Studying neural dynamics and neuropathological burden in Alzheimer's disease with complex systems analysis

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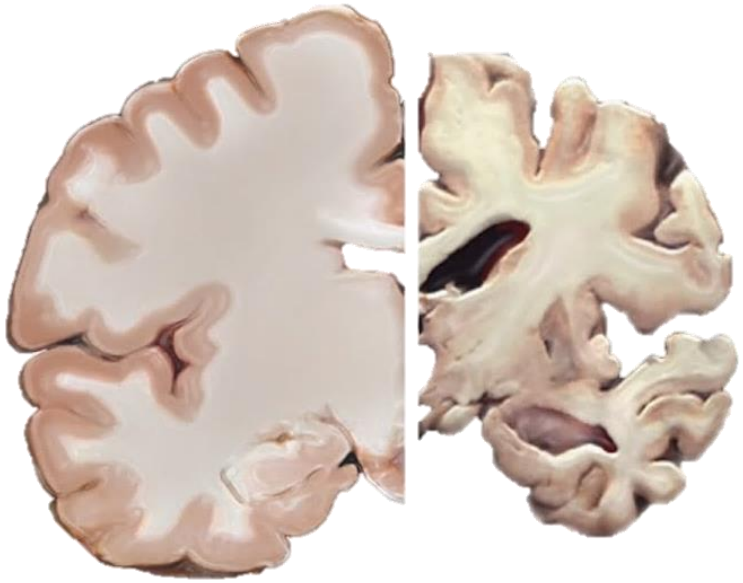
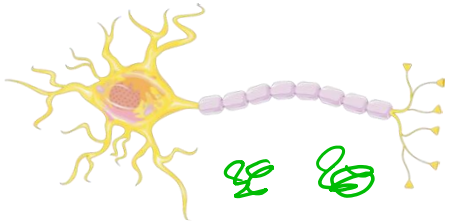
The **neuropathological hallmarks** of Alzheimer's disease (AD): tau tangles, **amyloid plaques**, and cortical atrophy



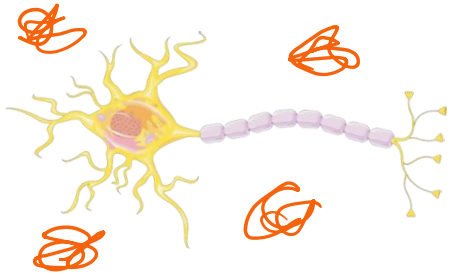
Healthy brain **AD** brain

Lerch et al. (2005)

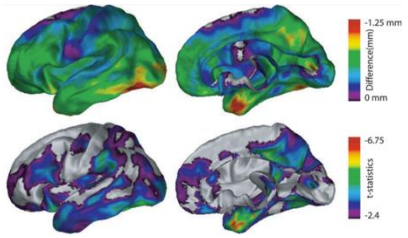
Tau tangles



Amyloid plaques



Cortical thinning



Lerch et al. (2005)

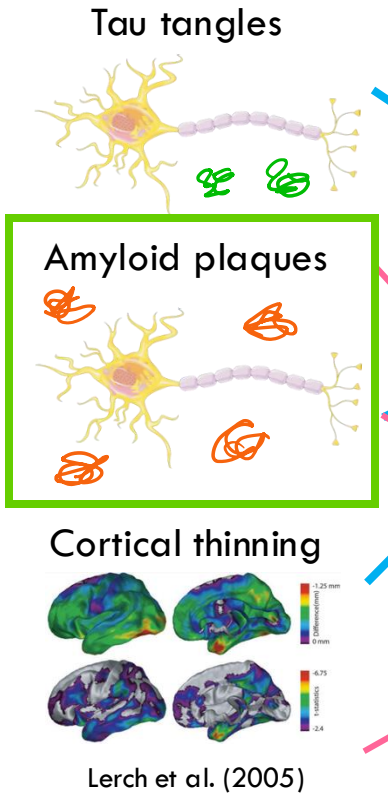
Local disruptions to activity within **individual brain regions**

Broader disruptions to **communication patterns** between **pairs of brain regions**

The **neuropathological hallmarks** of Alzheimer's disease (AD): tau tangles, **amyloid plaques**, and cortical atrophy

Healthy brain **AD** brain

Lerch et al. (2005)

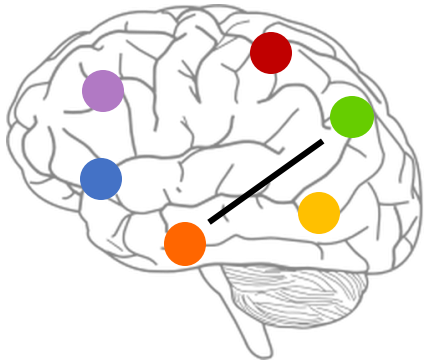


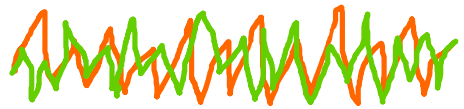
Lerch et al. (2005)

Local disruptions to activity within **individual brain regions**

Broader disruptions to **communication patterns** between **pairs of brain regions**

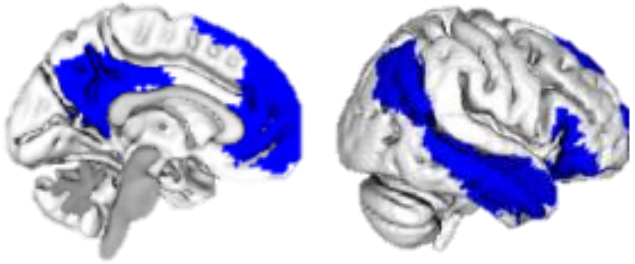
Represent **local regional dynamics** with univariate time-series features like fALFF



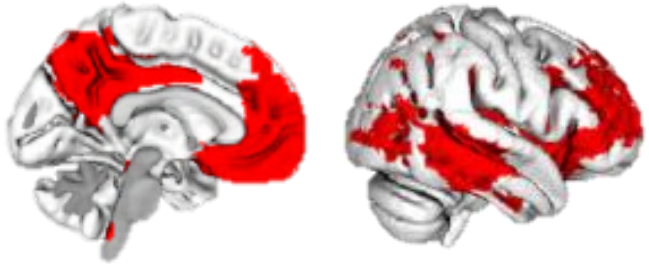


Represent **pairwise functional coupling** with features like the Pearson correlation coefficient

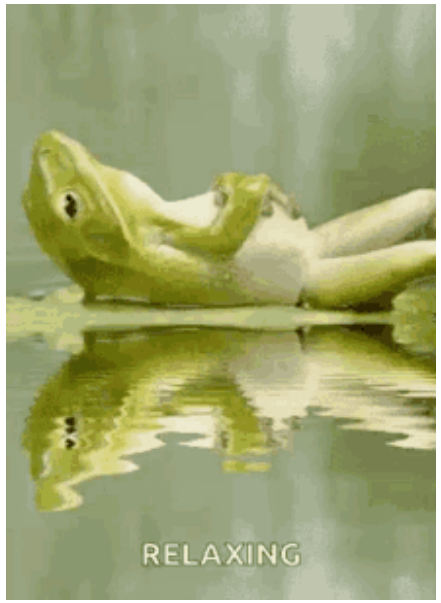
Aβ plaque deposition is related to neural activity alterations in the **default mode network**



