Leveraging **highly-comparative time-series analysis** to study properties of **neural activity** related to **amyloid-beta plaque burden**

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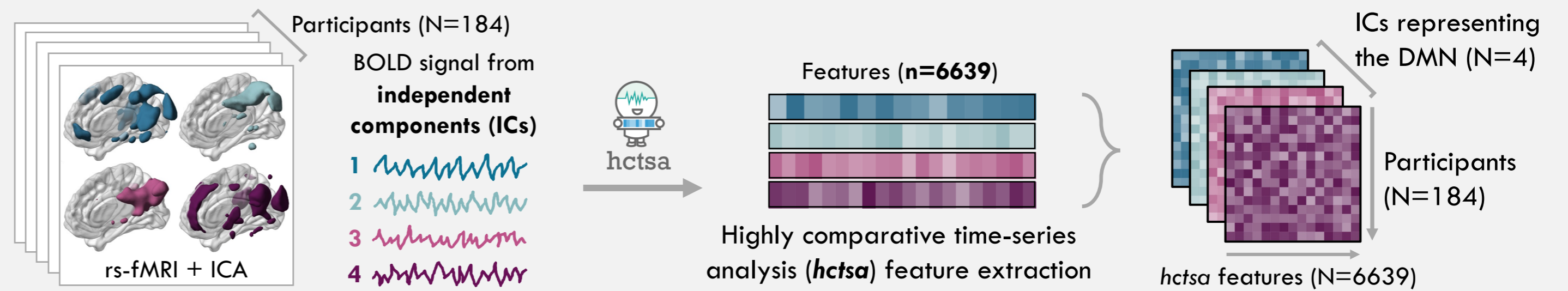✉ abry4213@uni.sydney.edu.au

