

Brain Fluid Pulsation Energy May Increase With Amyloid Burden Early In The Alzheimer's Pathophysiological Spectrum

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Introduction

Neurofluid flow may be important for removing brain waste, such as β -amyloid (A β). However, how and when neurofluid dynamics change, both spatially and temporally across the Alzheimer's disease (AD) pathophysiological spectrum, remains unclear. Here, we used 7T magnetic resonance imaging (MRI) to characterize neurofluid pulsatility across the whole brain in relation to PET-assessed A β and astrogliosis.

Methods

- 7T MRI acquisitions using the Tac-G2 coil system (Fig. 1), with echo planar imaging (EPI) multiband MR sequence.
- Whole-brain coverage: divided into 5 slabs, each consisting of 15 axial slices with 2mm thickness. TR = 150 ms.
- Concurrent acquisition of physiological rhythms.
- Regions:** 4th ventricle, lateral ventricles, all CSF regions combined, cortical gray matter (GM), and cerebral white matter (WM).
- Dependent Variables:** Participants also underwent ¹¹C-PiB and ¹⁸F-SMBT-1 PET imaging, for A β load and monoamine oxidase B (MAO-B) astrogliosis assessment.

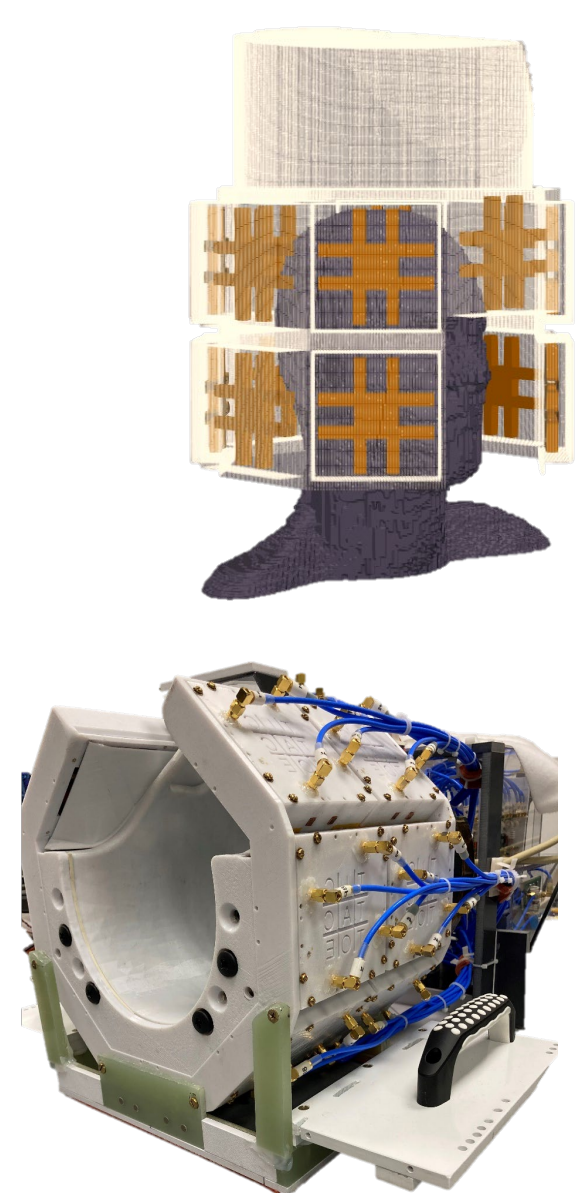


Fig. 1: 60-channel Tac-G2 coil design and implementation.

- Normalizations:** percentage signal change (PSC) and z-score.
- Pulsatility Metric:** Power Spectral Density (PSD) estimated using Multitaper Spectral Analysis (Fig. 2 and Fig. 3). Very-low-frequency (VLF) band power and total power were calculated. Their ratio, the fractional amplitude of low-frequency fluctuation (fALFF), was also computed.
- Sex differences between pulsatility metrics were assessed with the Mann-Whitney U Test. Associations between pulsatility metrics and age, intracranial volume, precuneus and global Pittsburgh compound B (PiB), precuneus ¹⁸F-SMBT-1, and MK6240 mesial temporal cortex SUVR were assessed with the Pearson and Spearman's correlation coefficients.

