31 (61%)
CDR Sum of Boxes	0	0	1.53 $\pm$ 1.1	4.91 $\pm$ 2.2
mPACCdigit score	0.47 $\pm$ 3.0	0.24 $\pm$ 3.0	-7.10 $\pm$ 4.8	-16.46 $\pm$ 5.1
Memory composite score	0.99 $\pm$ 0.5	0.90 $\pm$ 0.5	0.009 $\pm$ 0.4	-0.81 $\pm$ 0.4
Executive composite score	0.95 $\pm$ 0.5	0.84 $\pm$ 0.6	0.25 $\pm$ 0.6	-0.40 $\pm$ 0.9
Entorhinal tau-PET SUVR (PVC)	1.19 $\pm$ 0.2	1.32 $\pm$ 0.3	1.72 $\pm$ 0.5	2.04 $\pm$ 0.5
Cortical A β -PET (centiloids)	1.52 $\pm$ 8.1	57.8 $\pm$ 34.2	81.4 $\pm$ 41.6	101.1 $\pm$ 32.8

Mean $\pm$ standard deviation; Tau PET: [¹⁸F]Flortaucipir PET; Amyloid positivity threshold: 1.11 SUVR for [¹⁸F]Flortaucipir-PET, 1.08 SUVR for [¹⁸F]Florbetaben-PET; [†]Missing values: 13 (8 for CN A β -, 1 for CN A β +, and 4 for MCI A β); Memory and executive composite scores are derived from the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium

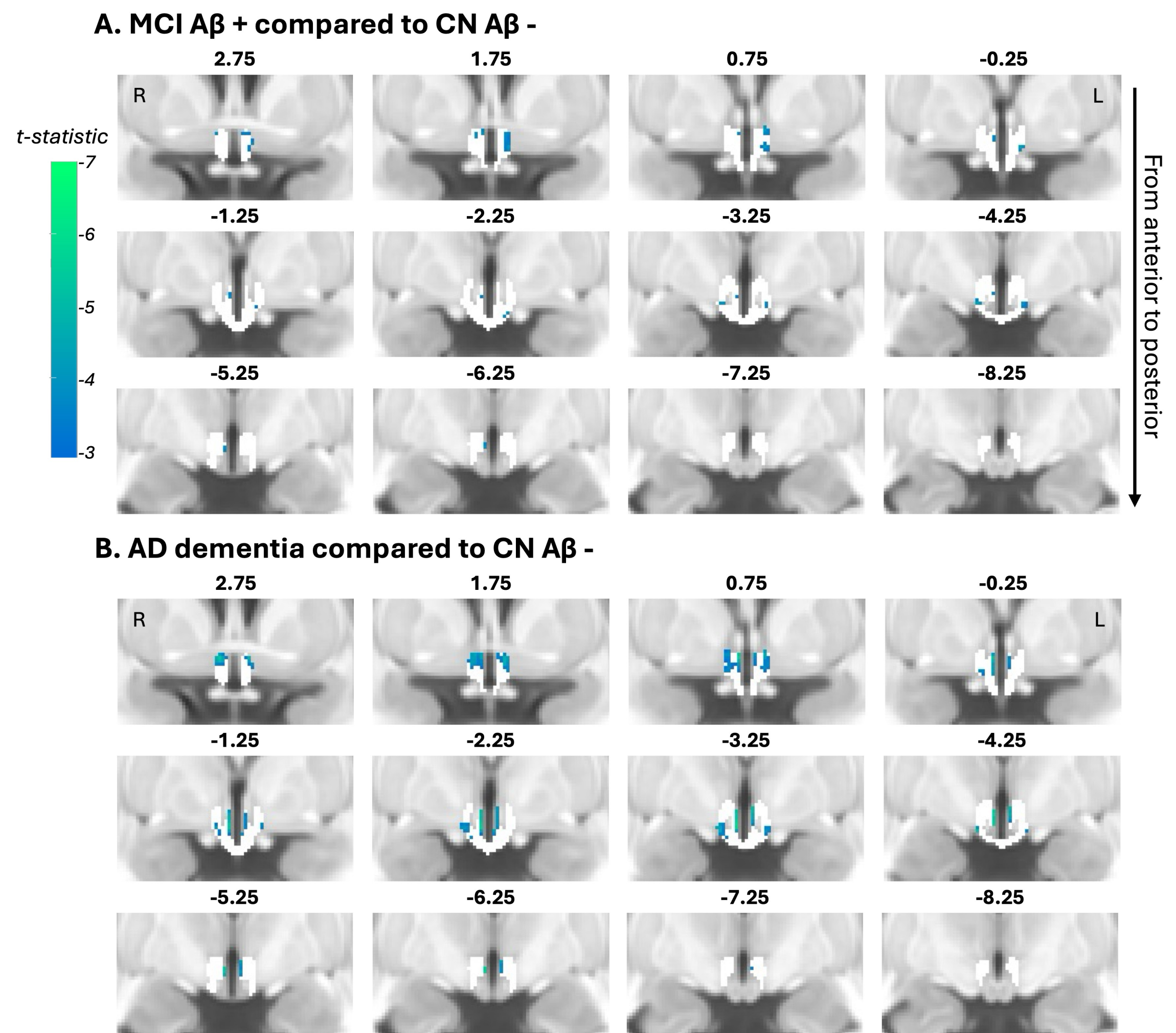
Structural MRI.