Background

Alzheimer's disease is characterized by diverse neuropathological changes like **neurodegeneration** and the aggregation of **amyloid-beta (Aβ) plaques** throughout the brain. Prior neuroimaging studies suggest a link between **Aβ plaque deposition** and **altered neural activity**, particularly in the **default mode network (DMN)**. However, such previous work has generally focused on just a **few statistical properties of neural activity data** like the fractional amplitude of low-frequency fluctuations or regional homogeneity, which could overlook **nuanced changes in activity dynamics** throughout the brain.
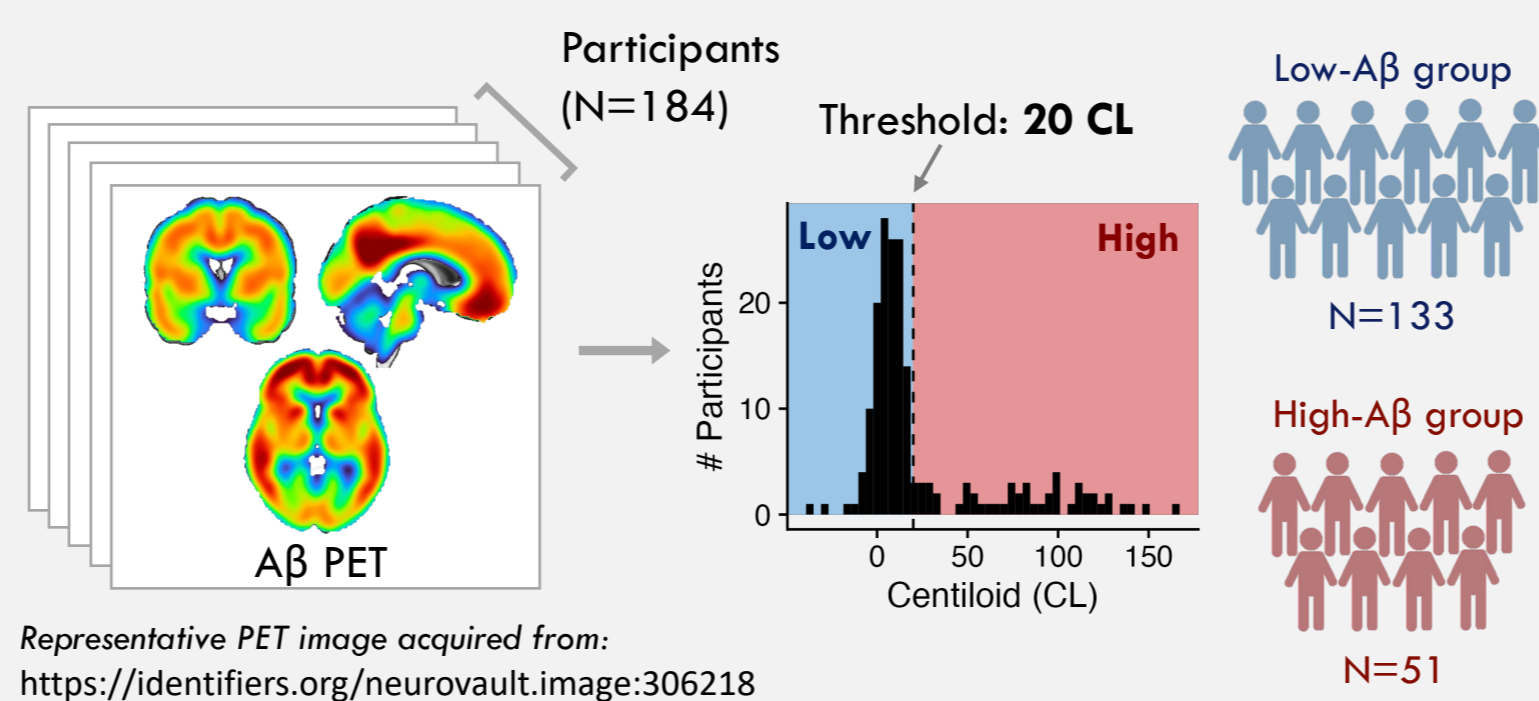
Here, we comprehensively analyse 6,639 univariate properties of **DMN activity dynamics** from resting-state functional magnetic resonance imaging (**rs-fMRI**) data. We compare these dynamics in high- versus low-amyloid individuals across the cognitive spectrum, revealing a **signature of disrupted activity** across the DMN characterized largely by changes in the **power spectrum shape** and time-series **correlation structure**.
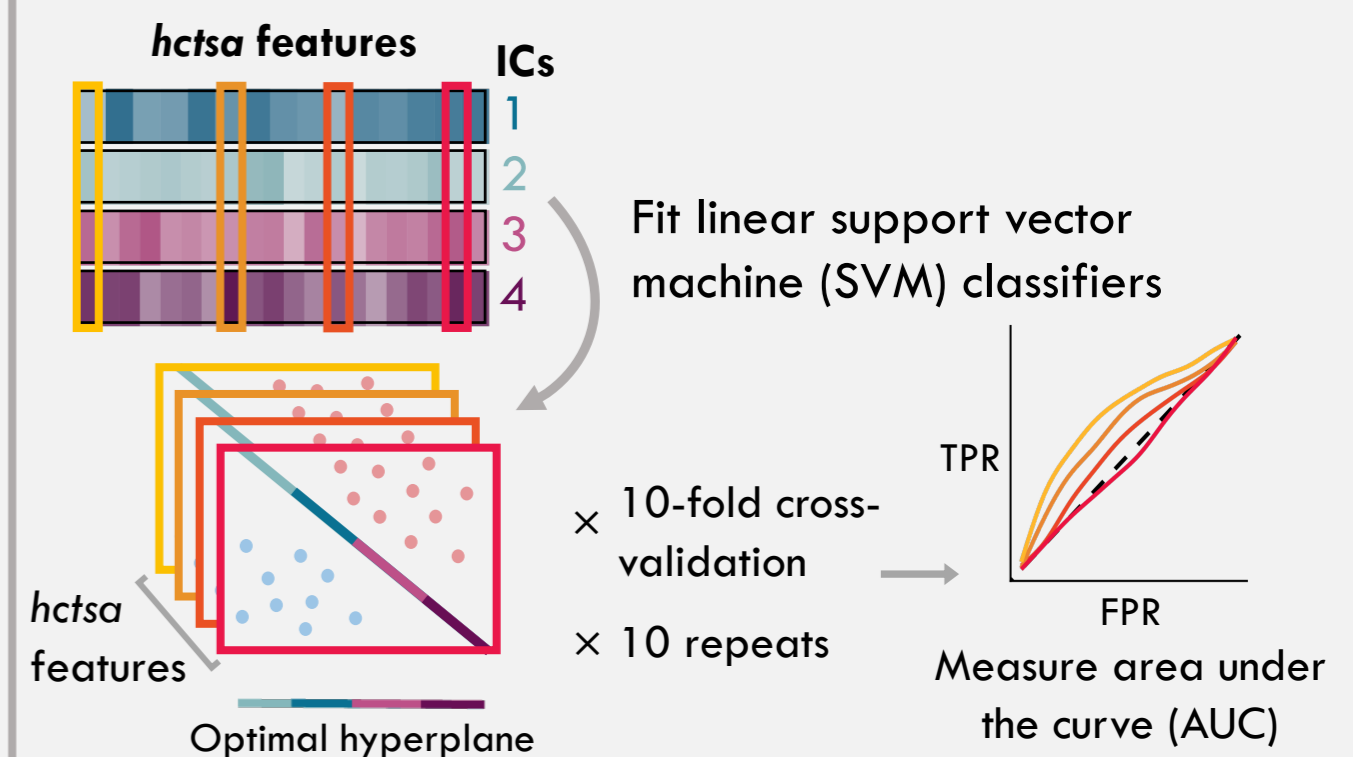
Methods