Conclusions

- Dominant PSD peaks consistently align with independently measured cardiac and respiratory rates, supporting the physiological validity and internal consistency of this approach (Fig. 3).
- The variability across ROIs may reflect differences in bulk fluid dynamics and potential waste clearance mechanisms, as regions with higher pulsatility energy or altered spectral composition could exhibit distinct neurofluid flow profiles (Table 1 and Fig. 4).
- Female participants exhibited greater VLF band power and fALFF than males (Table 2 and Fig. 4).
- These results suggest neurofluid pulsatility is modified early in the AD pathophysiological spectrum and may serve as a predictor of A β burden. Increased VLF pulsation energy may reflect a compensatory or resilience mechanism related to A β aggregation.

Results

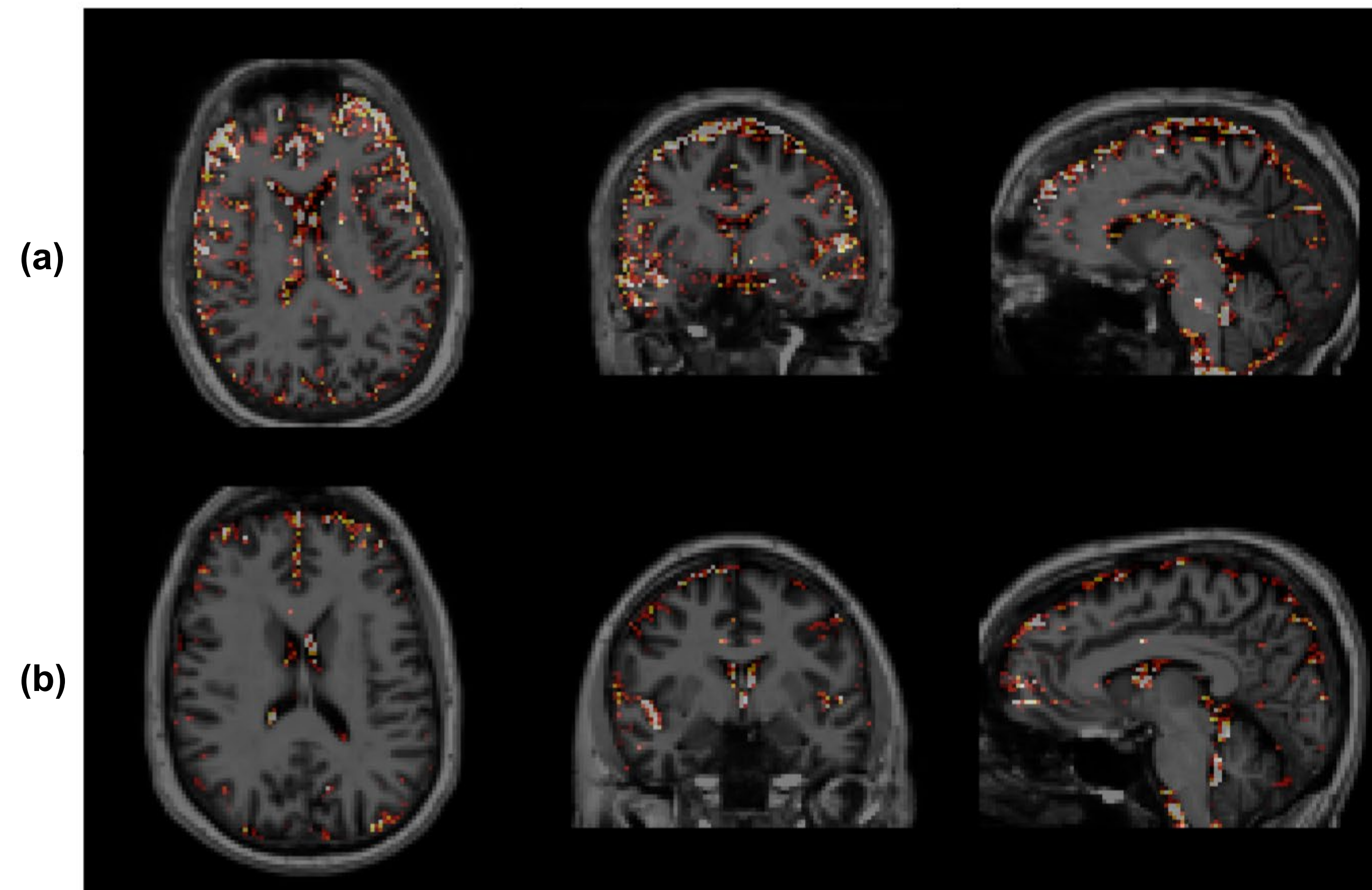


Fig. 2: Pulsatility spectral maps in the VLF band (<0.1 Hz) overlaid on structural T1w images for (a) a regional PiB+ participant and (b) a PiB- participant. These maps use the original EPI signal; in this project, both PSC and z-score normalizations are also considered. VLF, very-low-frequency; PiB, Pittsburgh compound B; EPI, echo planar imaging; PSC, percentage signal change.

Table 1: Highest correlation coefficients and respective p-values for brain regions, A β load, and MAO-B astrogliosis assessment. A β , β -amyloid; monoamine oxidase B (MAO-B); GM, gray matter; WM, white matter; CSF, cerebrospinal fluid; PiB, Pittsburgh compound B; SUVR, Standardized Uptake Value Ratio; PSC, percentage signal change.