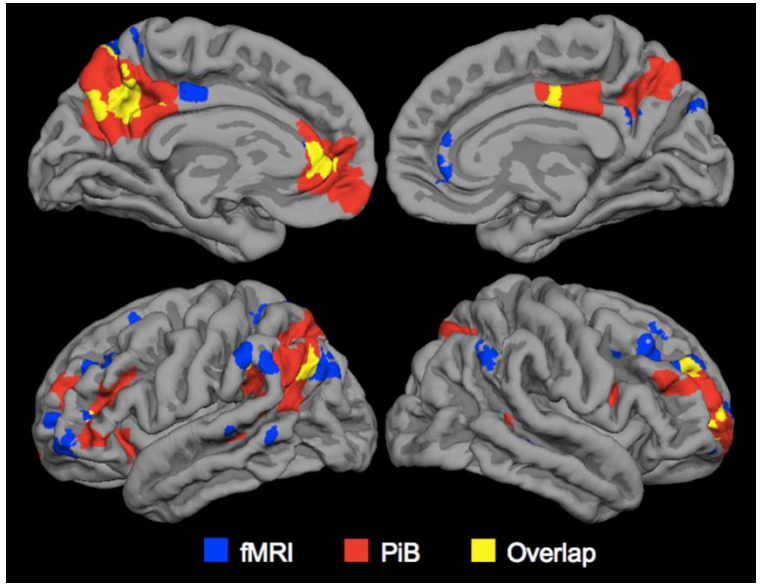
Default Mode Network (DMN)



Early Aβ plaque accumulation



DMN is active during:
Wakeful rest
Autobiographical memory
Thinking about others



Aβ plaque deposition colocalizes with **altered resting-state activity** relative to controls
(Sperling et al. *Neuron* 2009)

Images adapted from Palmqvist et al. (2017) *Nature Comms*

▶II : How does **Aβ plaque** deposition affect **neural function?**

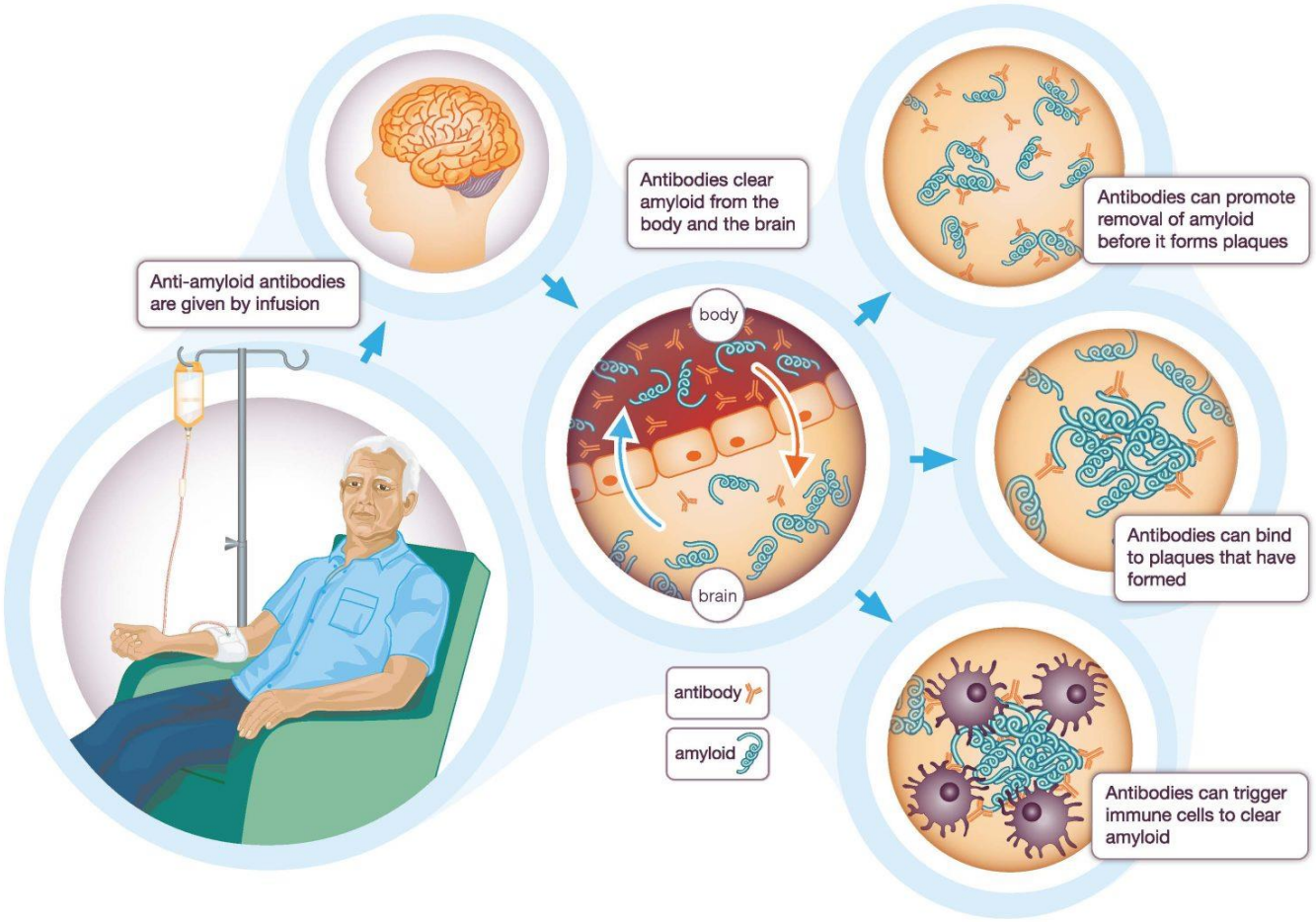


Image source: Alzheimer's Research UK

Aduhelm® (aducanumab-avwa) | 100 mg/mL injection, for intravenous use

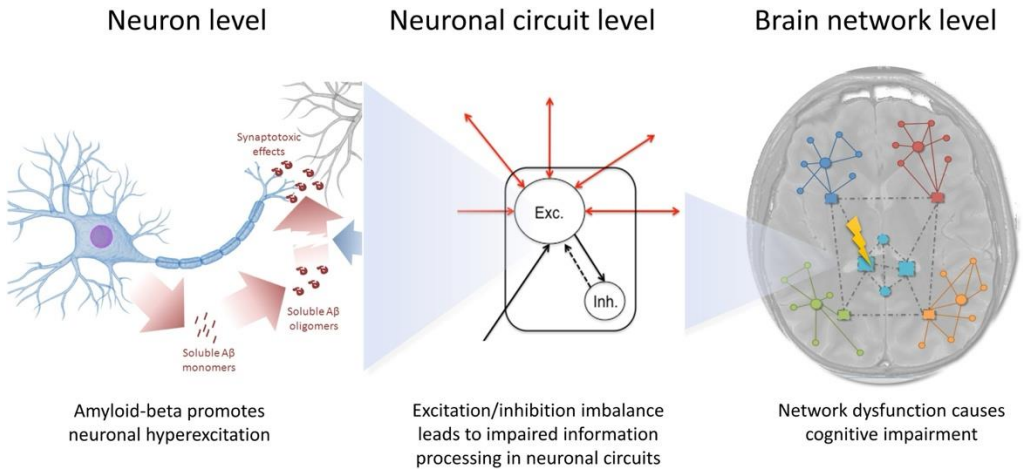
LEQEMBI® (lecanemab-irmb) 100 mg/mL INJECTION FOR INTRAVENOUS USE