Step 1: Compute a comprehensive set of **6,639** from rs-fMRI blood oxygen level dependent (**BOLD**) time series across a set of four independent components (ICs) representing the **DMN**
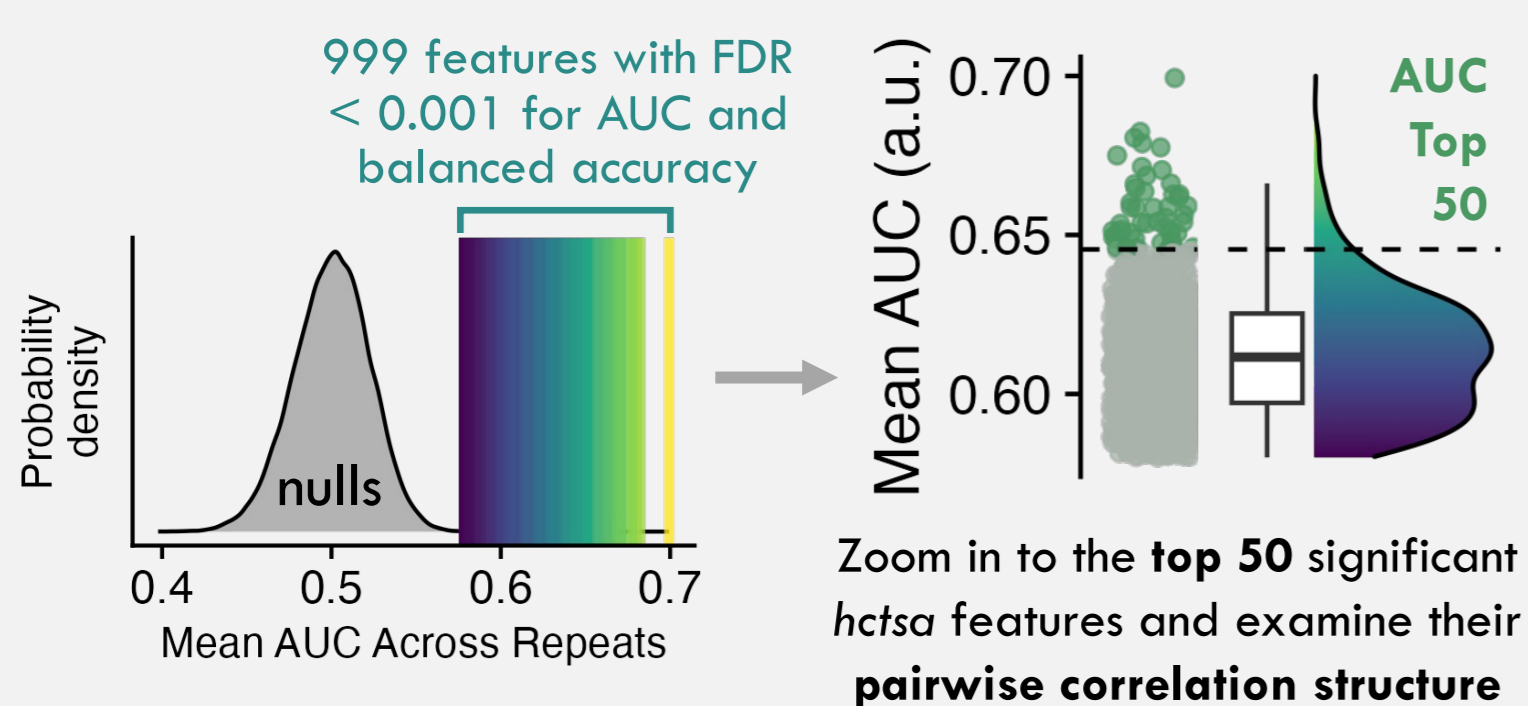

Participants (N=184) — BOLD signal from **independent components (ICs)** — Highly comparative time-series analysis (*hctsa*) feature extraction — Features (**n=6639**) — ICs representing the DMN (N=4) — Participants (N=184) — *hctsa* features (N=6639)

