Multimodal Analysis of Neural Dynamics across Neurological Disorders

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THE UNIVERSITY OF SYDNEY

Fudan-Cambridge-Sydney Young Scholars Symposium 2
15 June 2023

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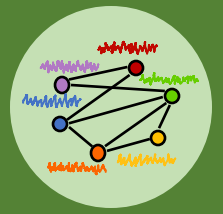
My research interests



Alzheimer's disease: A progressive neurodegenerative disease characterized by build-up of amyloid-beta plaques and tau neurofibrillary tangles in the brain; the leading cause of dementia worldwide

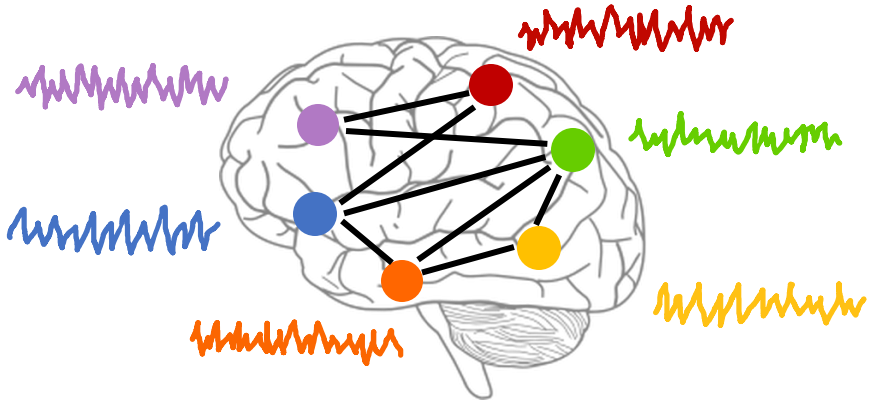
Single-cell transcriptomics: Measuring genes in individual cells (or nuclei) to understand cell type- and brain region-specific gene expression changes in a given disease space

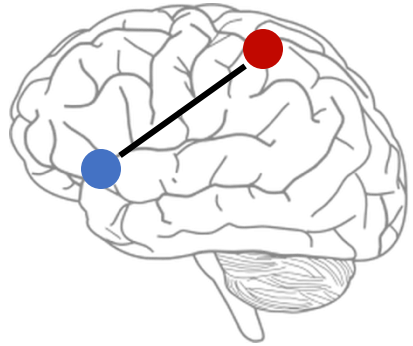
Multimodal neuroimaging: Integrating different types of structural and functional neuroimaging to study complex and longitudinal disease-related change in real-time

Neural activity dynamics: Studying the temporal patterns of activity in brain regions and distributed networks.

Using functional neuroimaging to measure **local**, **pairwise**, and **network** activity

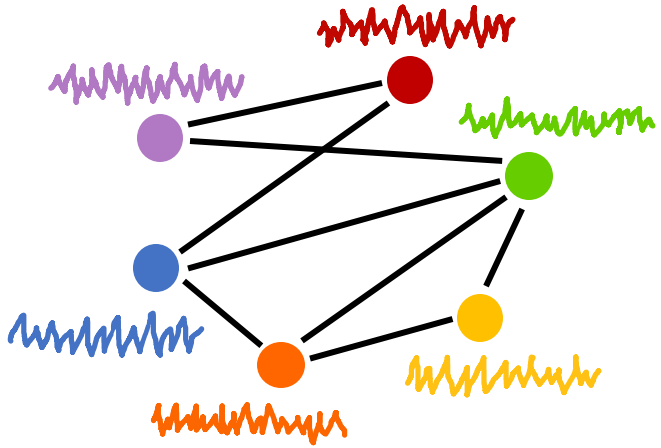
Neuroimaging: blood oxygen level-dependent (**BOLD**) functional magnetic resonance imaging (**fMRI**)



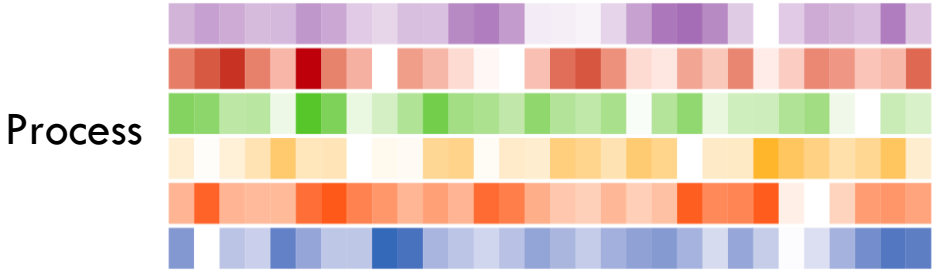
Local	**Pairwise**	Global
		
		
Fractional amplitude of low-frequency fluctuations (fALFF) Regional homogeneity (ReHo) Voxel-mirrored homotopic connectivity (VMHC)	Pearson correlation coefficient Partial correlation Granger causality	Deep learning (e.g. recurrent neural networks) Multi-voxel pattern analysis (MVPA) Co-fluctuation pattern analysis

What can we learn from representing **brain networks** as a **complex system**?

A complex system is a collection of **interconnected elements** that exhibit **emergent behaviors** that are **not explicitly present** in the individual parts



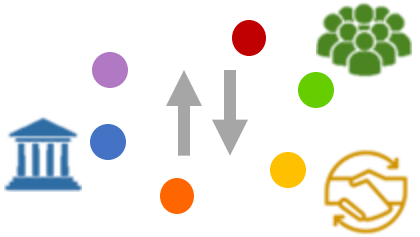
Multivariate time series (**MTS**) representation



Biology

Brain function: perception, emotion, movement

Economics

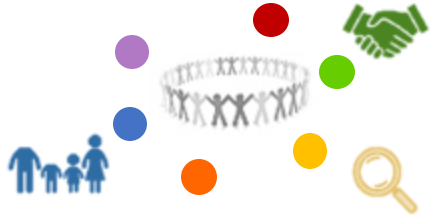


National economy: economic growth, recession

Physics

Fluid dynamics: vortices, turbulence

Social networks



Facebook friends: community formation

➡ Can we leverage statistics derived from **interdisciplinary domains** to more **comprehensively** characterize **brain dynamics** in health and disease?

