

Discoordination between brain pulsation and CSF flow is associated with cognitive deficits, greater tau burden, lower synaptic density, and lower glucose metabolism

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Introduction

Impaired glymphatic system – a perivascular brain waste clearance system mediated by CSF flow – may contribute to Alzheimer’s disease (AD) pathogenesis. Anti-phase coordination between brain pulsations and CSF flow, reflecting compensatory CSF displacement during each vascular pulsation cycle, supports glymphatic activity. This study examines the association between the brain pulsation-CSF dynamics and core AD pathologies defined by the ATN (Amyloid, tau, neurodegeneration) framework using positron emission tomography (PET), as well as global cognition.

Methods

Sample Individuals along the AD spectrum who were first degree family members of individuals diagnosed with Alzheimer’s disease.

Characteristics	N=107 Median (IQR) or n (%)
Age	68 (61-73)
Male sex	56 (52 %)
White	98 (92 %)
Cognitive status	
Normal, ab-	36 (33%)
Normal, ab+	32 (30%)
MCI	26 (26%)
Dementia	13 (11%)
[11C]PiB PET	85 (79%)
[18F]MK-6240 PET	92 (86%)
[11C]UCB-J PET	90 (84%)
[18F] FDG PET	88 (82%)

MRI sequence parameters

- 6-minute, wake, resting-state fMRI session with a fixation cross (TR=1000 msec, TE=30 msec, FoV=220 mm, voxel size= 2x2x2mm³)
- High-resolution MPRAGE (TR=2300 msec, TE=2.95 msec, TI=900 msec, FoV=270 mm, voxel size=1x1x1mm³)

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Discoordination between brain pulsations and CSF flow is associated with greater AD burden, especially in the temporal and parietal lobes

gBOLD-CSF coupling. Coordination between brain pulsation and CSF flow, which support glymphatic activity.

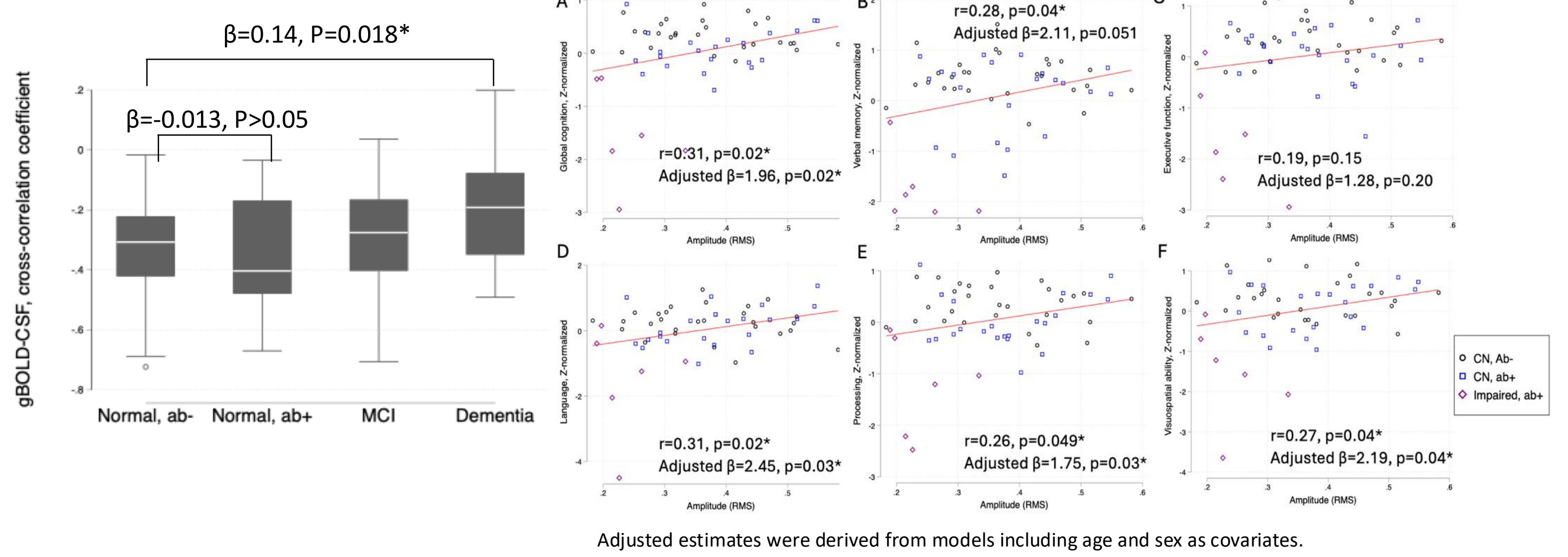
- Strength of anti-phase correlation between low frequency (<0.1 Hz) CSF pulsations in the cisterna magna and low frequency gray-matter-wide BOLD (gBOLD) signal oscillations.