Step 2: Calculate **brain-wide Aβ centiloids** and classify participants as **low- or high-amyloid**

Aβ PET — Participants (N=184) — Threshold: **20 CL** — Low-Aβ group N=133 — High-Aβ group N=51

Representative PET image acquired from: https://identifiers.org/neurovault.image:306218

Step 3: Use **DMN neural activity properties** to predict low- vs. high-Aβ participants

hctsa features — ICs 1 2 3 4 — Fit linear support vector machine (SVM) classifiers — × 10-fold cross-validation × 10 repeats — Optimal hyperplane — Measure area under the curve (AUC)

Results

1. The feature-wise approach identifies **999 distinguishing *hctsa* features** across 4 DMN ICs

999 features with FDR < 0.001 for AUC and balanced accuracy — Mean AUC Across Repeats — nulls — AUC Top 50 — Zoom in to the **top 50** significant *hctsa* features and examine their **pairwise correlation structure**

Spearman rank correlation (ρ) 0 0.5 1

Power spectrum shape and lagged self-correlation structure

State-space and autoregressive model fitting
Miscellaneous (incl. nonlinear autocorrelation and force potentials with sine functions)

hctsa feature category examples:

Power spectrum shape: SP_Summaries_fft_wmax_75

Time domain → Fast Fourier transform (FFT) → Frequency domain — CumSum — 75% max

Find the **BOLD frequency** for which the **power spectral density** cumulative sum is at **75% of its maximum** (★)