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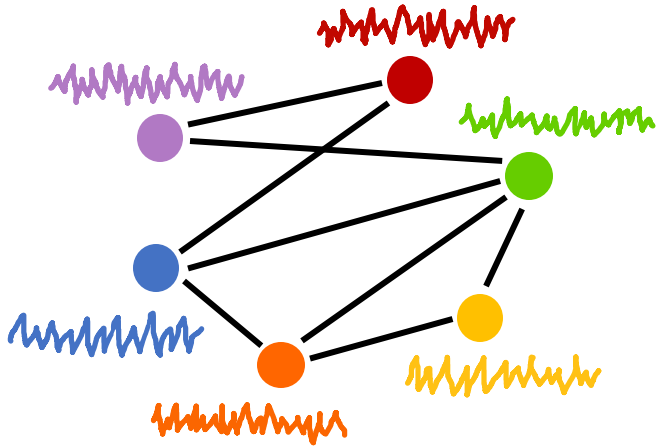
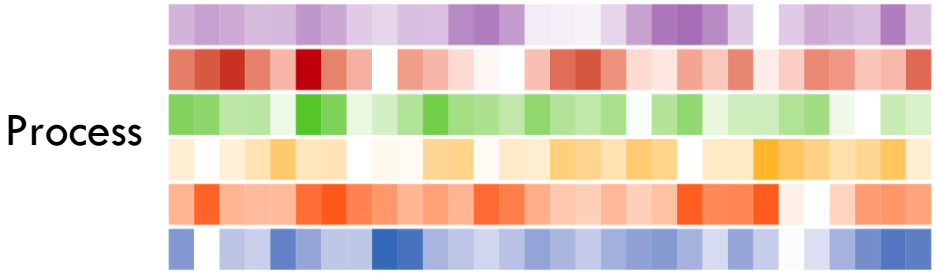
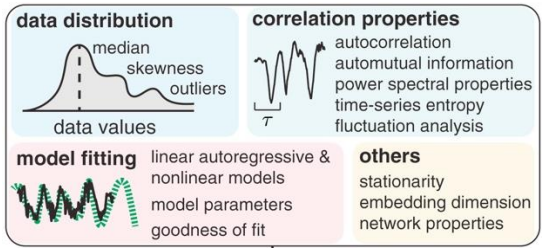


Multivariate time series (**MTS**) representation



hctsa

highly comparative time-series analysis



Fulcher & Jones, *Cell Systems* (2017)

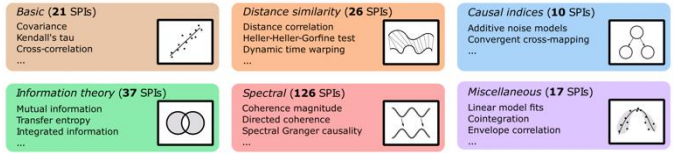
fALFF

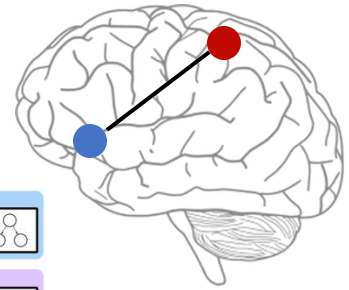
…

And 7,000+ others

pyspi

Python toolkit for the **s**tatistics of **p**airwise **i**nteractions





Cliff et al., *arXiv* (2022) /Manuscript under review

Pearson correlation

…

And 230+ others

Highly comparative time-series analysis for **case-control** classification

UCLA Consortium for Neuropsychiatric Phenomics LA5c Study

Control (N=116) SCZ (N=48)

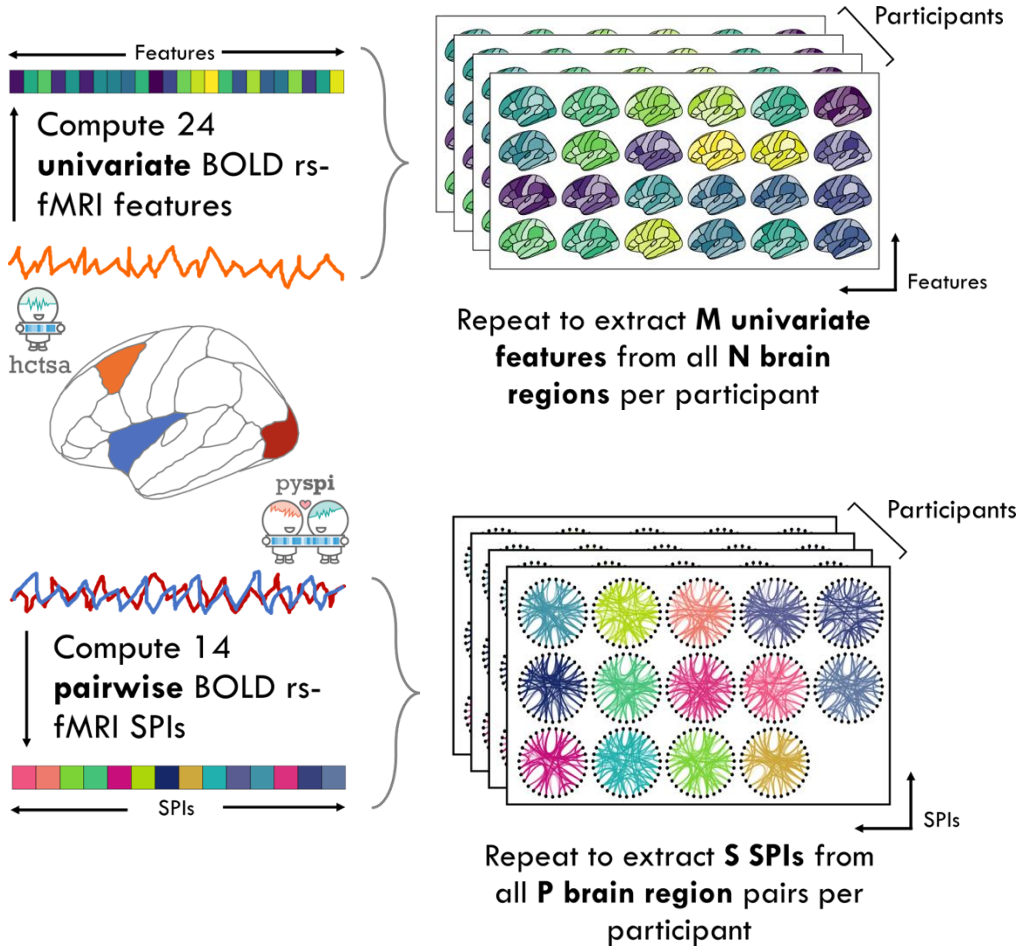
BPD (N=49) ADHD (N=39)