Region	Dependent Variable	Normalization	Pulsatility Metric	Statistics	R	p-value
Cortical GM	Precuneus PiB SUVR	PSC	Total	Pearson	0.53	0.020
Cortical GM	Precuneus ¹⁸ F-SMBT-1	PSC	Total	Spearman	0.52	0.022
4 th Ventricle	Precuneus PiB SUVR	PSC	Band	Spearman	0.51	0.026
Cortical GM	Precuneus PiB SUVR	PSC	Band	Pearson	0.51	0.027
Cerebral WM	Global PiB SUVR	Z-Score	Total	Spearman	0.49	0.035
Cortical GM	Precuneus ¹⁸ F-SMBT-1	PSC	Band	Spearman	0.48	0.036
4 th Ventricle	Global PiB SUVR	Z-Score	Total	Spearman	0.46	0.050
4 th Ventricle	Precuneus PiB SUVR	Z-Score	Total	Spearman	0.44	0.059
Cortical GM	Global PiB SUVR	Z-Score	Total	Spearman	0.43	0.066
Cortical GM	Global PiB SUVR	PSC	Total	Pearson	0.41	0.084
ALL CSF	Global PiB SUVR	Z-Score	Total	Spearman	0.40	0.090

Table 2: Largest sex differences and respective p-values for brain regions, using Mann-Whitney U test. GM, gray matter; WM, white matter; CSF, cerebrospinal fluid; PSC, percentage signal change; fALFF, fractional amplitude of low-frequency fluctuation.

Region	Normalization	Pulsatility Metric	U	p-value
Cortical GM	Z-Score	Band	16	0.020
Lateral Ventricles	PSC	fALFF	17	0.025
Lateral Ventricles	Z-Score	Band	17	0.025
Lateral Ventricles	Z-Score	fALFF	17	0.025
Cerebral WM	Z-Score	Band	17	0.025
ALL CSF	Z-Score	Band	18	0.030
Cerebral WM	PSC	fALFF	20	0.045
Cerebral WM	Z-Score	fALFF	20	0.045