AUC=0.66
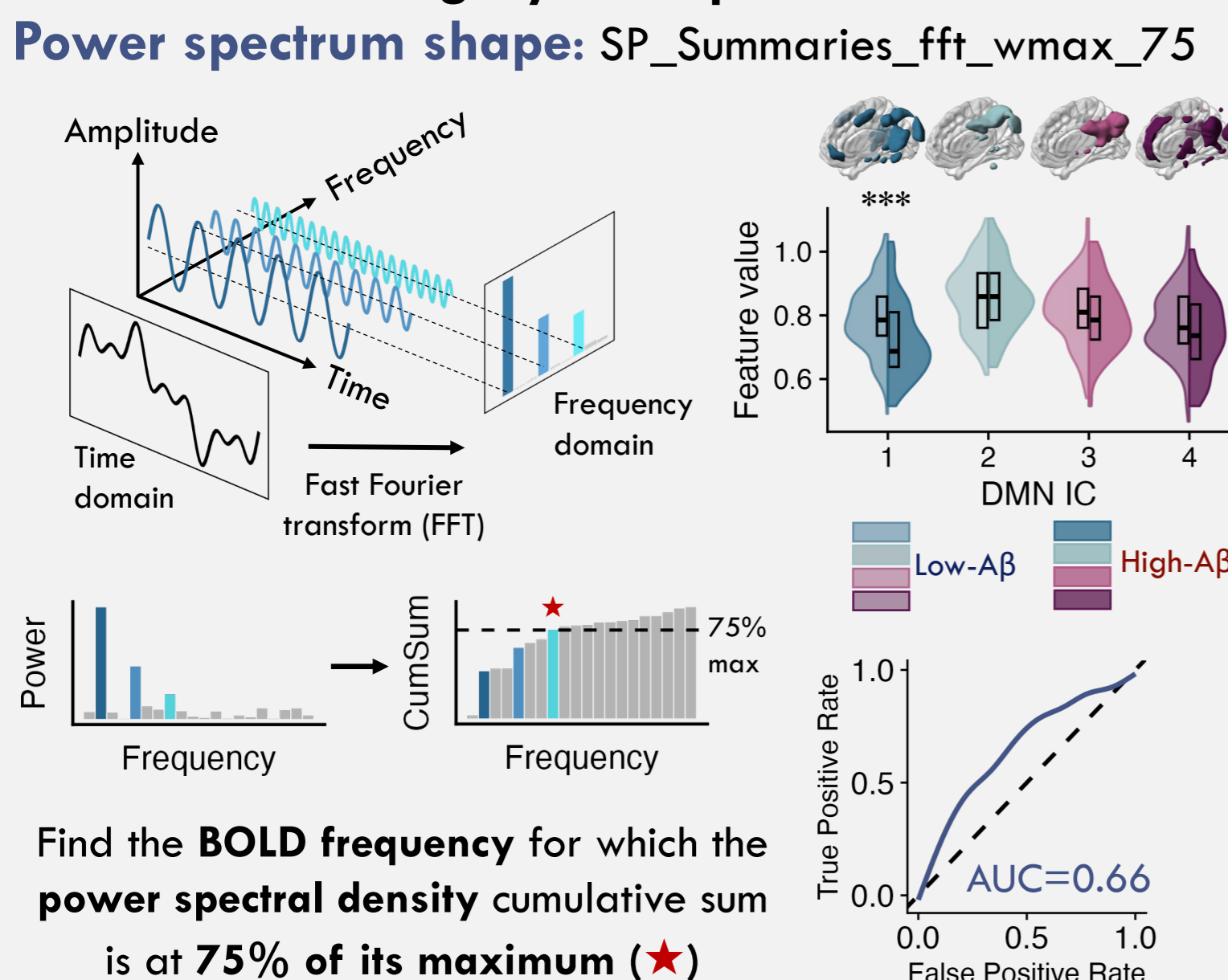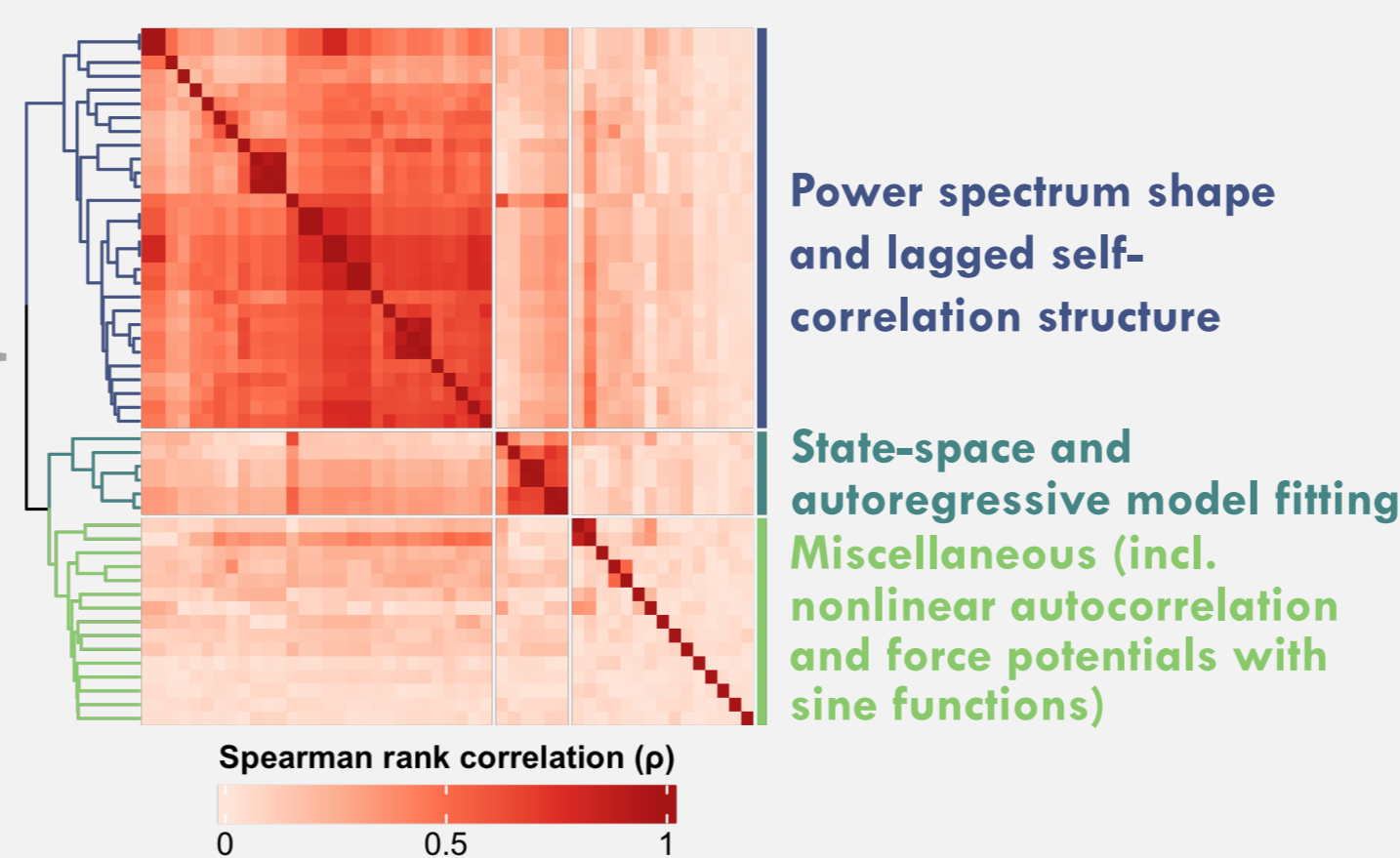