Alzheimer’s disease burden measured using Positron Emission Tomography (PET) & cognitive testing

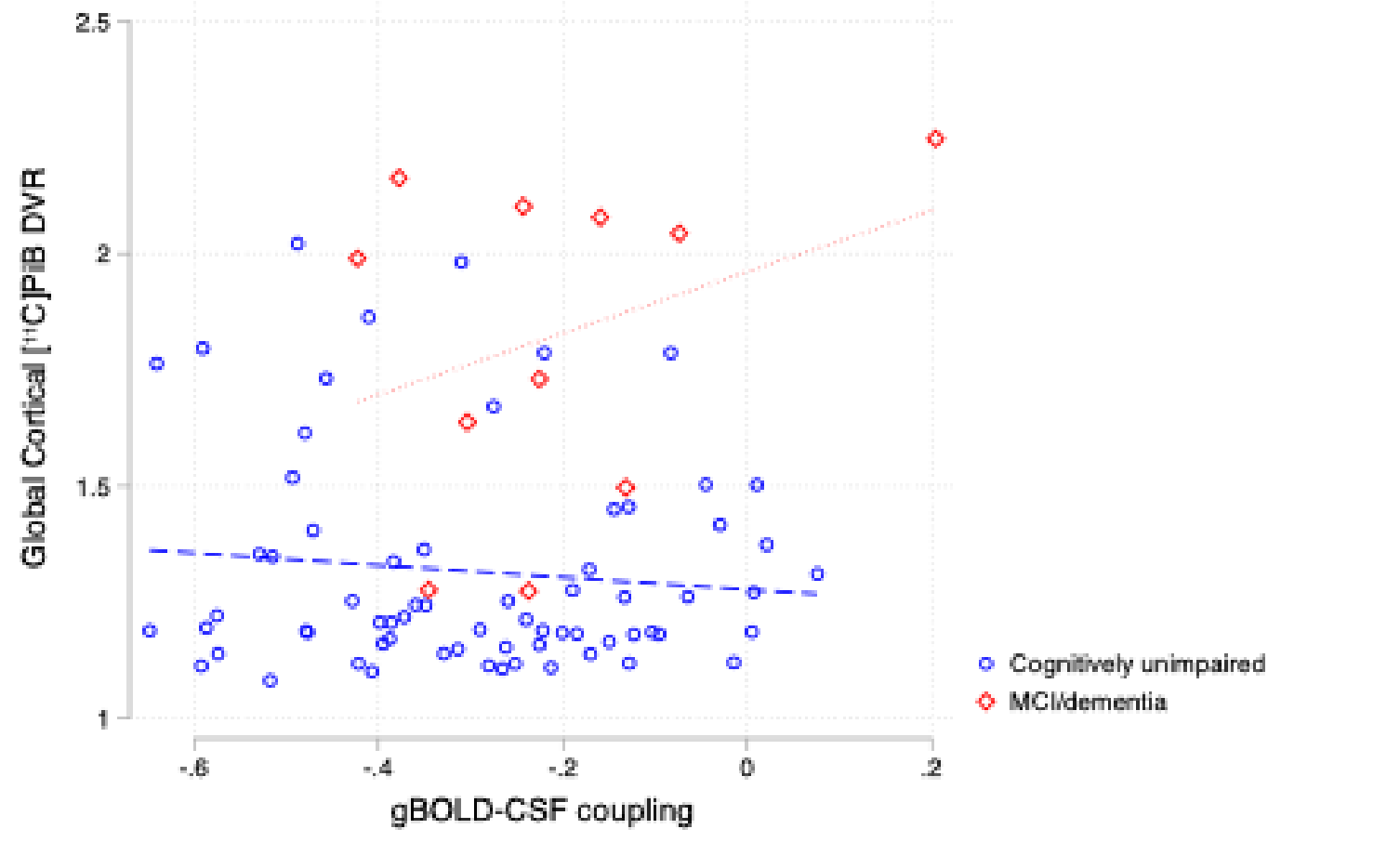
- Global cortical Aβ.** Using [11C]PiB PET, distribution volume ratios (DVRs) were calculated using a simplified reference tissue model 2 (SRTM2, reference=whole cerebellum)
- Regional tau.** Using [18F]MK-6240 PET, standardized uptake value ratios (SUVRs) were calculated (reference=inferior cerebellar gray matter)
- Regional synaptic density (early marker of neurodegeneration).** Using [11C]UCB-J PET, DVRs were generated using SRTM2 (reference=inferior cerebellum)
- Regional glucose metabolism.** SUVRs of [18F] FDG PET (reference=cerebellum)
- Cognition.** Z-normalized scores of verbal memory (Logical Memory I and II, Rey Auditory Verbal Learning Test), language (Boston Naming Test, Category Fluency), executive function (Stroop Color Word Test, Trail Making Test (TMT) Part B), processing speed (Stroop Word Test, TMT-A, Digit Symbol Substitution), and visuospatial ability (Rey–Osterrieth Complex Figure, WAIS-III Block Design, WAIS-III Picture Completion)