Preprocessed in-house by Dr Kevin Aquino

Autism Brain Imaging Data Exchange (ABIDE)

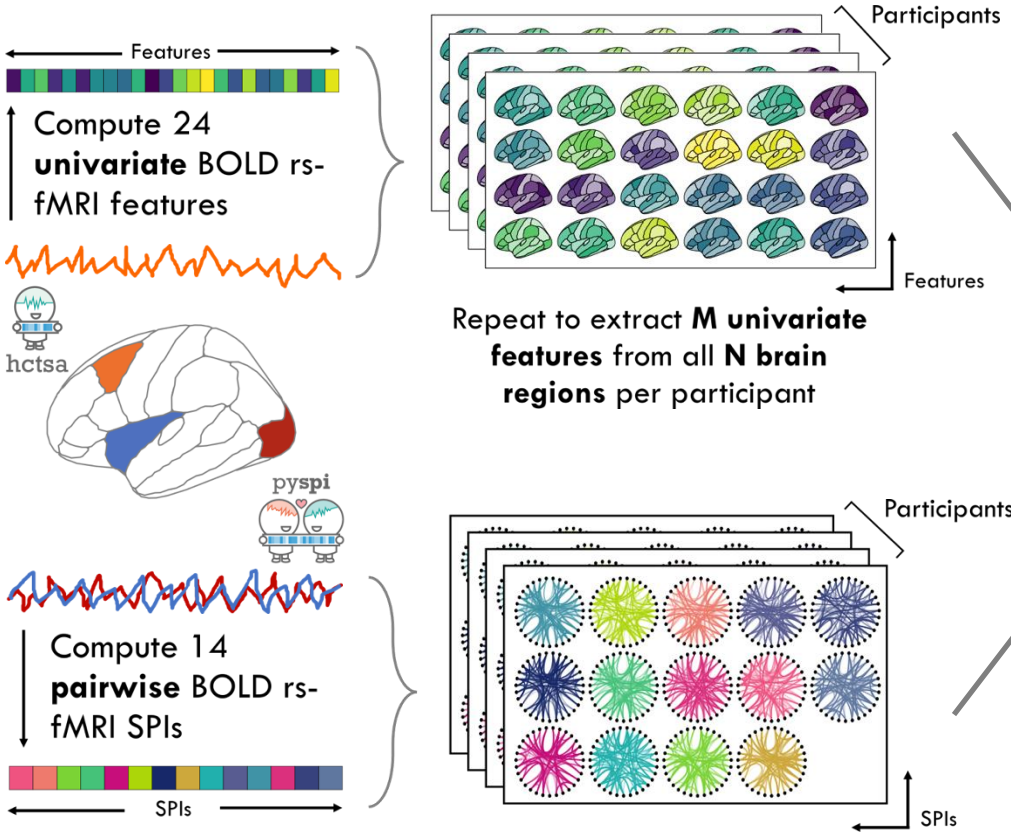
Control (N=578) ASD (N=513)

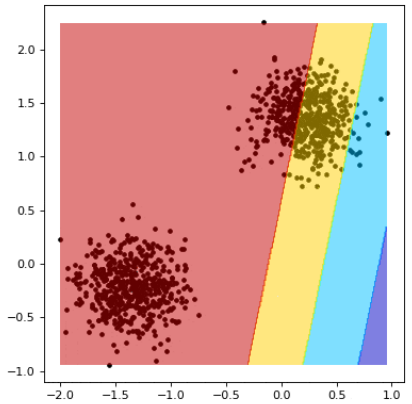
Preprocessed by Traut et al. *NeuroImage* (2022)



SCZ = Schizophrenia; BPD = Bipolar disorder; ADHD = Attention-deficit hyperactivity disorder; ASD = Autism spectrum disorder