Donanemab

Understanding specific **mechanism(s)** through which Aβ plaques **disrupt neuronal function and communication** will be vital for ongoing AD drug development

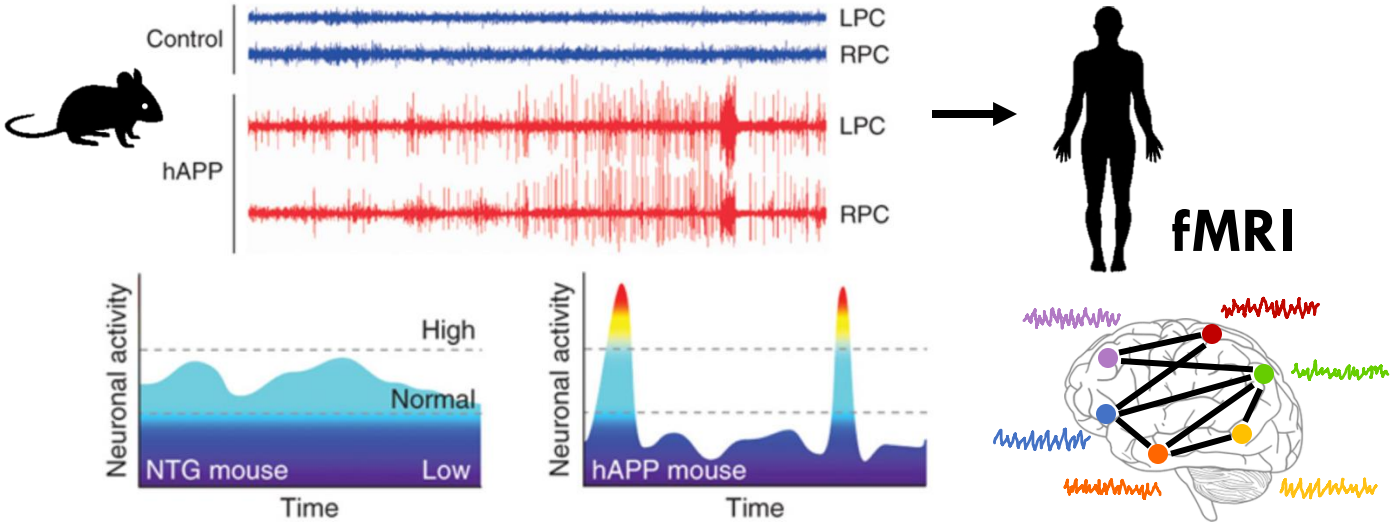
- Refining **drug mechanisms**
- Optimizing **biomarkers** for **neural activity** following clearance of Aβ plaques

Potential link between **Aβ plaques** and **altered neural activity in the DMN:** excitation-inhibition (E/I) imbalance



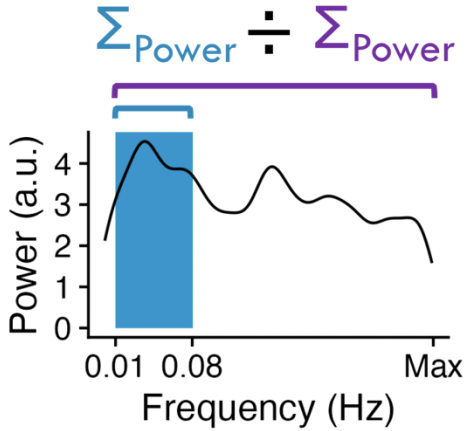
Mounting evidence suggests that **Aβ plaque** deposition drives **neuronal E/I balance** more towards **excitement,** disrupting network function

Image from Maestú et al. (2021) *Ageing Res Rev*

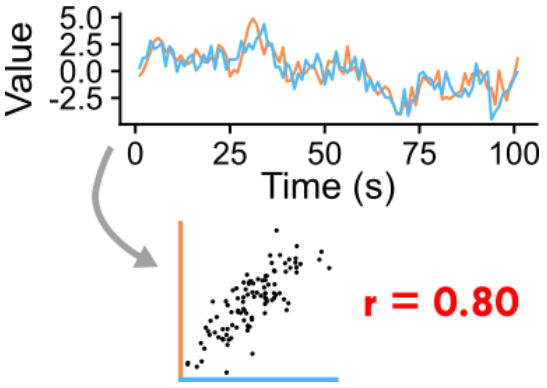


Images from Palop & Mucke *Nat Neuro* (2010) and Busche et al. *Science* (2008)

Fractional amplitude of low-frequency fluctuations (**fALFF**)

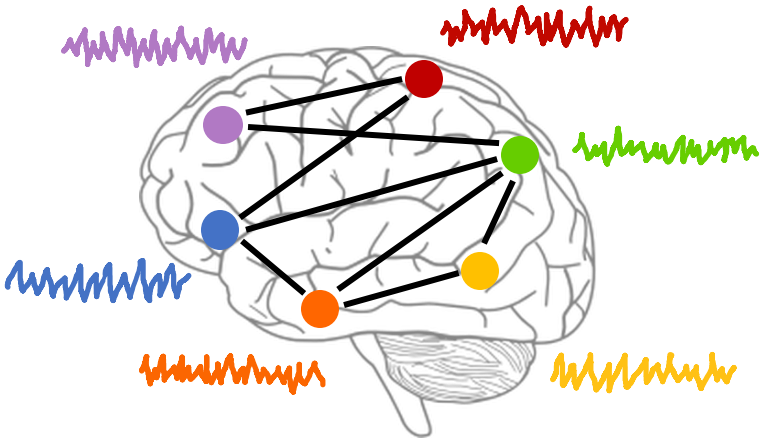


Pearson correlation coefficient

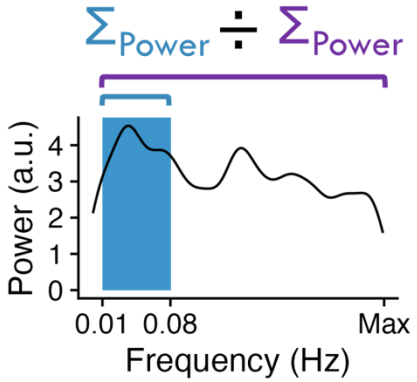


Potential link between **Aβ plaques** and **altered neural activity in the DMN:** excitation-inhibition (E/I) imbalance

Neuroimaging: blood oxygen level-dependent (**BOLD**) functional magnetic resonance imaging (**fMRI**)



Fractional amplitude of low-frequency fluctuations (**fALFF**)