Results

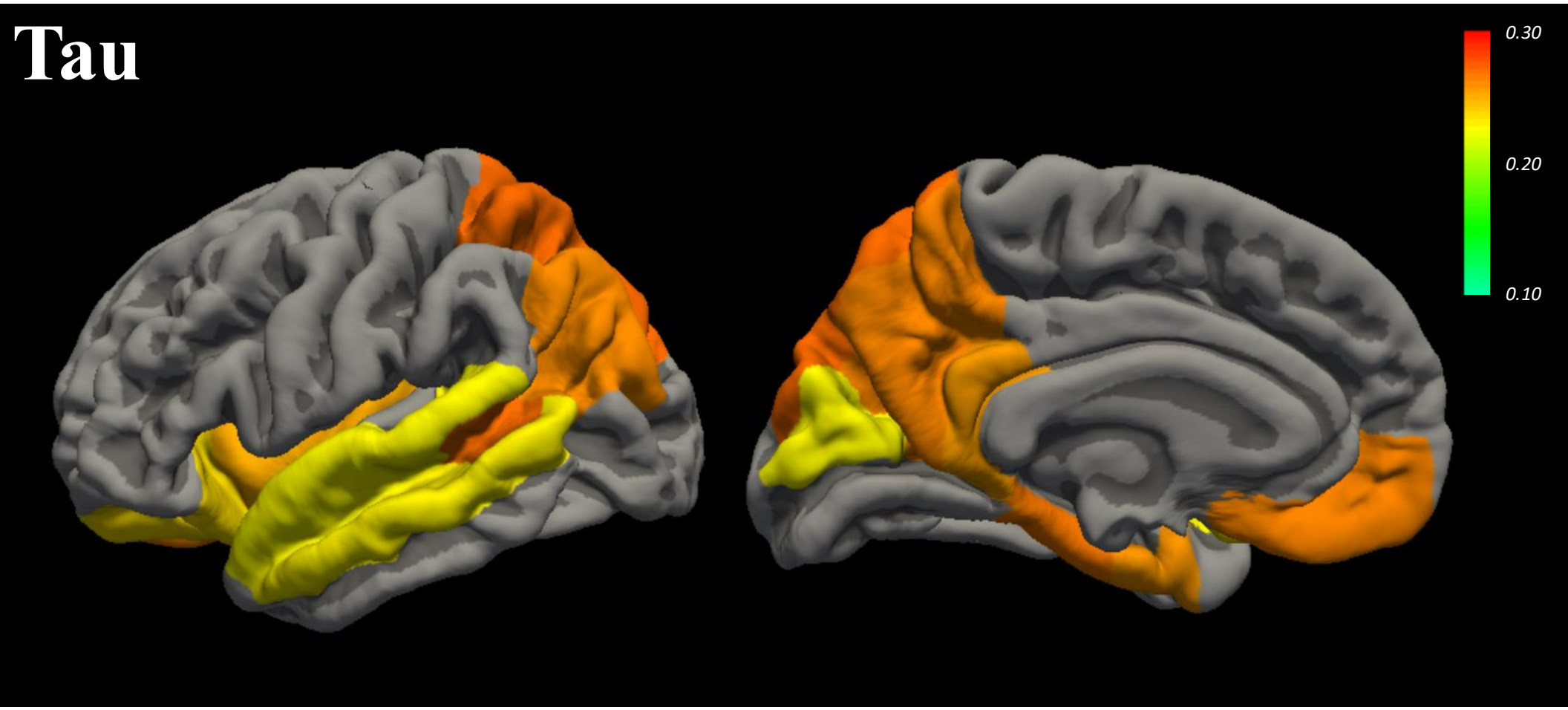
- Cognition**



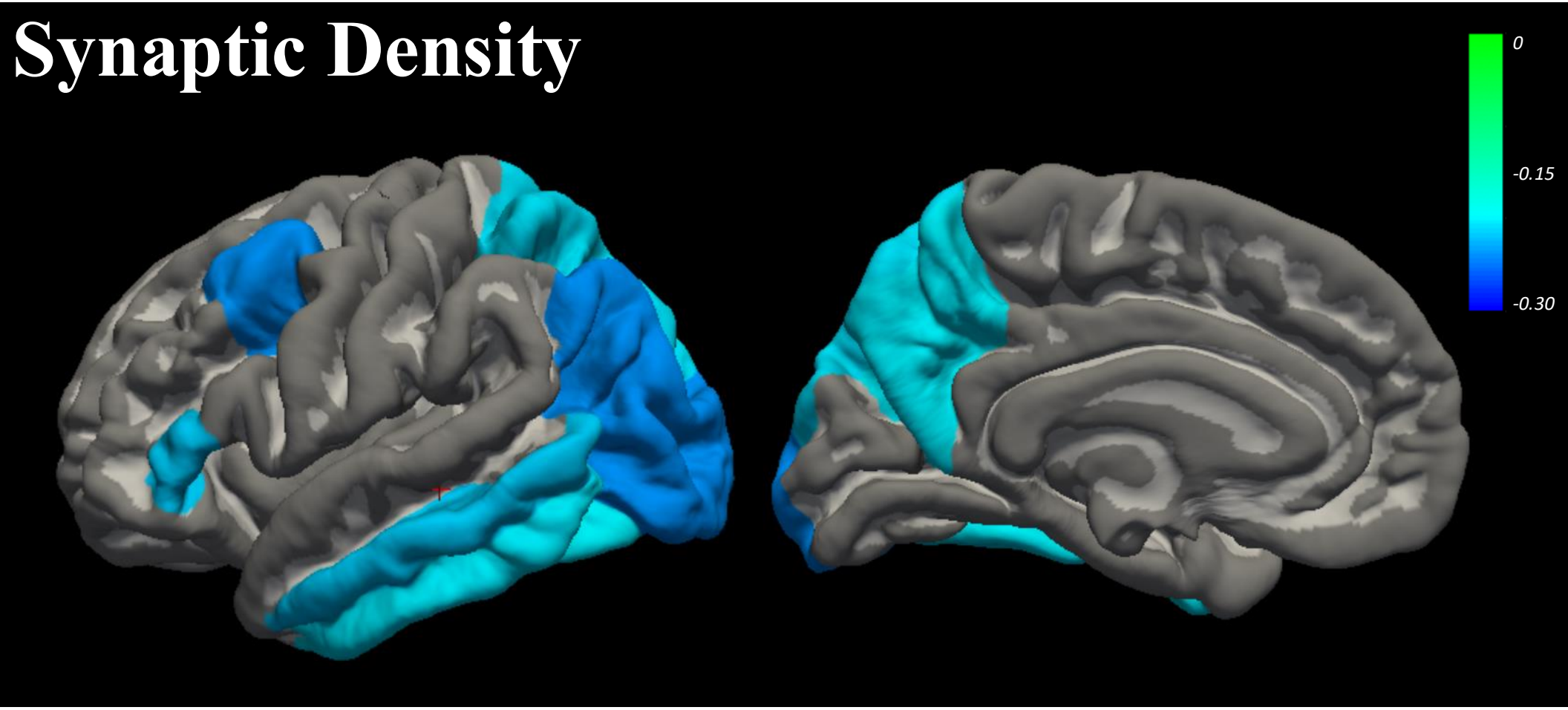
Amyloid



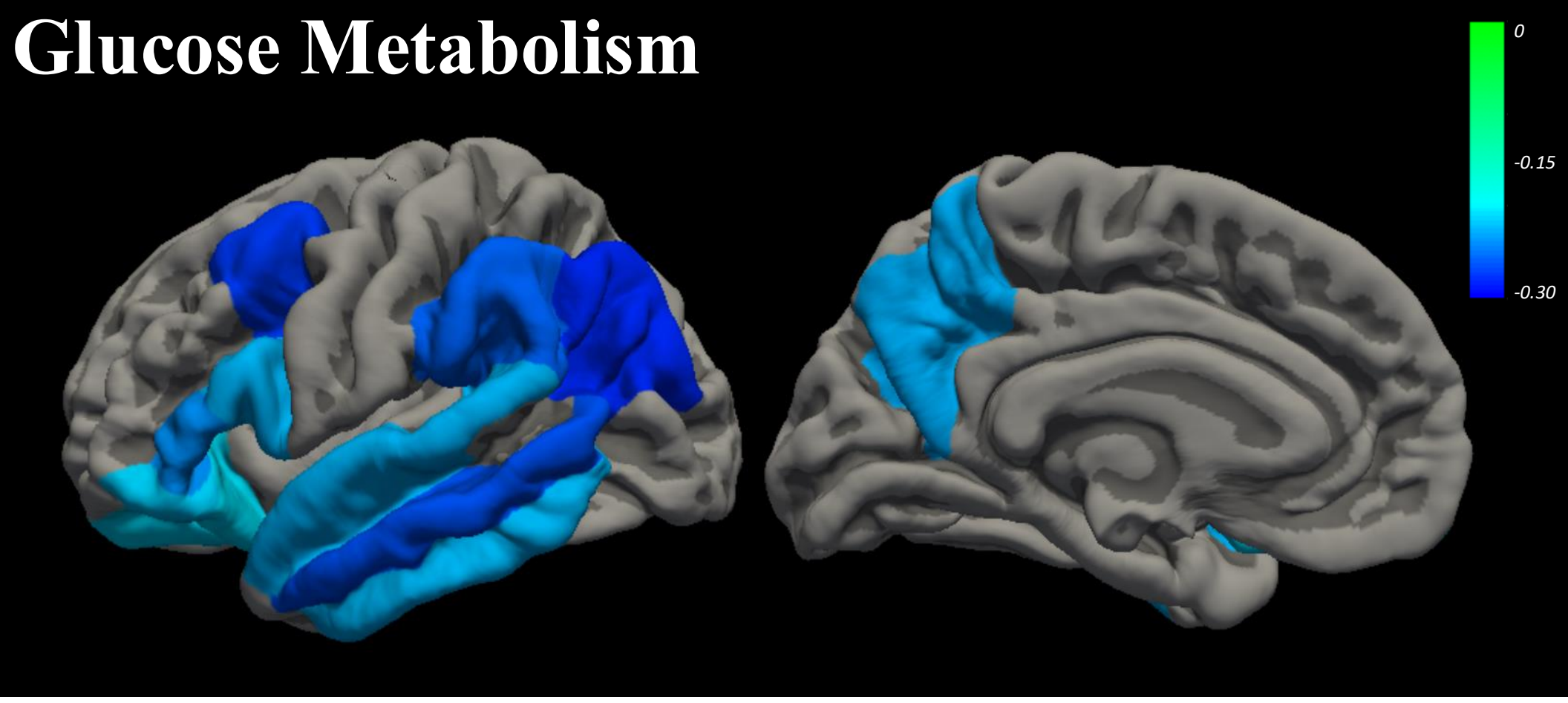
Tau



Synaptic Density

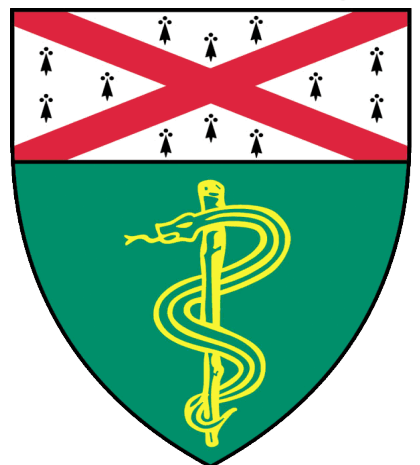


Glucose Metabolism



Conclusions

- Discoordination of brain pulsations with CSF flow was associated with multiple core AD features.
- These associations were consistently observed in temporal and parietal regions across tracers.
- Lack of an association between amyloid burden and gBOLD-CSF coupling among cognitively unimpaired participants suggests that deficits in brain pulsation-CSF dynamics may emerge in the symptomatic phase.
- Cognitive domain-specific analysis showed lower brain pulsation amplitude to be associated with lower global performance, verbal memory, language, processing, and visuospatial ability.



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