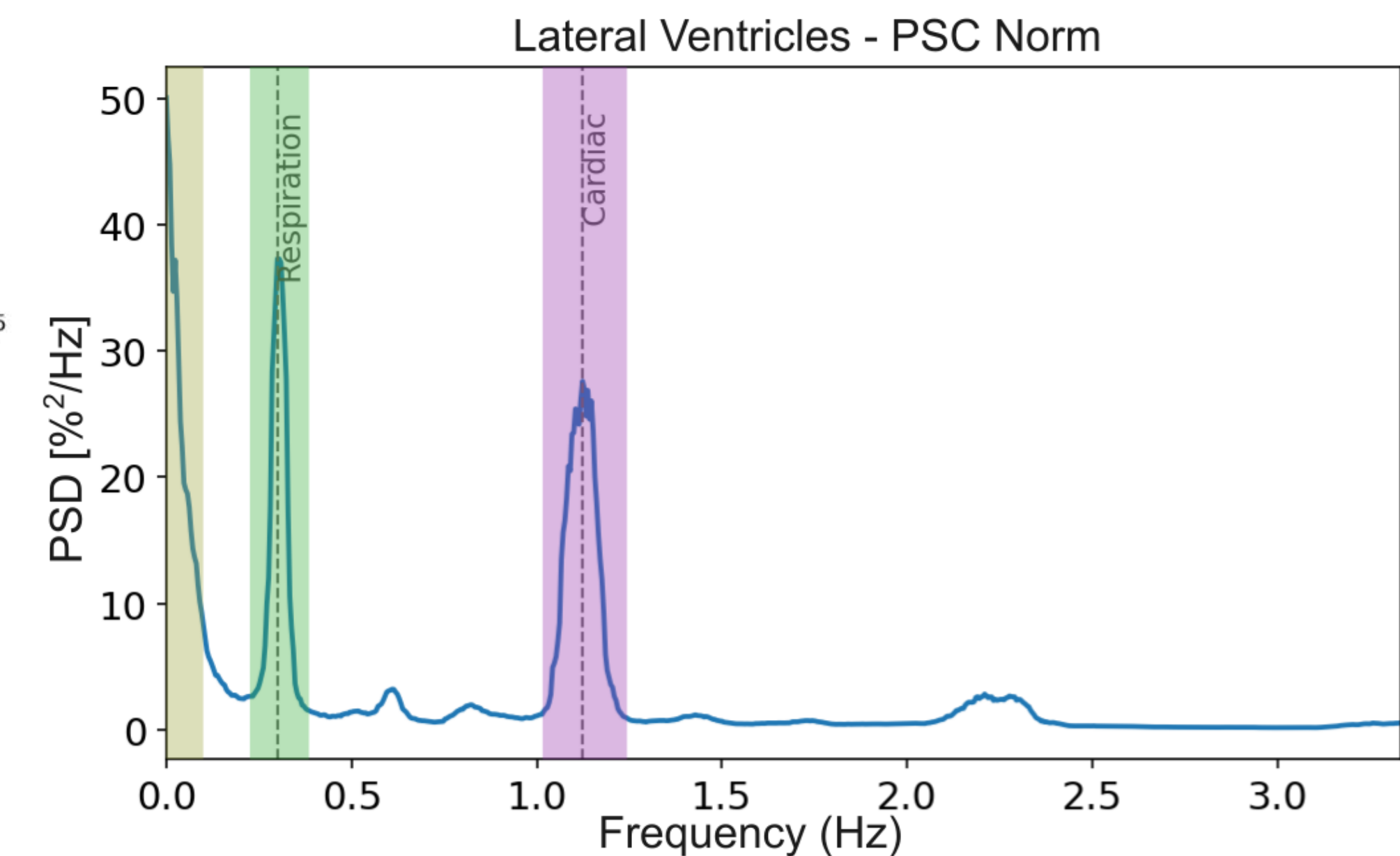