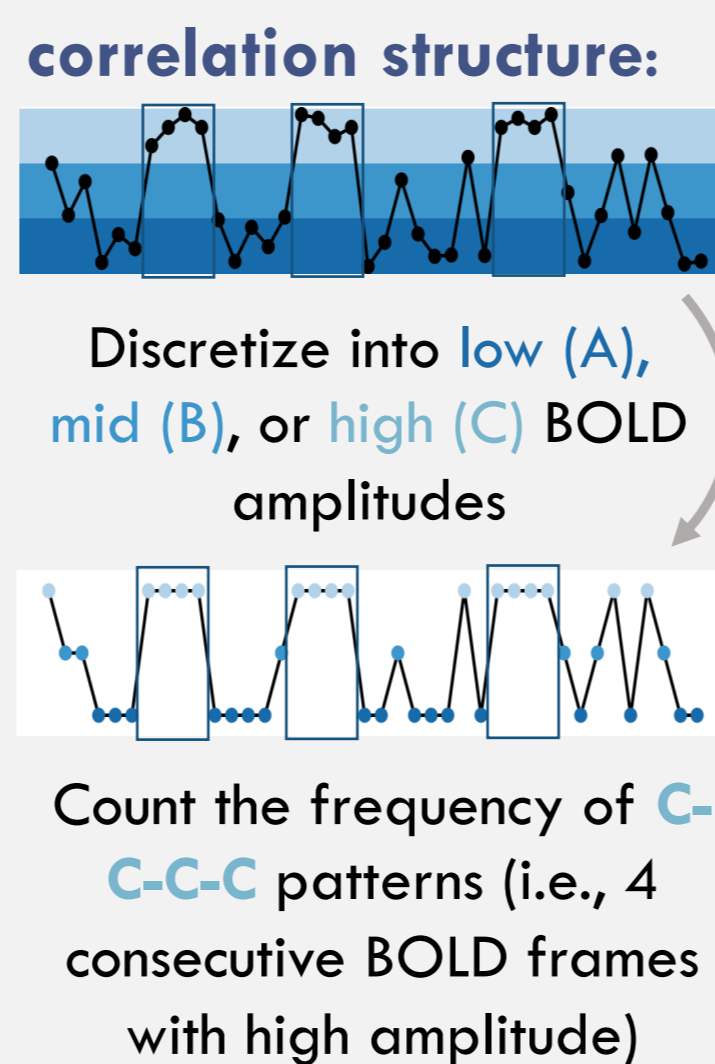
Lagged self-correlation structure: SB_MotifThree_quantile_cccc