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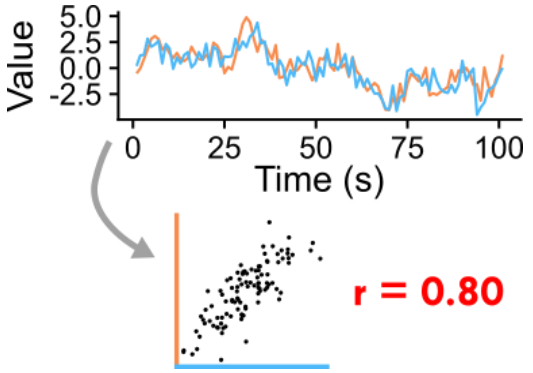
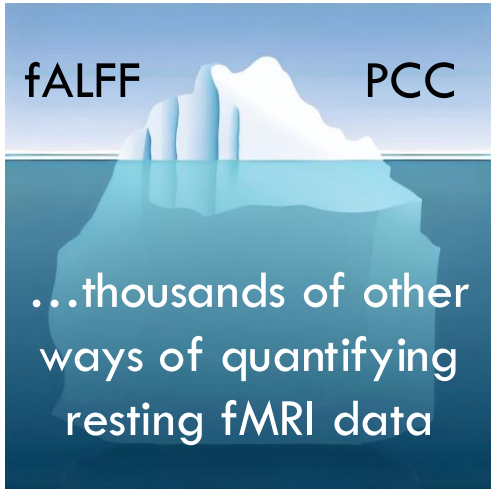
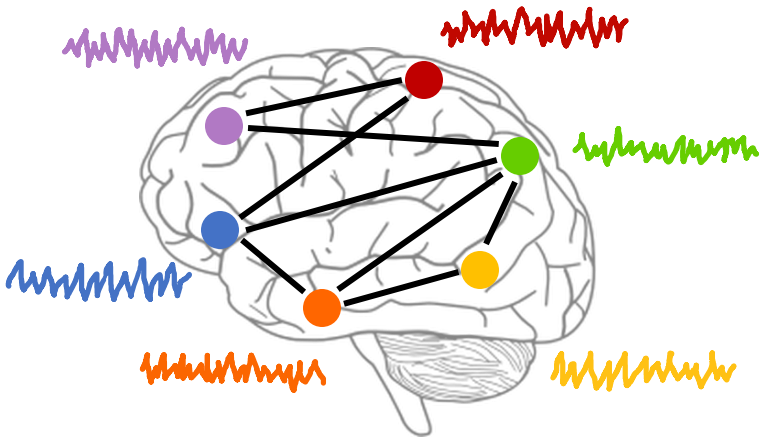


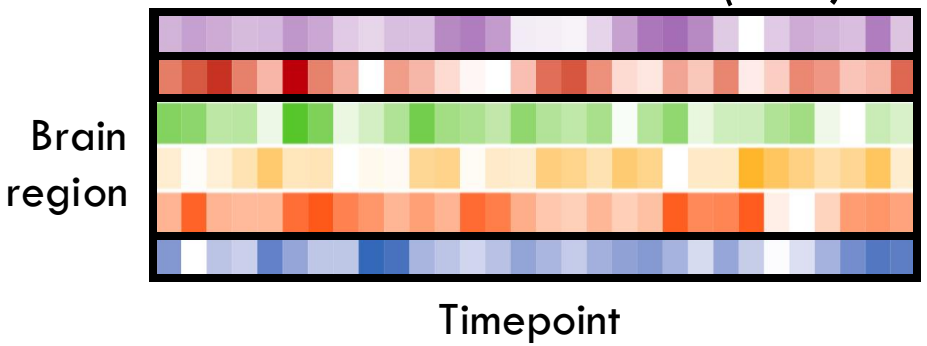


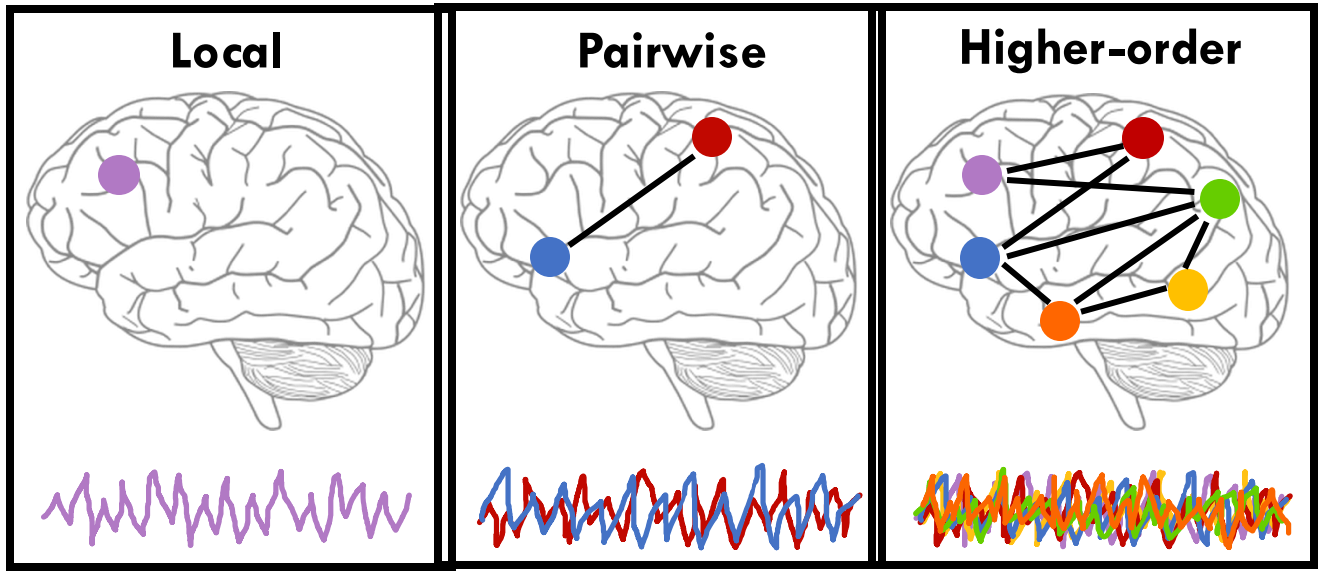
How can we leverage **complex systems analysis** to better understand how **Aβ plaques** modulate **neural activity in the DMN**?

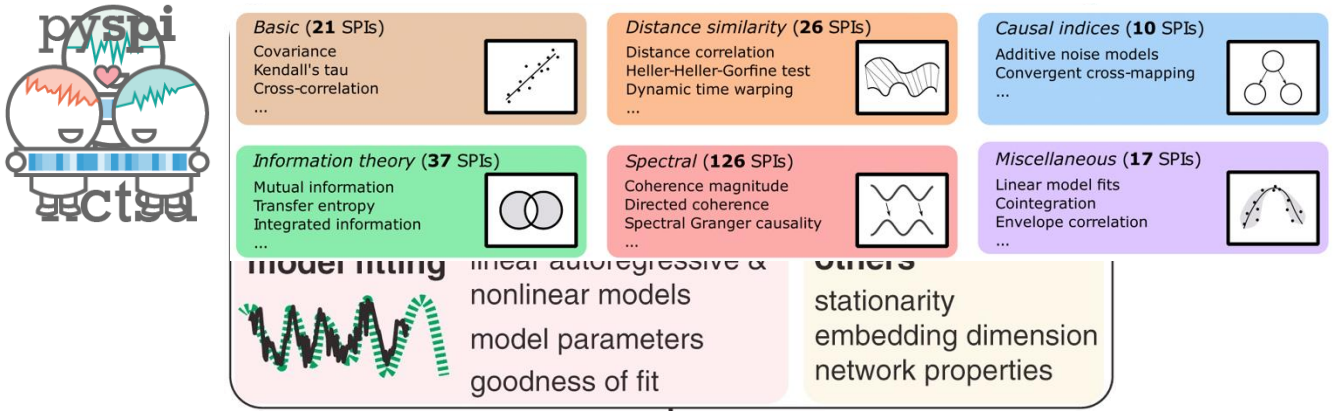
Neuroimaging: blood oxygen level-dependent (**BOLD**) functional magnetic resonance imaging (**fMRI**)