Highly comparative time-series analysis for **case-control** classification

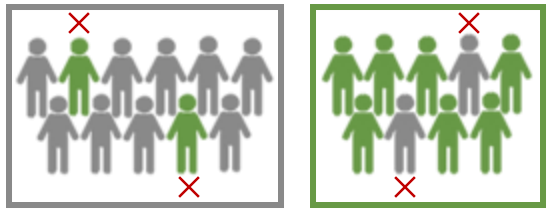




Fit a linear support vector machine (SVM) classifier

× 10-fold cross-validation

× 10 repeats



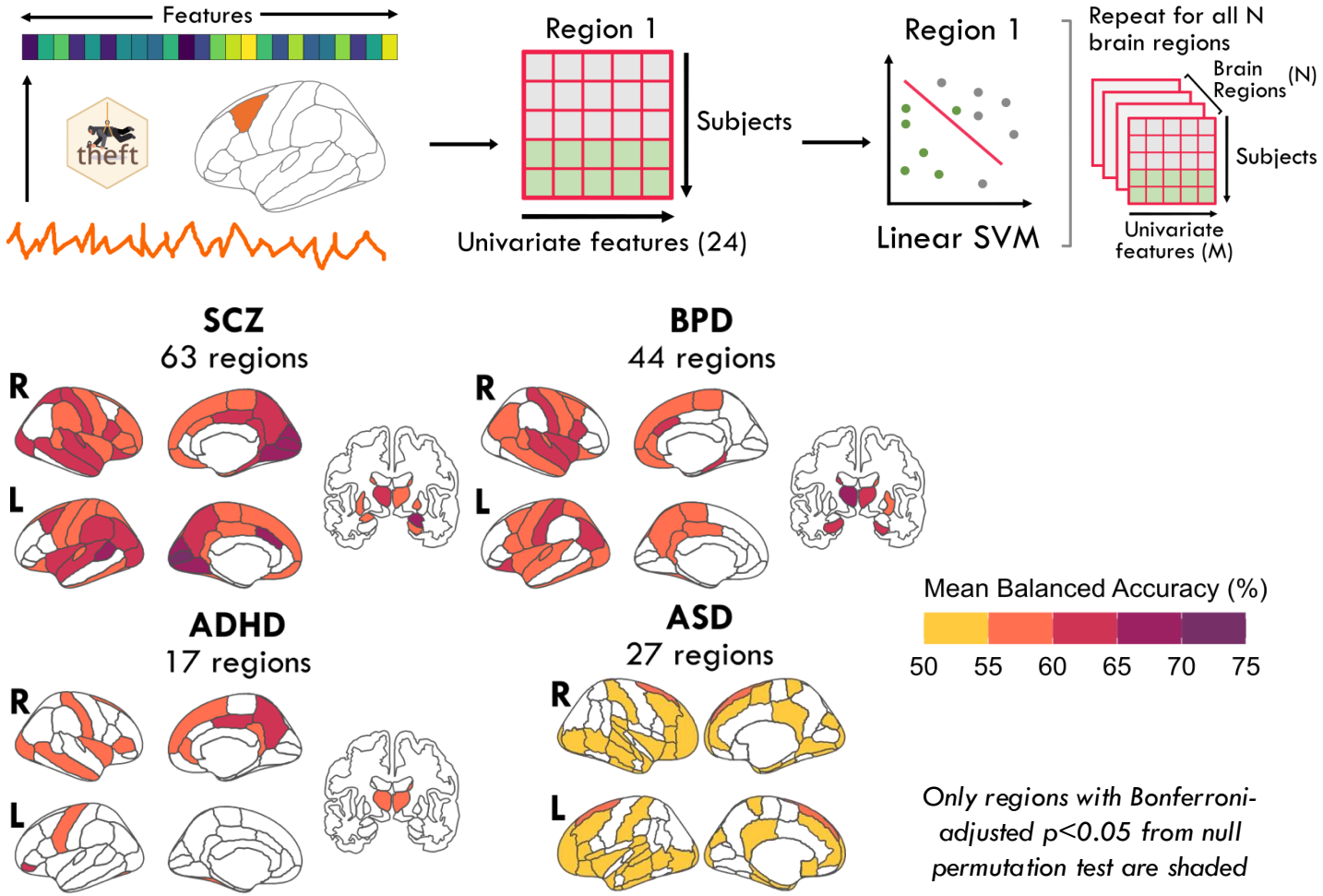
Predict class labels and measure (balanced) accuracy

- ✅ Computationally simple
- ✅ Interpretable outputs
- ✅ Interpretable feature weights*

SVM animation from https://torchbearer.readthedocs.io/en/0.1.7/examples/svm_linear.html

Bryant et al., *manuscript in preparation*

Finding #1: Individual **brain regions** exhibit **distinctively altered dynamics** across disease states

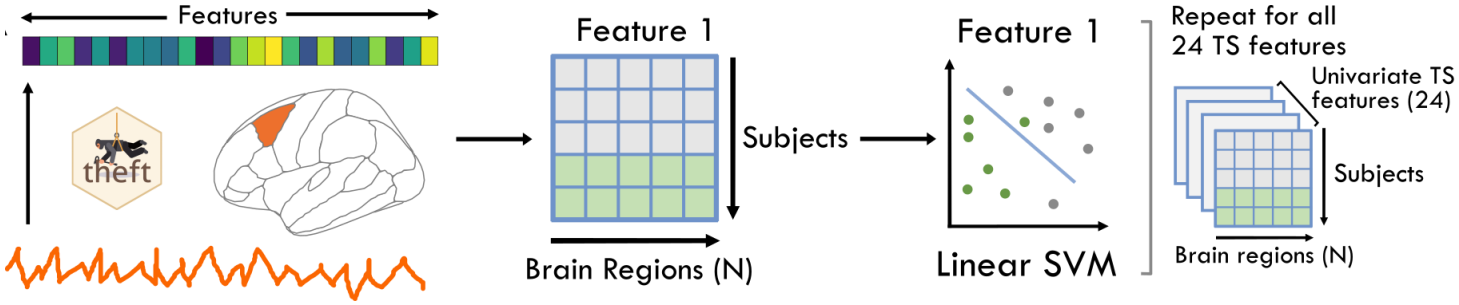


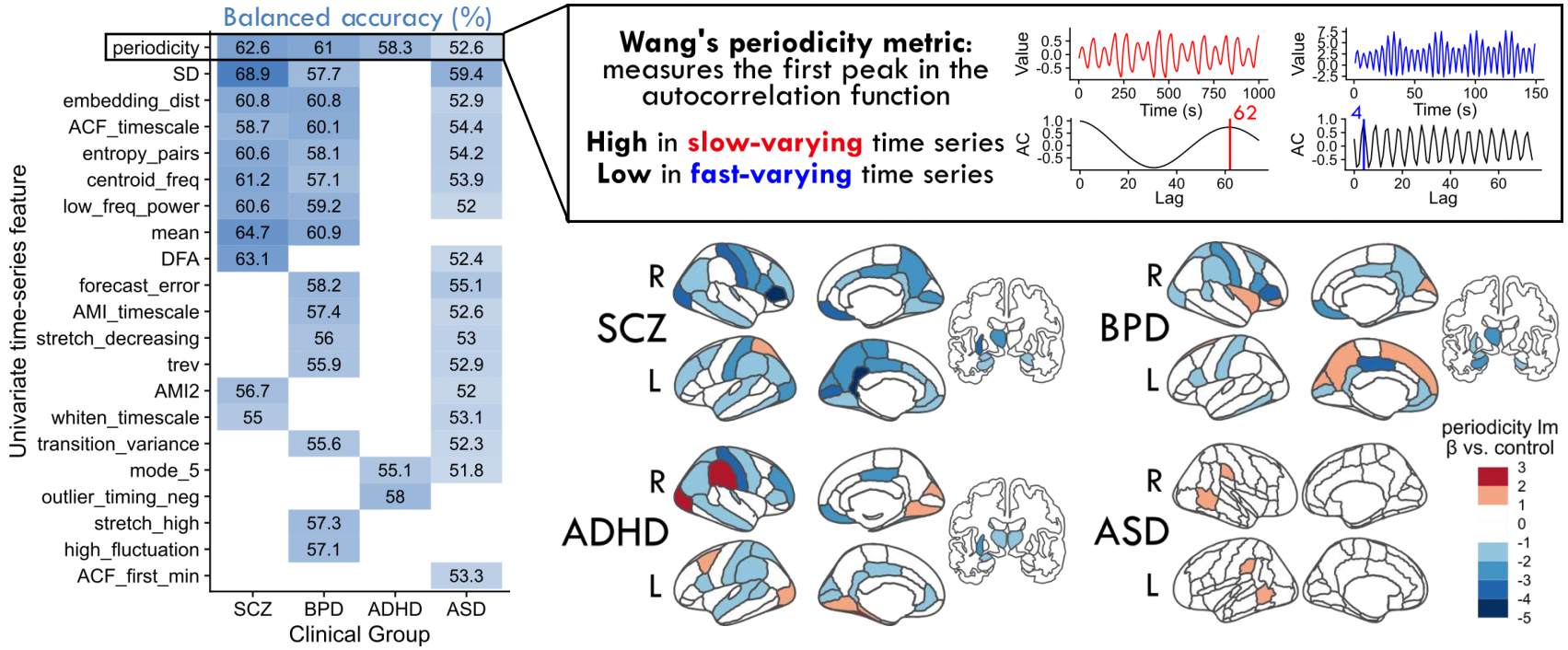
Key notes:

- Working with a **data-driven subset** of the available *hctsa* feature space (*cf.* Lubba et al. *Data Min Knowl Disc 2019*)
- Top performing regions in **schizophrenia** classification are in the **medial occipital lobe** (bilateral **cuneus** + **pericalcarine**)
- Statistically significant performance of **subcortical structures** like the **thalamus** across conditions (where available)
- **Interhemispheric asymmetry** in **ADHD** classification performance

Bryant et al., *manuscript in preparation*

Finding #2: Individual **properties of neural activity** are **globally altered** throughout the brain **across disorders**



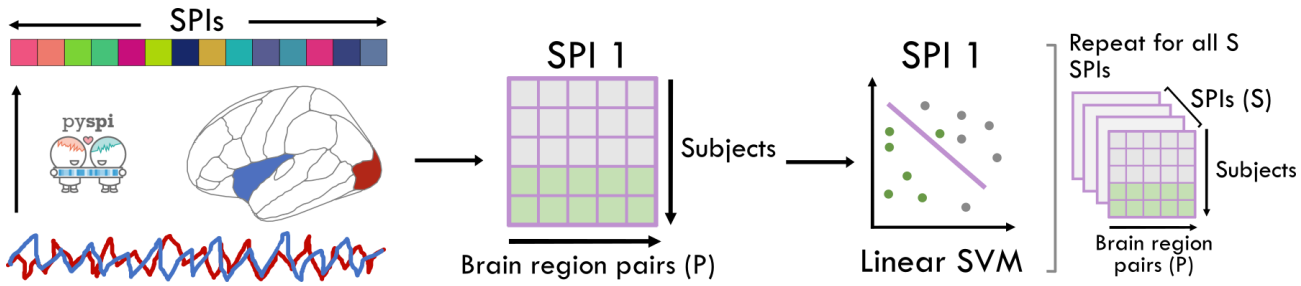


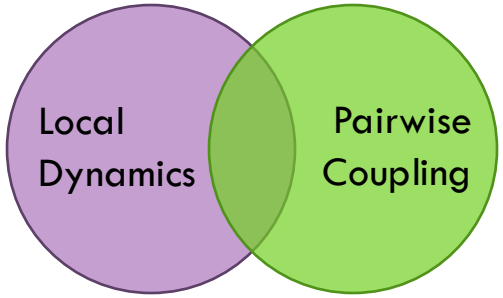
Key notes:

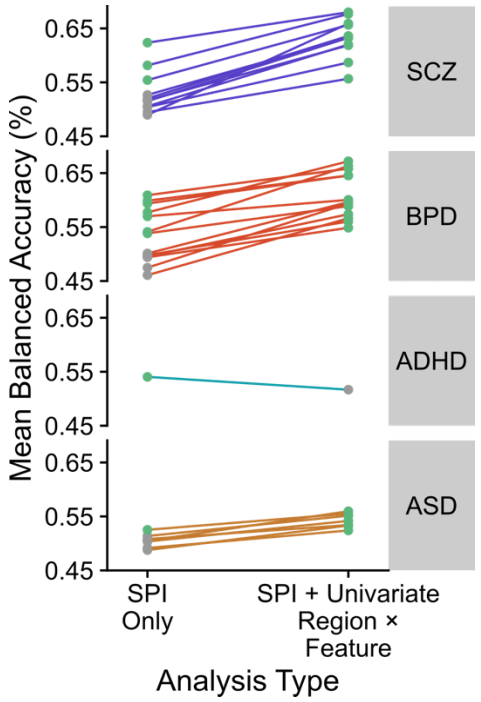
- **Periodicity** is altered **throughout the brain** across disorders, although in **different ways**
- **Lower** Wang's periodicity suggests **faster fluctuations in BOLD activity** in the given brain region relative to controls
- **Standard deviation** and **mean** are stronger performers in SCZ and BPD