Discretize into low (A), mid (B), or high (C) BOLD amplitudes

Count the frequency of C-C-C-C patterns (i.e., 4 consecutive BOLD frames with high amplitude)

*** * DMN IC 1 2 3 4 — Low-Aβ High-Aβ — AUC=0.68
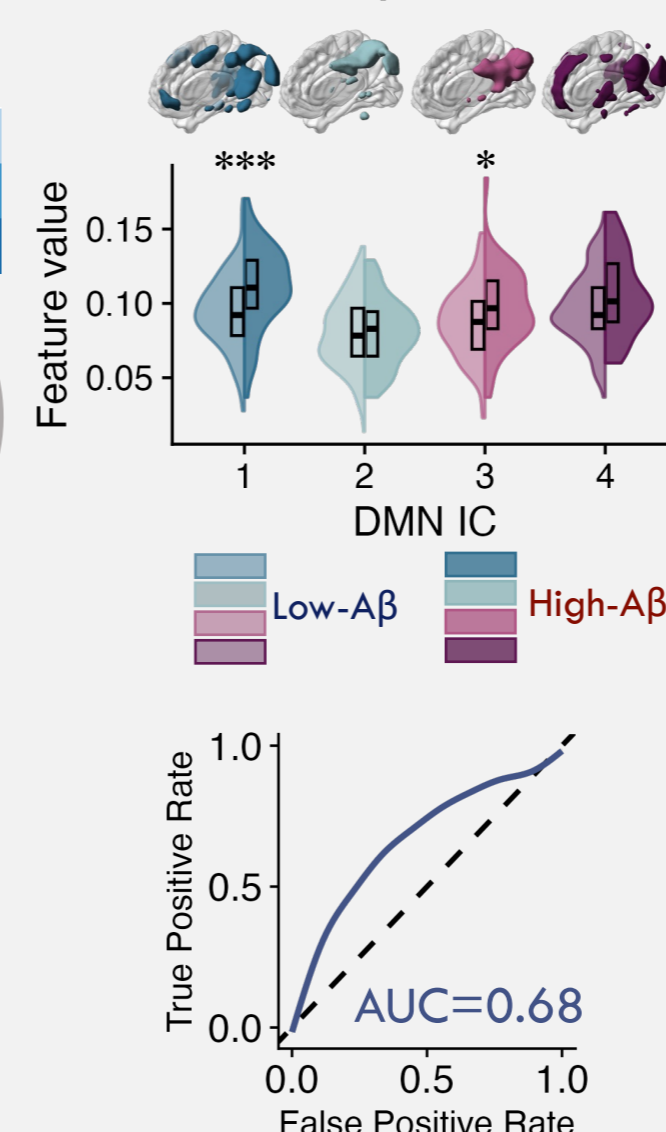
2. Many *hctsa* features **outperform the fractional amplitude of low frequency fluctuations (fALFF)**