Multivariate time series (**MTS**)







Comparing Aβ plaque burden and DMN activity with the **Prospective Imaging Study of Ageing (PISA)**

Neuroimage Clin. 2021; 29: 102527. PMCID: PMC7750170
Published online 2020 Dec 8. doi: 10.1016/j.nicl.2020.102527 PMID: 33341723

A prospective cohort study of prodromal Alzheimer's disease: Prospective Imaging Study of Ageing: Genes, Brain and Behaviour (PISA)

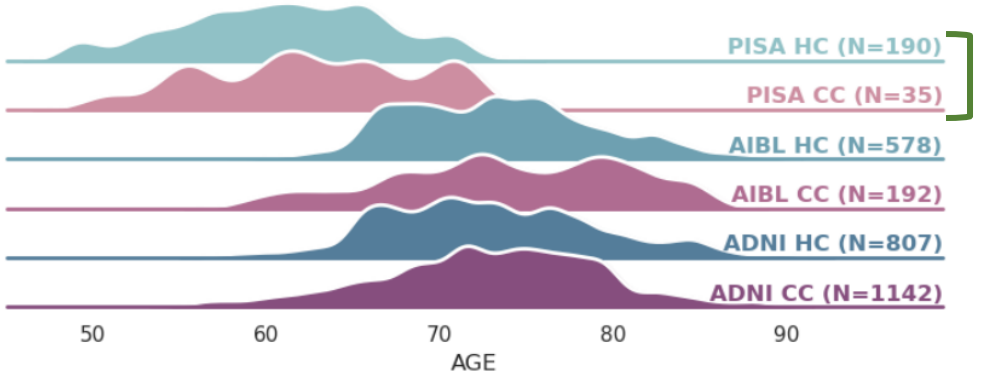
Michelle K. Lupton,[a,*] Gail A. Robinson,[b,c] Robert J. Adam,[a,d,e,f] Stephen Rose,[g] Gerard J. Byrne,[e,f] Olivier Salvado,[g] Nancy A. Pachana,[b] Osvaldo P. Almeida,[h,i] Kerrie McAloney,[a] Scott D Gordon,[a] Parnesh Raniga,[g] Amir Fazlollahi,[g] Ying Xia,[g] Amelia Ceslis,[b] Saurabh Sonkusare,[a] Qing Zhang,[g] Mahnoosh Kholghi,[g] Mohan Karunanithi,[g] Philip E Mosley,[a,c,k] Jinglei Lv,[l] Léonie Borne,[j] Jessica Adsett,[a] Natalie Garden,[a] Jurgen Fripp,[g] Nicholas G. Martin,[a] Christine C Guo,[a,1] and Michael Breakspear[a,j,1]

QIMR Berghofer Medical Research Institute

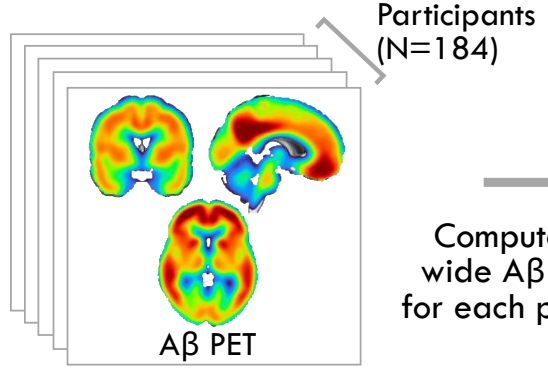
The University of Queensland Australia

The University of Newcastle Australia

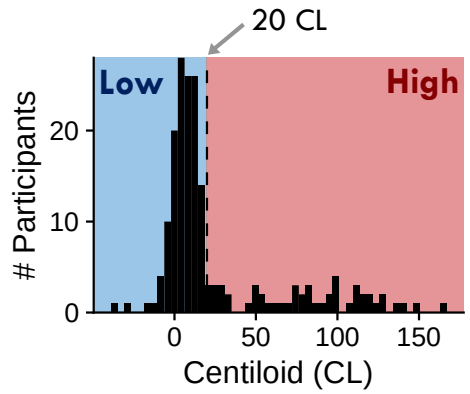
Michelle Lupton
Michael Breakspear



Borne et al. *biorXiv* (2022)



Compute brain-wide Aβ centiloid for each participant

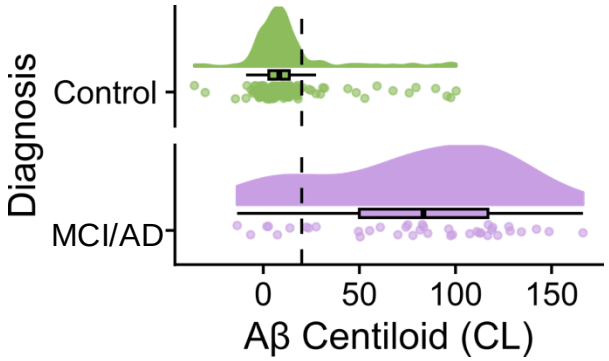


Low-Aβ group

N=133

High-Aβ group

N=51

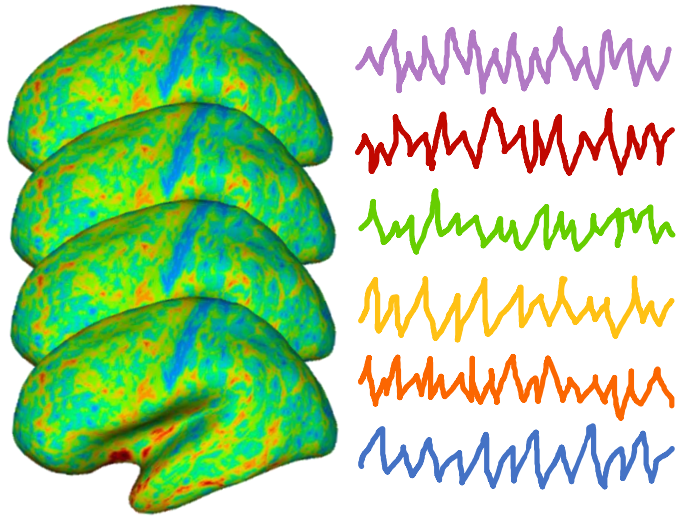


Data preprocessed by
Dr Joseph Giorgio

Unpublished work

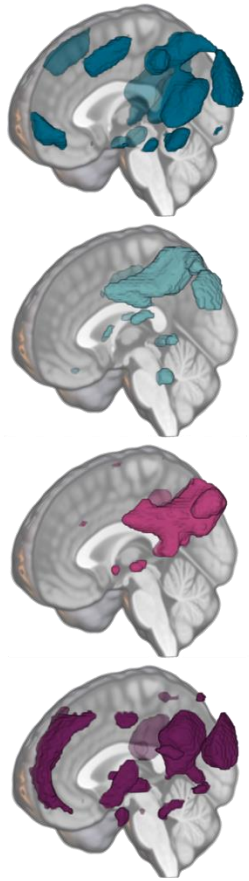
Identifying the DMN with spatial independent component analysis (ICA)

Data: Time series from all fMRI voxels per participant (TR=2.68s)