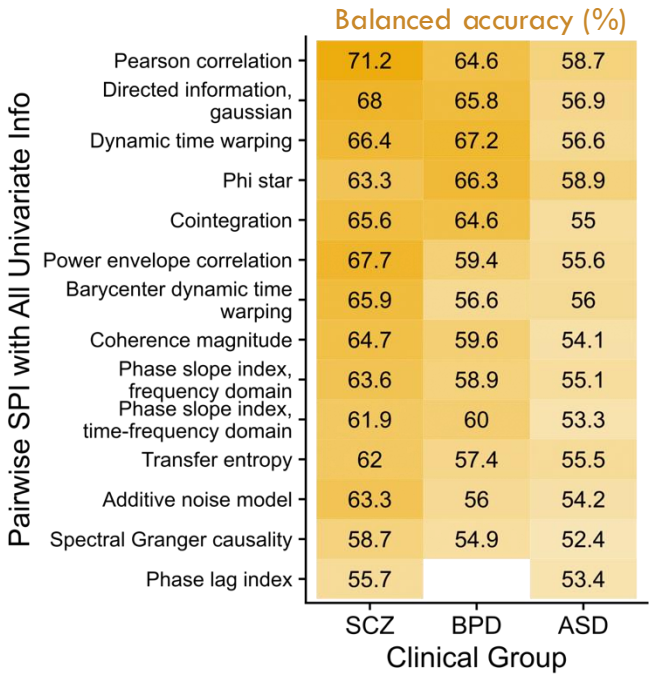
Bryant et al., *manuscript in preparation*

Finding #3: **Pairwise feature analysis** suggests alterations to diverse types of **functional connectivity** across the brain per disorder

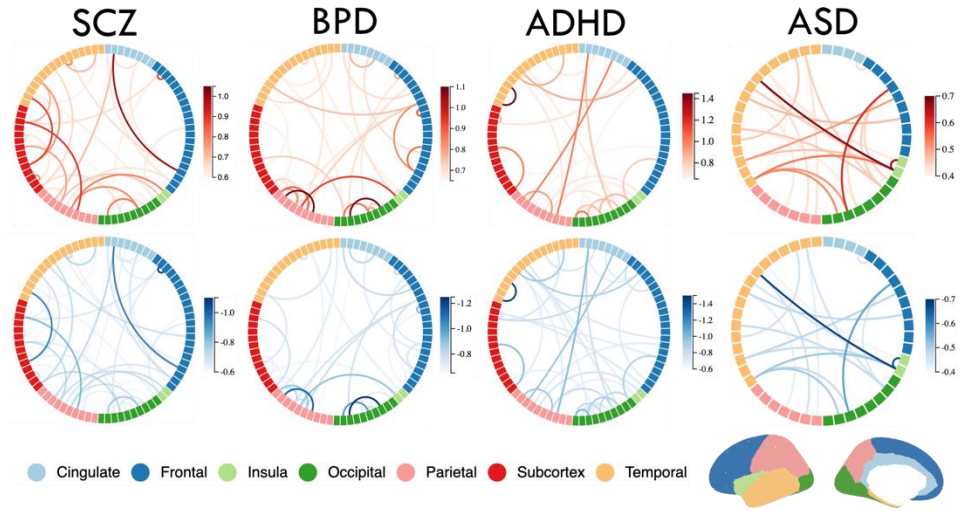








Intersection of **local (regional) dynamics** and **pairwise coupling** as features that distinguish clinical groups from control groups



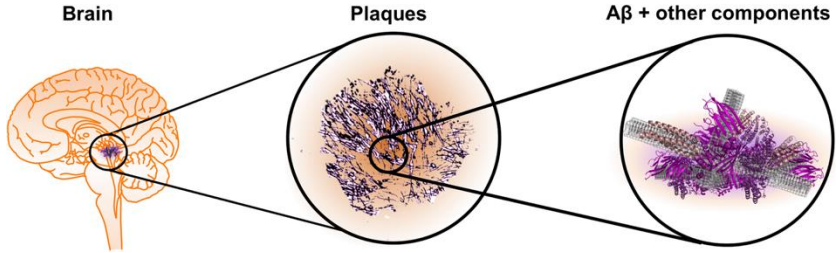
Bryant et al., *manuscript in preparation*

Shifting ⚙: Thinking about how **neural activity** changes relate to **Alzheimer's disease neuropathology**

Proof of principle:

- Extraction of **interpretable brain regions** and **time-series features** that are **informative** in case-control classification
- **Generalizable** framework to link **insights** from **univariate** and **pairwise neural activity dynamics** in any disease state

Amyloid-beta (Aβ) plaque deposition



Rahman & Lendel *Mol Neurodegen* (2021)

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

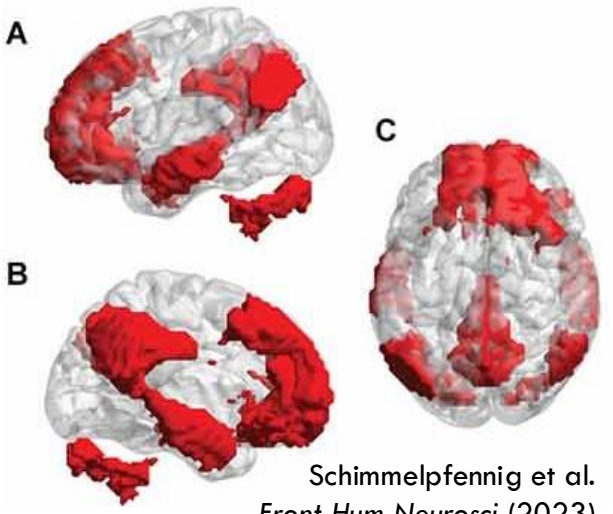
The University Of Queensland AUSTRALIA

Goals for second half of my PhD:

- Apply methods from the first half of my thesis to identify **early changes** in neural activity in **preclinical Alzheimer's disease**
- Investigate how the deposition of **Aβ plaques** disrupts neural activity in **specific brain regions** up through **distributed networks**

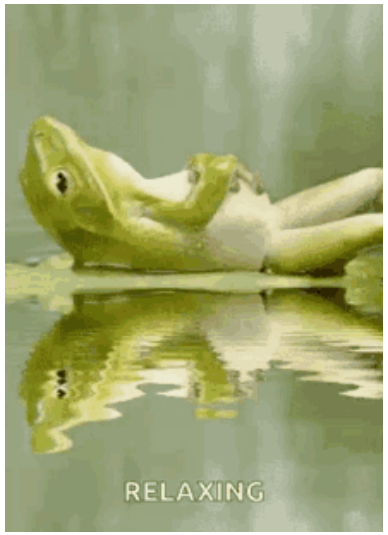
The **default mode network** is **spatially** and **functionally** associated with **Aβ plaque deposition**

Default Mode Network (DMN)



Schimmelpfennig et al.
Front Hum Neurosci (2023)