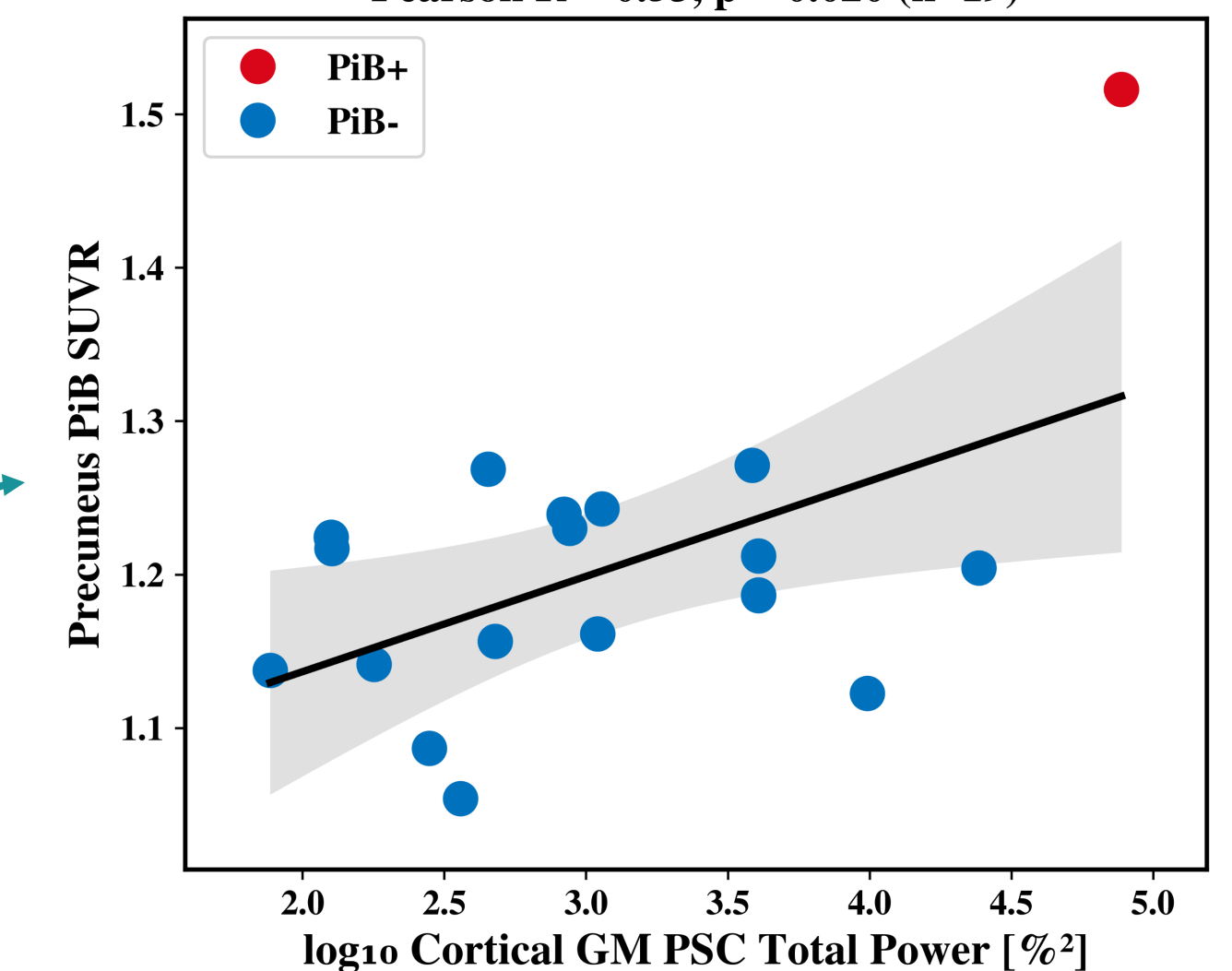