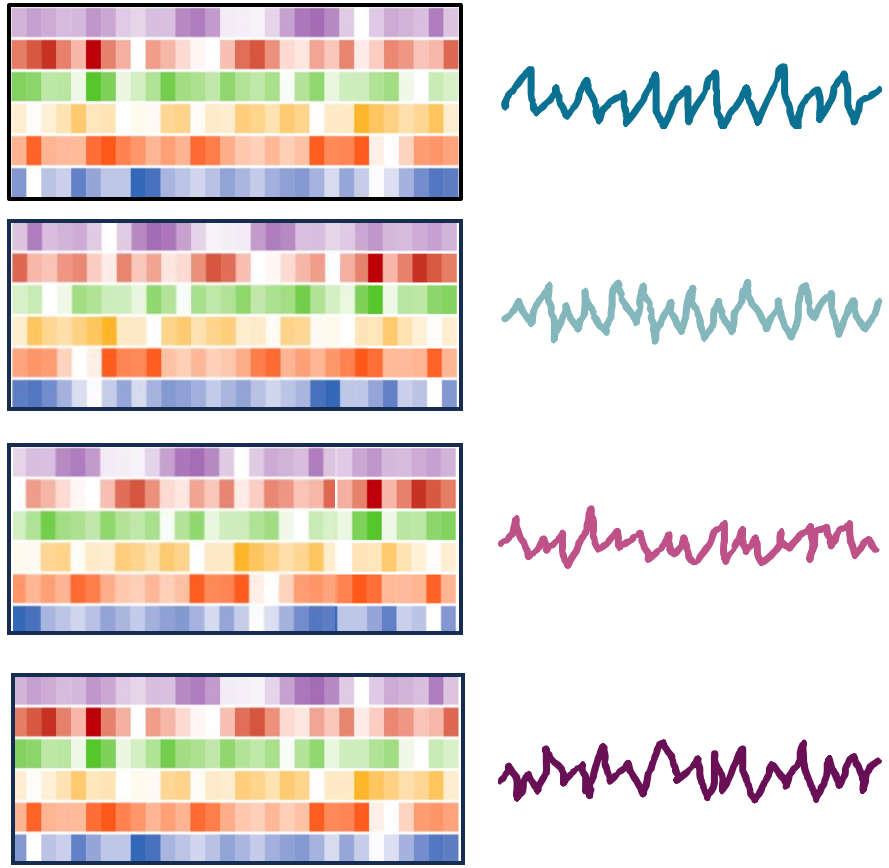
ICA

Source components: subregions of the DMN



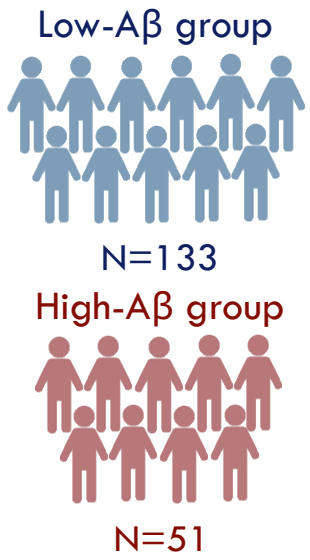
X

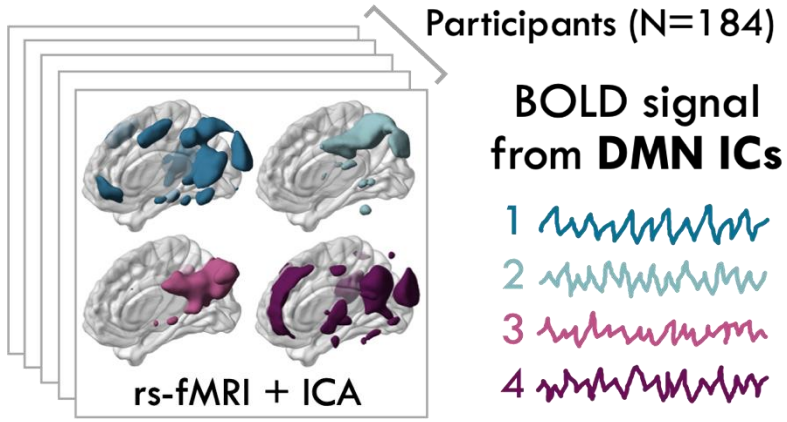
Weights: coefficient indicating how much a voxel contributes to the source component

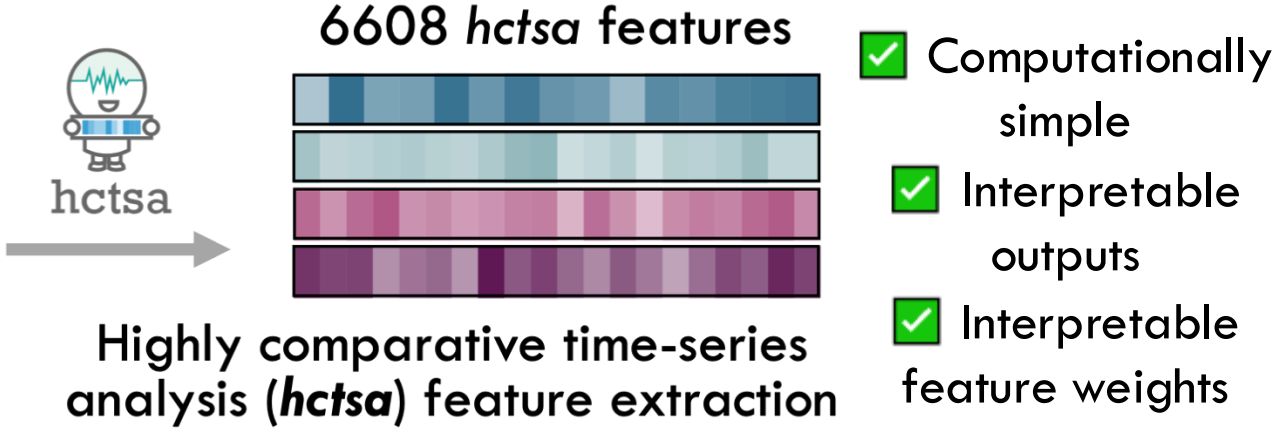


Data preprocessed by Dr Joseph Giorgio

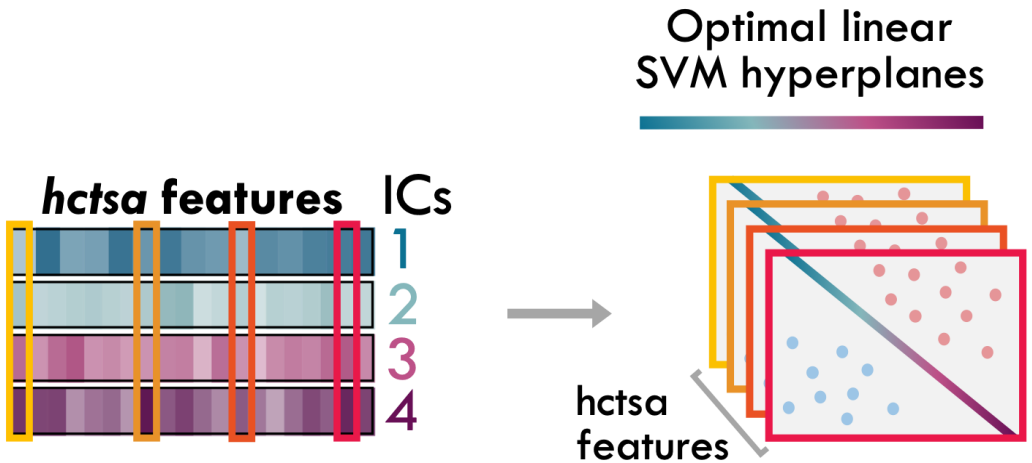
Analysing **DMN activity dynamics** in the context of high- vs. **low-amyloid plaque burden** in mild cognitive impairment + AD