Key players:
Posterior cingulate cortex
Cuneus
Medial prefrontal cortex
Inferior parietal lobule



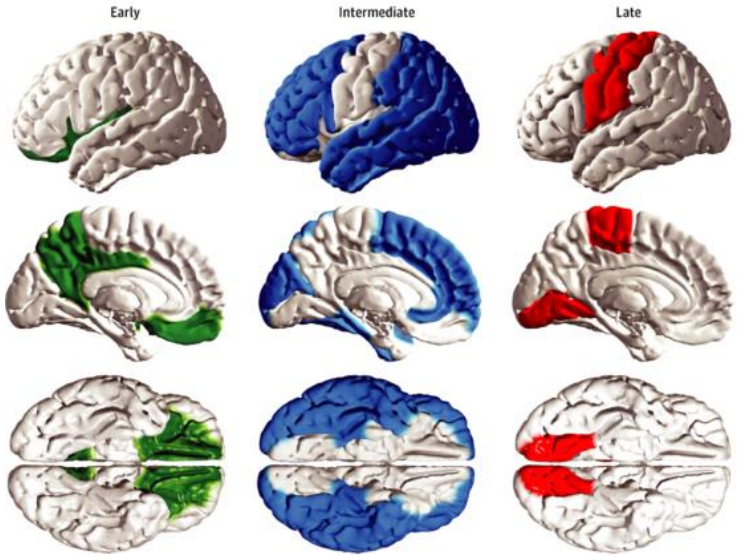
Active during:
Wakeful rest
Autobiographical memory
Thinking about others

Spatial overlap

⟷

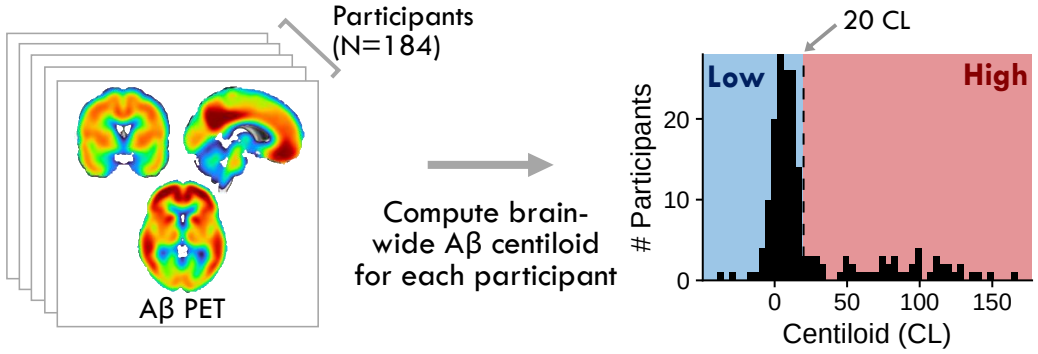
Functional associations

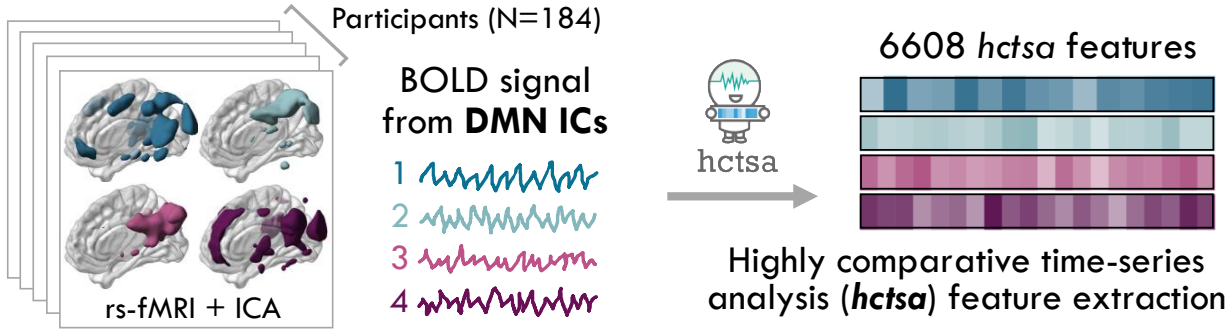
Spread of Aβ plaque pathology

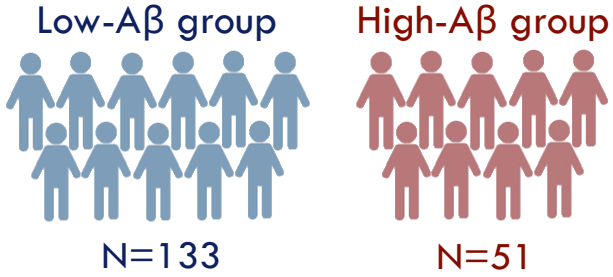


Hampel et al. *Mol Psych* (2021)

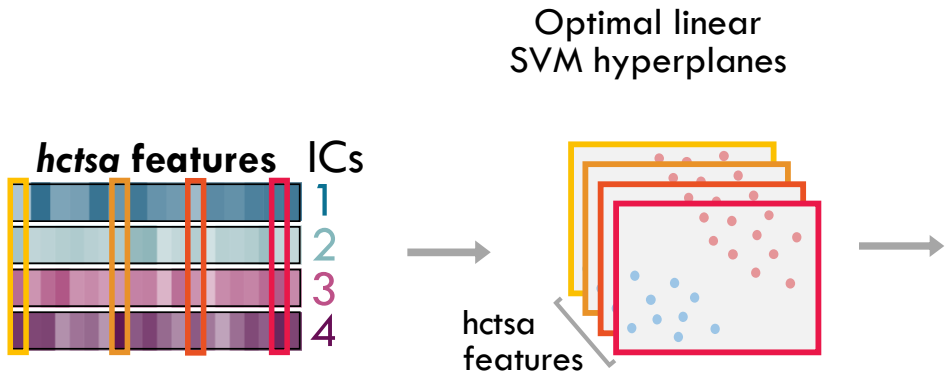
Analysing **DMN activity dynamics** in the context of high- vs. **low-amyloid plaque burden** in mild cognitive impairment