$\Sigma_{Power} \div \Sigma_{Power}$ — Power (a.u.) — Frequency (Hz) 0.01 0.08 Max

fALFF (a.u.) — DMN IC 1 2 3 4 — Low-Aβ High-Aβ — *

Mean AUC — Top 50 hctsa features + fALFF — fALFF

True Positive Rate / False Positive Rate — fALFF AUC=0.62

3. **Null results:**
Linear SVM with all **6,639 *hctsa* features** per DMN component **does not** perform well

True Positive Rate / False Positive Rate — ICs 1 2 3 4
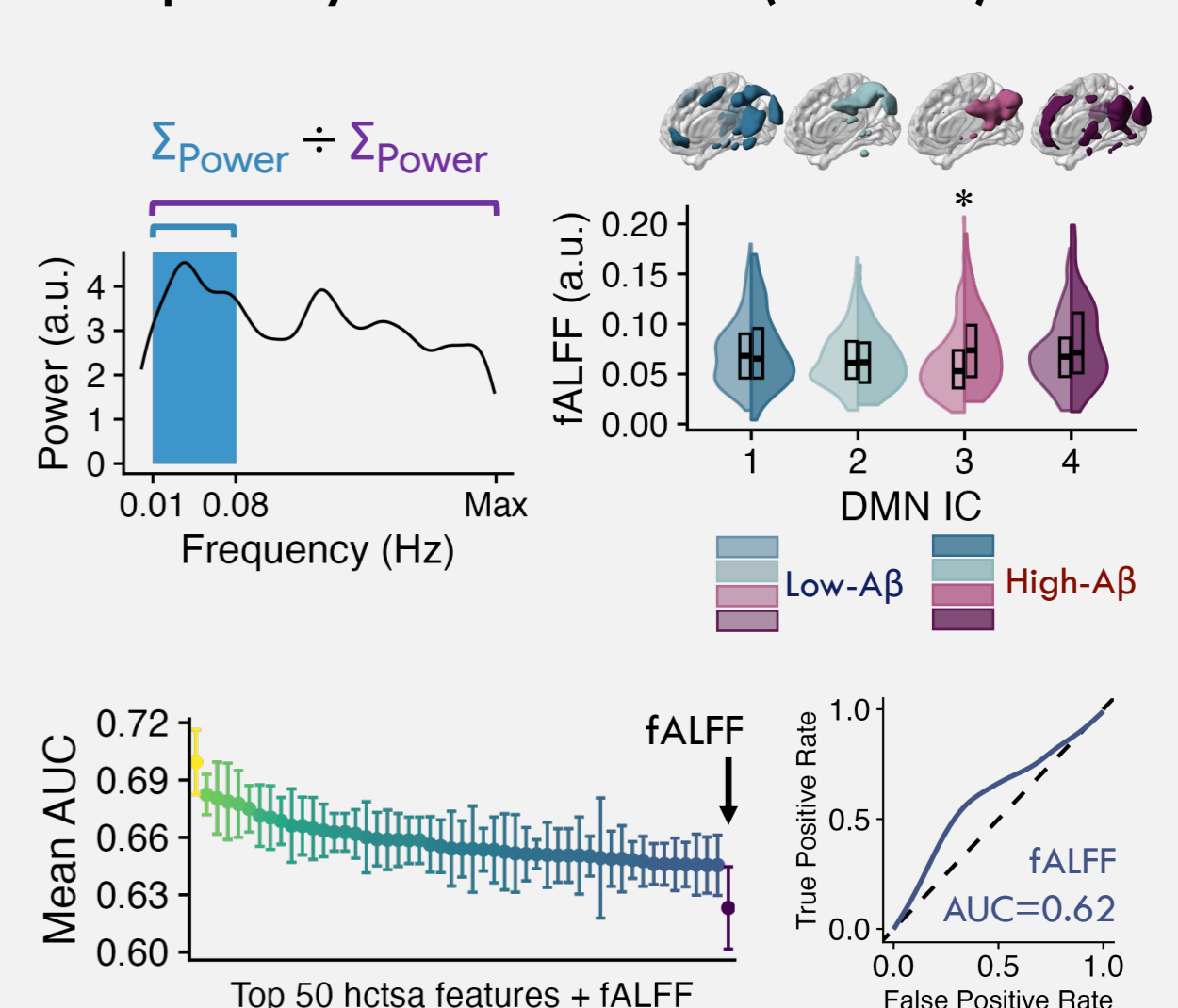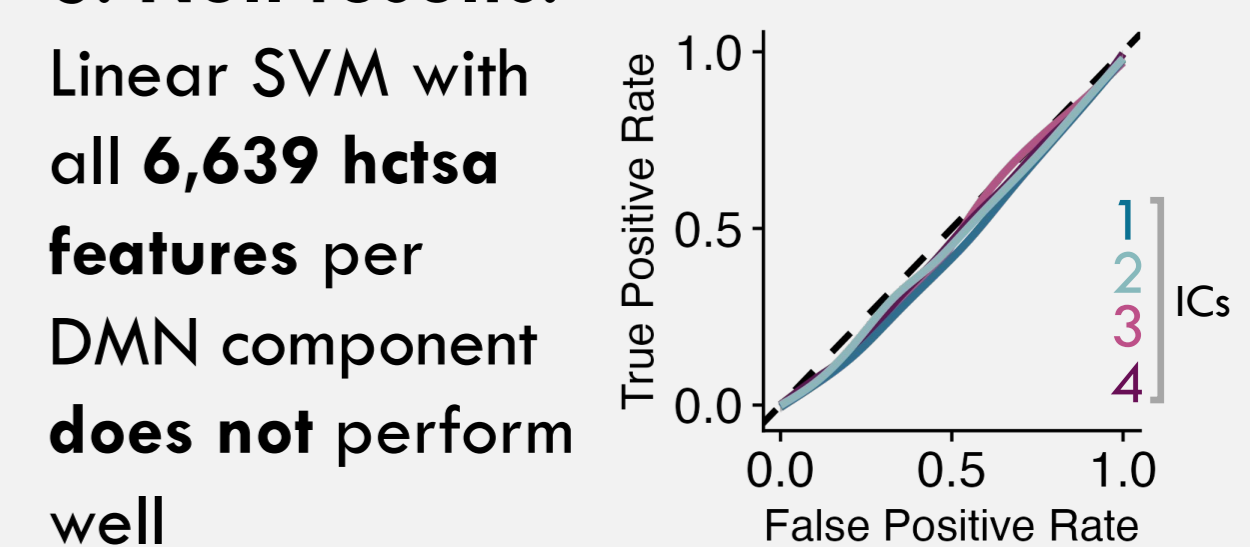
Key Conclusions

- The DMN exhibits **diverse altered neural activity dynamics** in high- versus low-amyloid burden individuals
- **Power spectrum shape** and **lagged self-correlation structure** features are among top-performing discriminators
- Many *hctsa* features are **more sensitive at identifying high-amyloid participants** than the fALFF, a commonly-used biomarker for univariate neural activity alterations in AD

Next steps

- Incorporate **tau PET** given evidence for altered **excitation:inhibition balance** in the DMN, which can promote tau aggregation
- Expand analysis to bivariate domain to examine **functional connectivity** between the DMN and other parts of the brain as it relates to **AD neuropathology**
- **Dimensionality reduction** and **feature selection** to better understand how activity dynamics **relate to each other**

Key References

1. Scheel, N., *et al. J. Cereb. Blood Flow Metab.* (2022)
2. Yang, L., *et al. Front. Neurosci.* (2018)
3. Klunk, W. E., *et al. J Alzheimers Assoc.* (2015)
4. Fulcher, B. D. & Jones, N. S. *Cell Syst.* (2017)
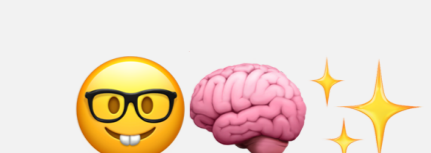5. Buckner, R. L. *J. Neurosci.* (2005)

Acknowledgements

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