Fig. 3: Example of neurofluid PSD from a single participant, computed across lateral ventricle voxels, with PSC normalization. The average physiological rates for respiratory (~0.3 Hz) and cardiac (~1.1 Hz) signals align with the CSF pulsatility peaks. PSD, power spectral density; PSC, percentage signal change; CSF, cerebrospinal fluid.

(a) Cortical GM PSC Total Power vs Precuneus PiB SUVR. Pearson R = 0.53, p = 0.020 (n=19)



(b) Cortical GM Z-score Band Power by sex. Mann-Whitney U = 16, p = 0.020

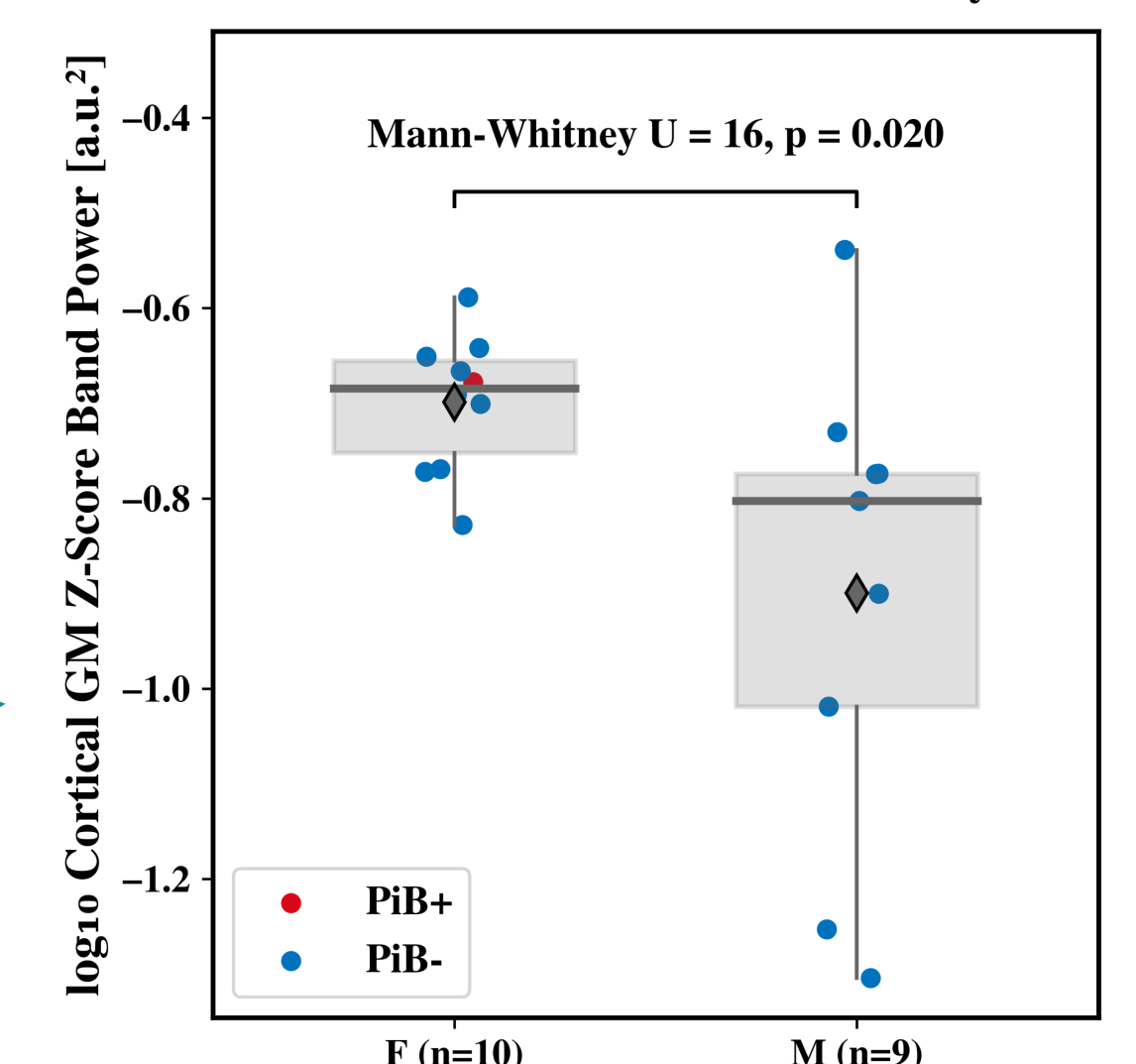


Fig. 4: (a) Regression plot representing the strongest correlation from Table 1 (PSC-norm cortical GM total power vs. Precuneus PiB SUVR), and (b) the largest sex difference from Table 2 (z-score-norm cortical GM band power). PSC, percentage signal change; GM, gray matter; PiB, Pittsburgh compound B; SUVR, Standardized Uptake Value Ratio.