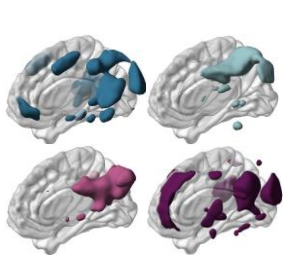
For each *hctsa* feature, we fit a linear SVM classifier using the 4 DMN components as inputs

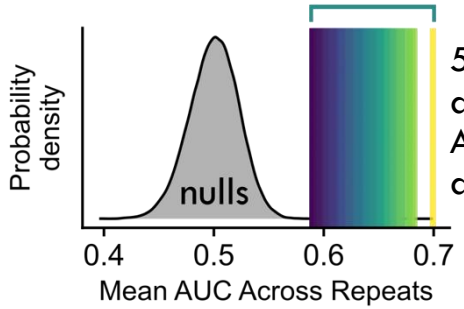


Identify **features** that **best distinguish** high- vs. low-Aβ individuals

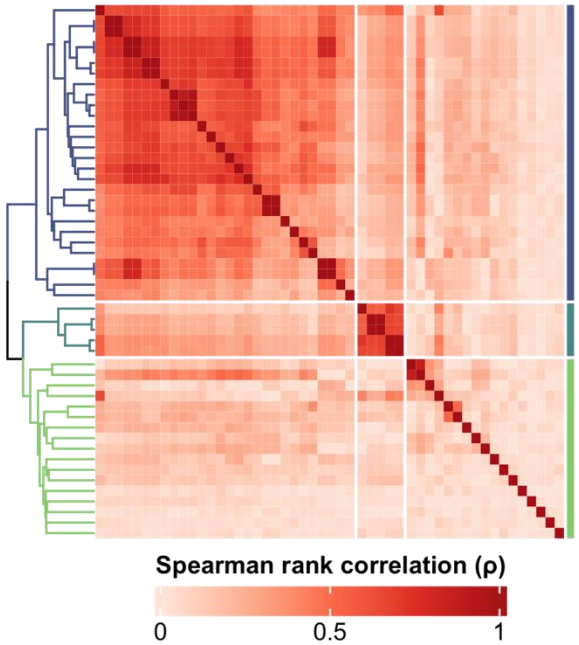
Unpublished work

Preliminary finding: features related to **power spectrum shape** and **lagged self-correlation structure** distinguish high- vs. low-amyloid brains





591 features with adjusted p<0.001 for AUC and balanced accuracy



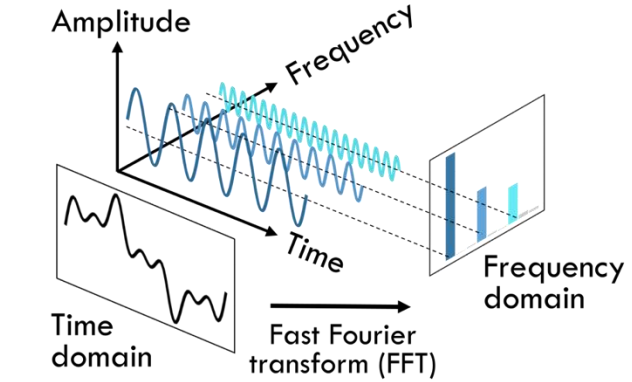
Power spectrum shape and lagged self-correlation structure

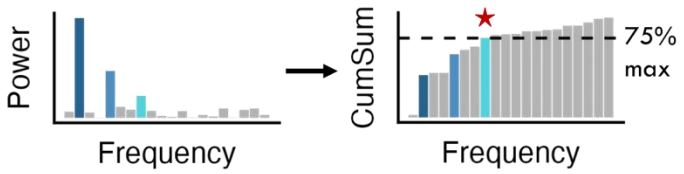
State-space model fitting

Miscellaneous (incl. nonlinear autocorrelation and force potentials with sine functions)

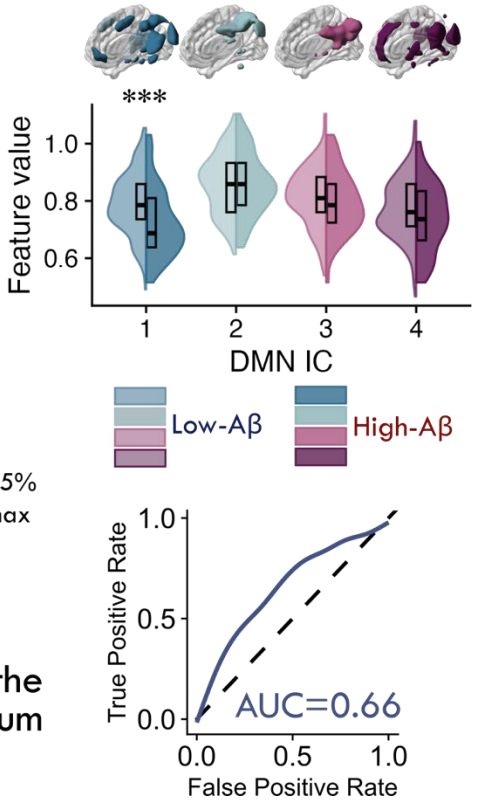
Example high-performing power spectrum shape feature 1:

SP_Summaries_fft.wmax_75



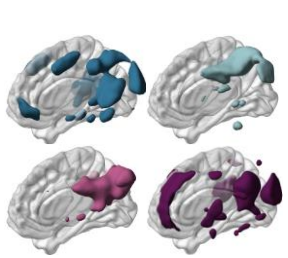


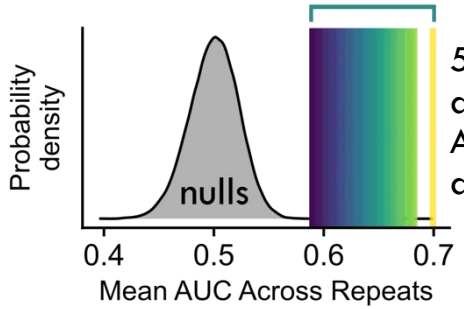
Find the **BOLD frequency** for which the **power spectral density** cumulative sum is at **75% of its maximum (★)**



Unpublished work

Preliminary finding: features related to **power spectrum shape** and **lagged self-correlation structure** distinguish high- vs. low-amyloid brains





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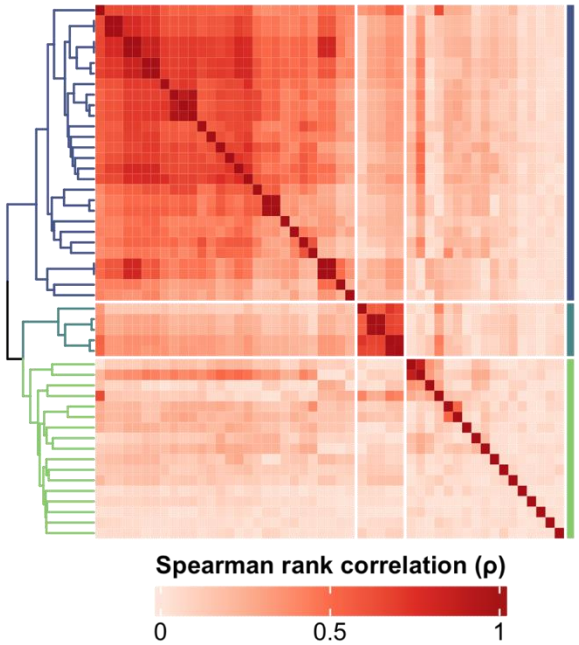