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



Neuroimage Clin. 2021; 29: 102527. PMCID: PMC7750170
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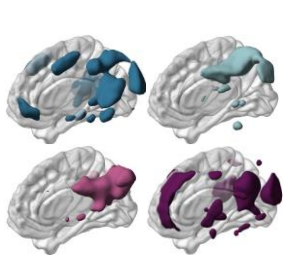
A prospective cohort study of prodromal Alzheimer's disease: Prospective Imaging Study of Ageing: Genes, Brain and Behaviour (PISA)

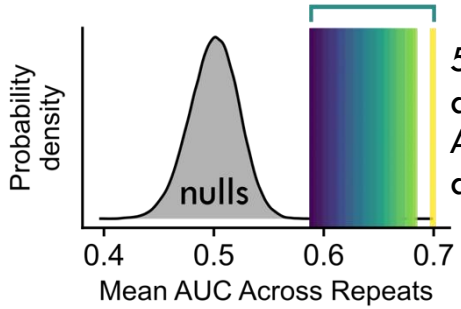
Michelle K. Lupton,[a,*] Gail A. Robinson,[b,c] Robert J. Adam,[a,d,e,f] Stephen Rose,[g] Gerard J. Byrne,[e,f] Olivier Salvado,[g] Nancy A. Pachana,[b] Osvaldo P. Almeida,[h,i] Kerrie McAloney,[a] Scott D Gordon,[a] Parnesh Raniga,[g] Amir Fazlollahi,[g] Ying Xia,[g] Amelia Ceslis,[b] Saurabh Sonkusare,[a] Qing Zhang,[g] Mahnoosh Kholghi,[g] Mohan Karunanithi,[g] Philip E Mosley,[a,c,k] Jinglei Lv,[j] 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]

Data preprocessed by Dr Joseph Giorgio

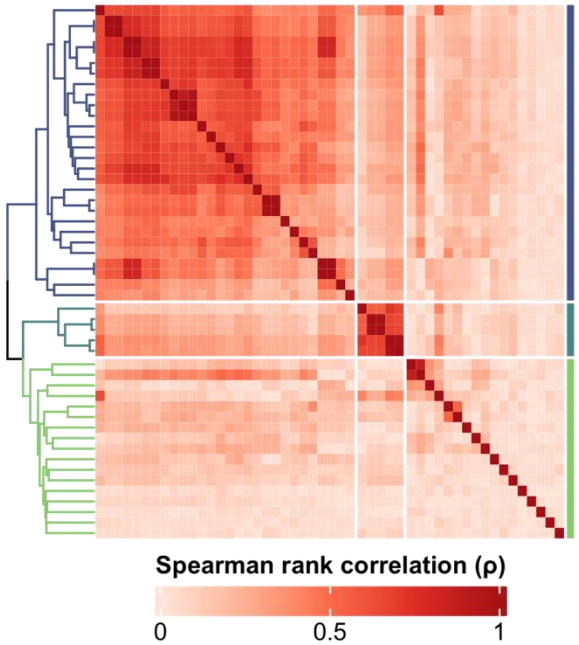
Unpublished work

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



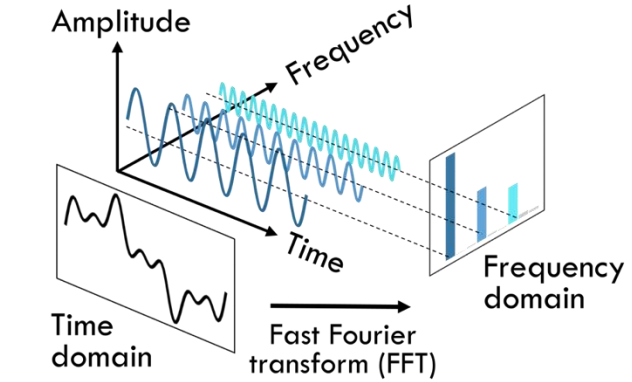


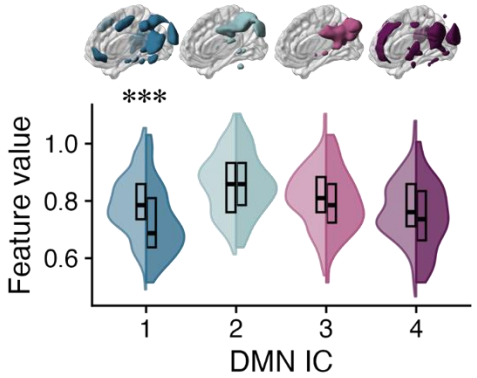
591 features with adjusted p<0.001 for AUC and balanced accuracy

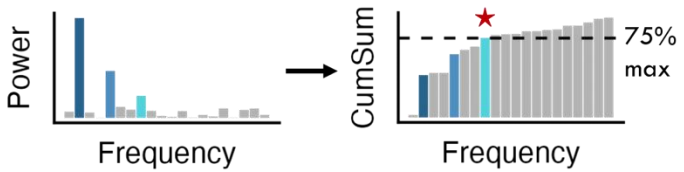


Example high-performing power spectrum shape feature:

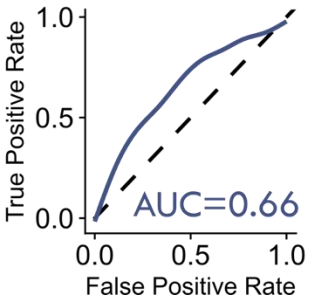
SP_Summaries_fft.wmax_75







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



Unpublished work

Thank you!

The Dynamics and Neural Systems Lab, The University of Sydney

Dr Ben Fulcher
Dr Oliver Cliff
Trent Henderson
Aria Nguyen
Rishi Maran
Dr Kieran Owens
Brendan Harris
Zilu (Lulu) Cao

Systems Neuroscience Group, The University of Newcastle

Prof Michael Breakspear
Dr Joseph Giorgio

Systems Neuroscience & Psychopathology Lab, Rutgers University

A/Prof Linden Parkes

Brain Key Inc.

Dr Kevin Aquino

QIMR Berghofer Medical Research Institute

A/Prof Michelle Lupton

PhD Funding Support from:

Australian Government

Australian Government Research Training Program

The University of Sydney Physics Foundation

The American Australian Association Graduate Education Fund

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