The hypothalamus was segmented on MPRAGE images using FastSurfer-HypVINN.⁷ Grey matter probability maps were generated with CAT12.9, modulated, and normalized to MNI space. Individual hypothalamic masks were then warped to MNI space, averaged, and binarized (threshold = 0.5) to create a population-specific mask for voxelwise analyses.

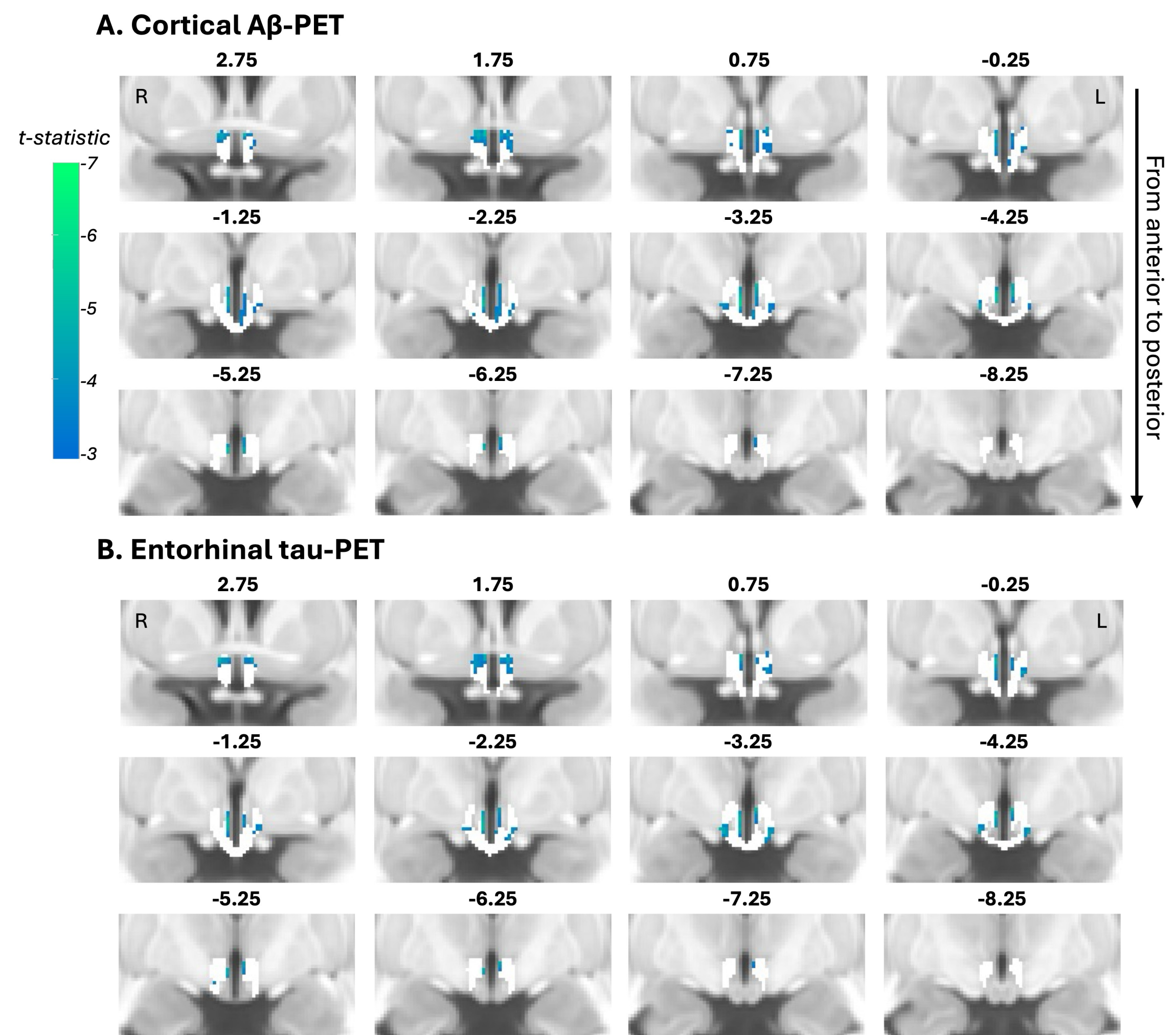


Statistical analysis. Voxelwise linear regression analyses examined associations between hypothalamic grey matter probability and **(1)** clinical diagnosis stratified by A β status, **(2)** A β burden (centiloids), **(3)** entorhinal tau-PET SUVR, and **(4)** cognitive performance. Models were adjusted for age, sex, scanner manufacturer, and intracranial volume, as well as education for cognitive analyses. Maps were thresholded using TFCE-enhanced statistics at $Z > 3.1$.