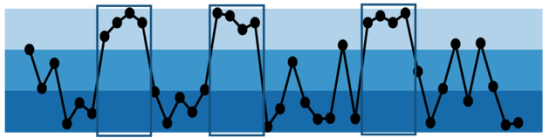
Power spectrum shape and lagged self-correlation structure

State-space model fitting

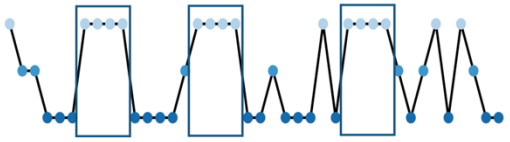
Miscellaneous (incl. nonlinear autocorrelation and force potentials with sine functions)

Example high-performing power spectrum shape feature 2:

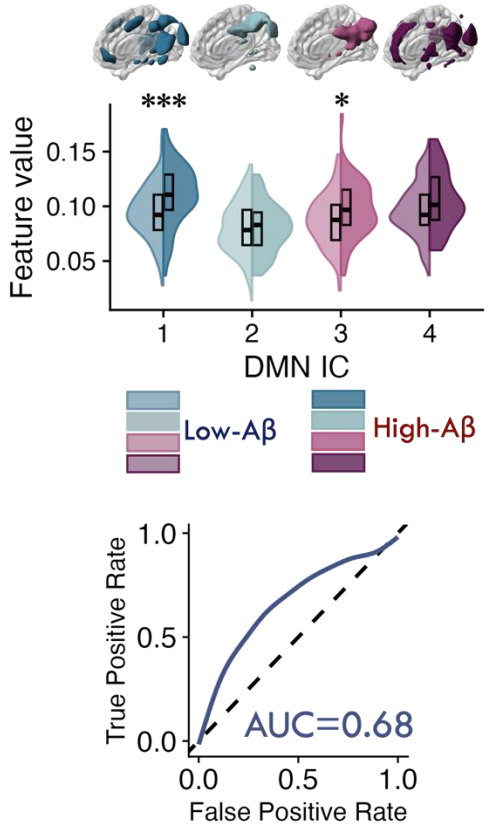
SB_MotifThree_quantile_cccc



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

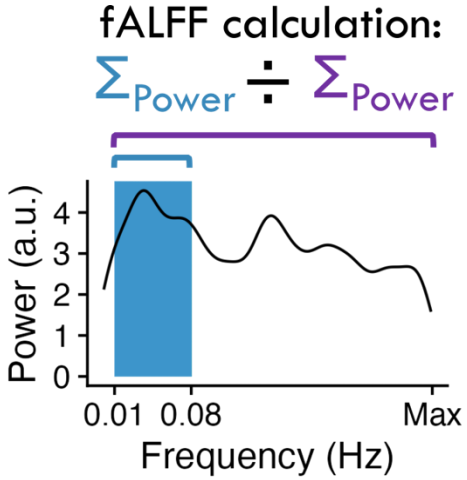


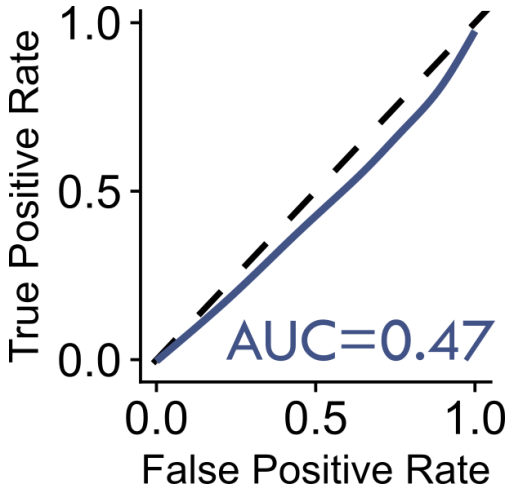
Count the frequency of C-C-C-C patterns (i.e., 4 consecutive BOLD frames with high amplitude)

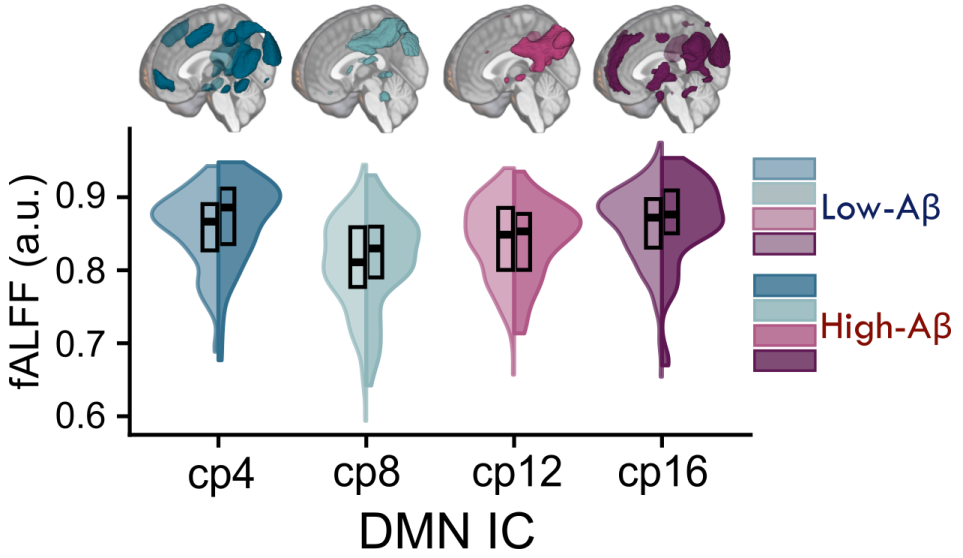


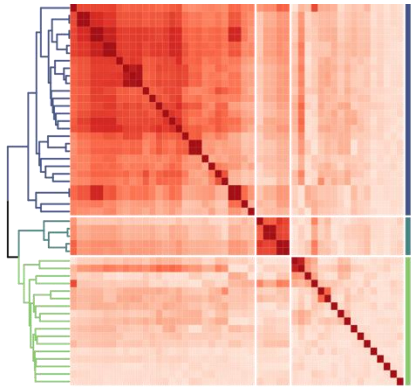
Unpublished work

Top 50(+) *hctsa* features outperform the fALFF









Unpublished work

Summary: the tl;dr

1. **Takeaway 1:** Time-series features related to the power spectrum shape and lagged self-correlation structure are significantly altered in the high-amyloid DMN, suggesting that BOLD activity is fluctuating at a lower frequency with greater periods of sustained high activity with high AB.

2. **Takeaway 2:** Our data-driven analysis identified many features that out-perform the standard fALFF, suggesting potential biomarkers for further analysis.

3. **Limitation:** Amyloid centiloid burden is not spatially specific to DMN, and high versus low amyloid do not directly align with clinical diagnosis.

4. **Future directions:** Include functional connectivity properties within DMN subcomponents, and compare information gained with fMRI activity relative to standard biomarkers.

Thank you!

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