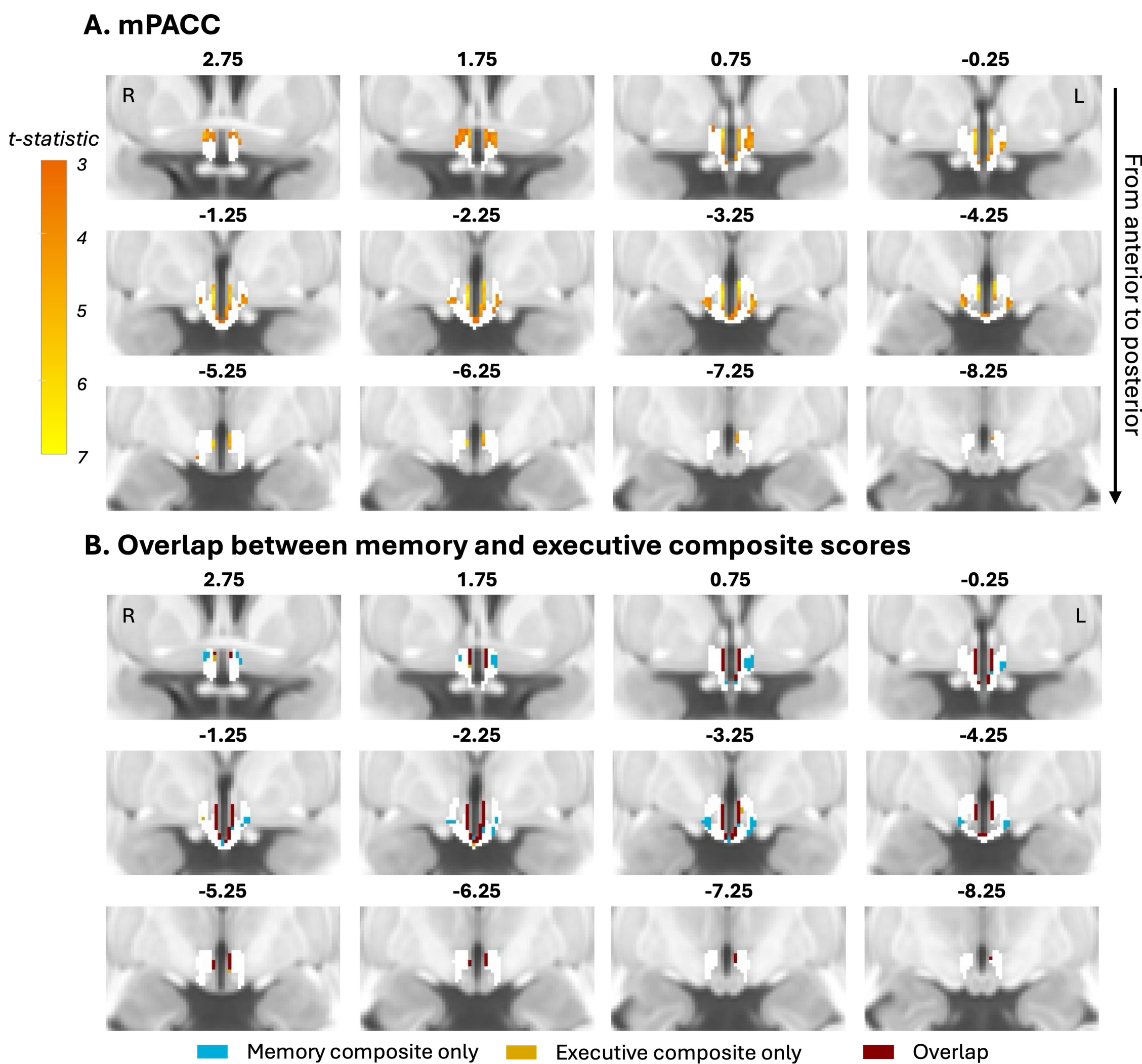
1 - Reductions in regional hypothalamic grey matter volume emerge at the MCI A β stage and become more extensive in AD



2 - Cortical A β and entorhinal tau-PET show spatially overlapping associations with hypothalamic grey matter volume



3 - Lower hypothalamic grey matter volume is associated with poorer global and domain-specific cognitive performance, particularly memory



Conclusion

Reductions in hypothalamic grey matter volume emerge at the MCI A β stage, become more widespread in AD, and are associated with both AD pathology and cognitive performance. These findings highlight selective vulnerability of hypothalamic regions involved in arousal, sleep-wake regulation, thermoregulation, stress responses, and energy homeostasis across the AD continuum.^{8,9,10}

Future studies will investigate hypothalamic microstructural integrity and the contribution of neuropsychiatric symptoms to cognitive performance.

References & Fundings

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