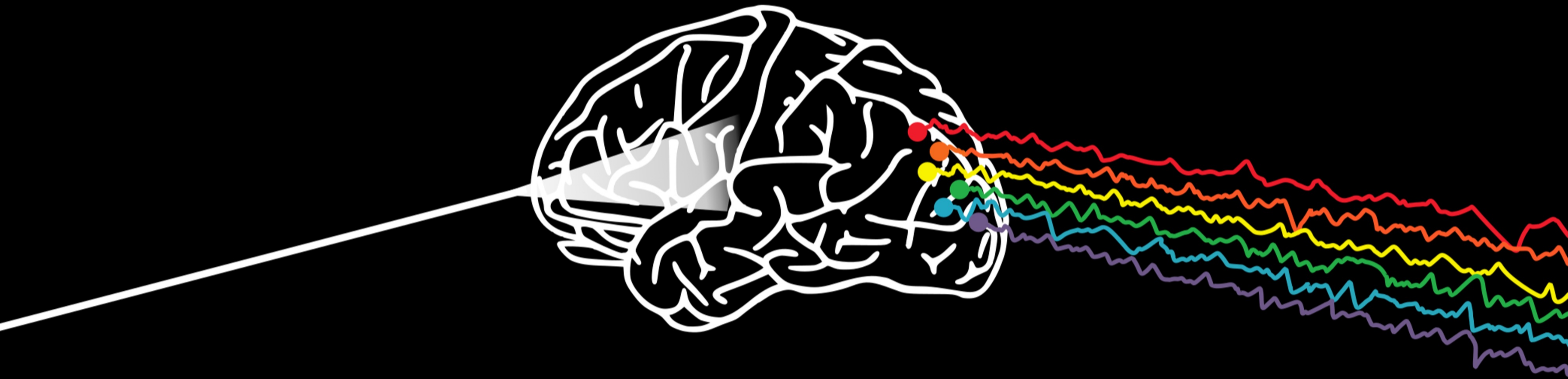
Studying the brain as a complex and nonlinear dynamical system with time-series analysis

CSYS5040

17 September 2024



Annie G. Bryant
PhD Candidate
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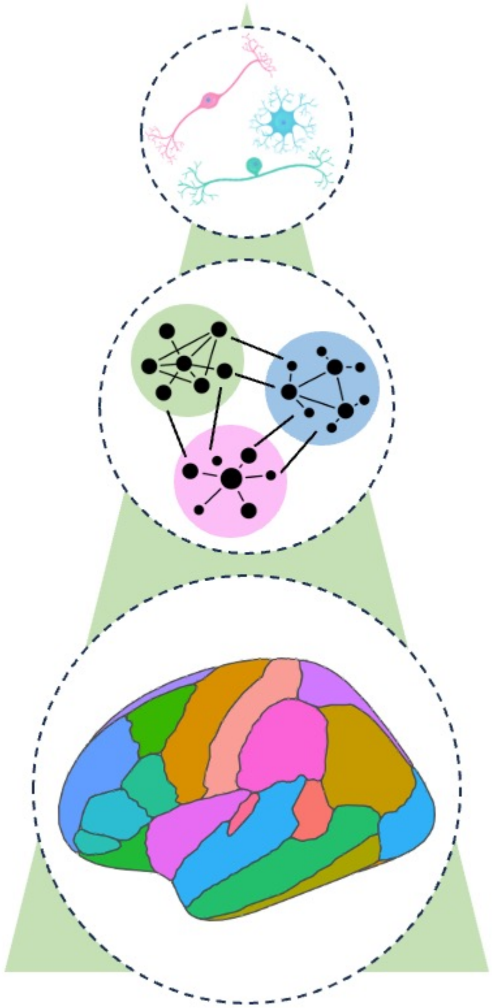
THE UNIVERSITY OF SYDNEY

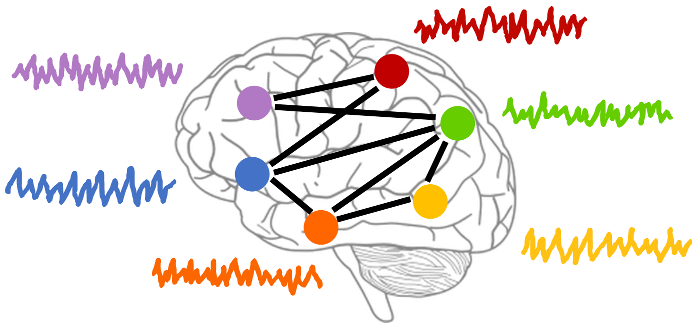
Mechanisms of brain activity **across scales**

Dynamics emerge at multiple **spatial** and **temporal scales**:



Before we delve into **modelling or analysing data** from a given **complex system**, let's think about the **underlying mechanisms** giving rise to **behaviours from micro to macro scales**.

Door #1:

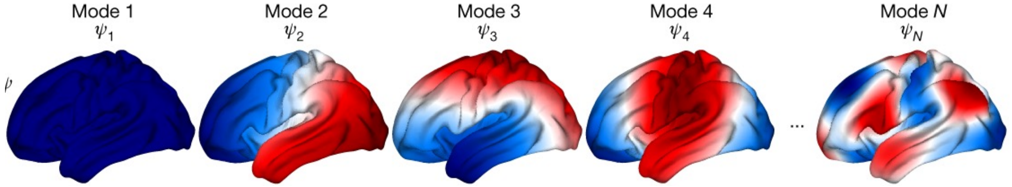


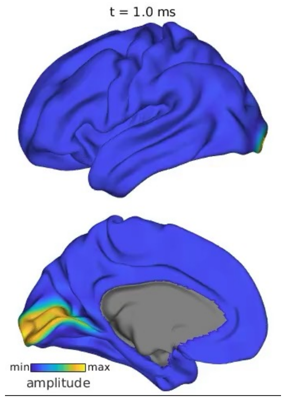
The brain as a network of interacting components

↓

Messages passing across a discrete network

Door #2:





The brain as a physically embedded system

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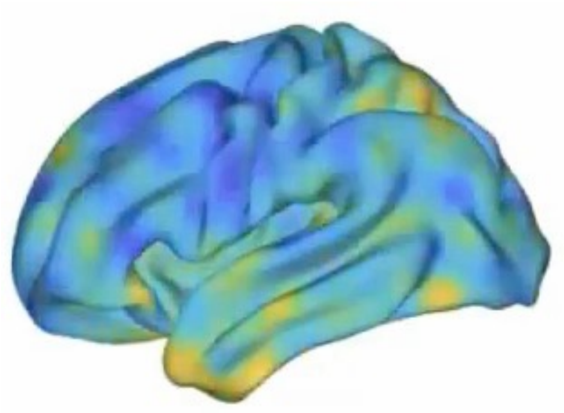
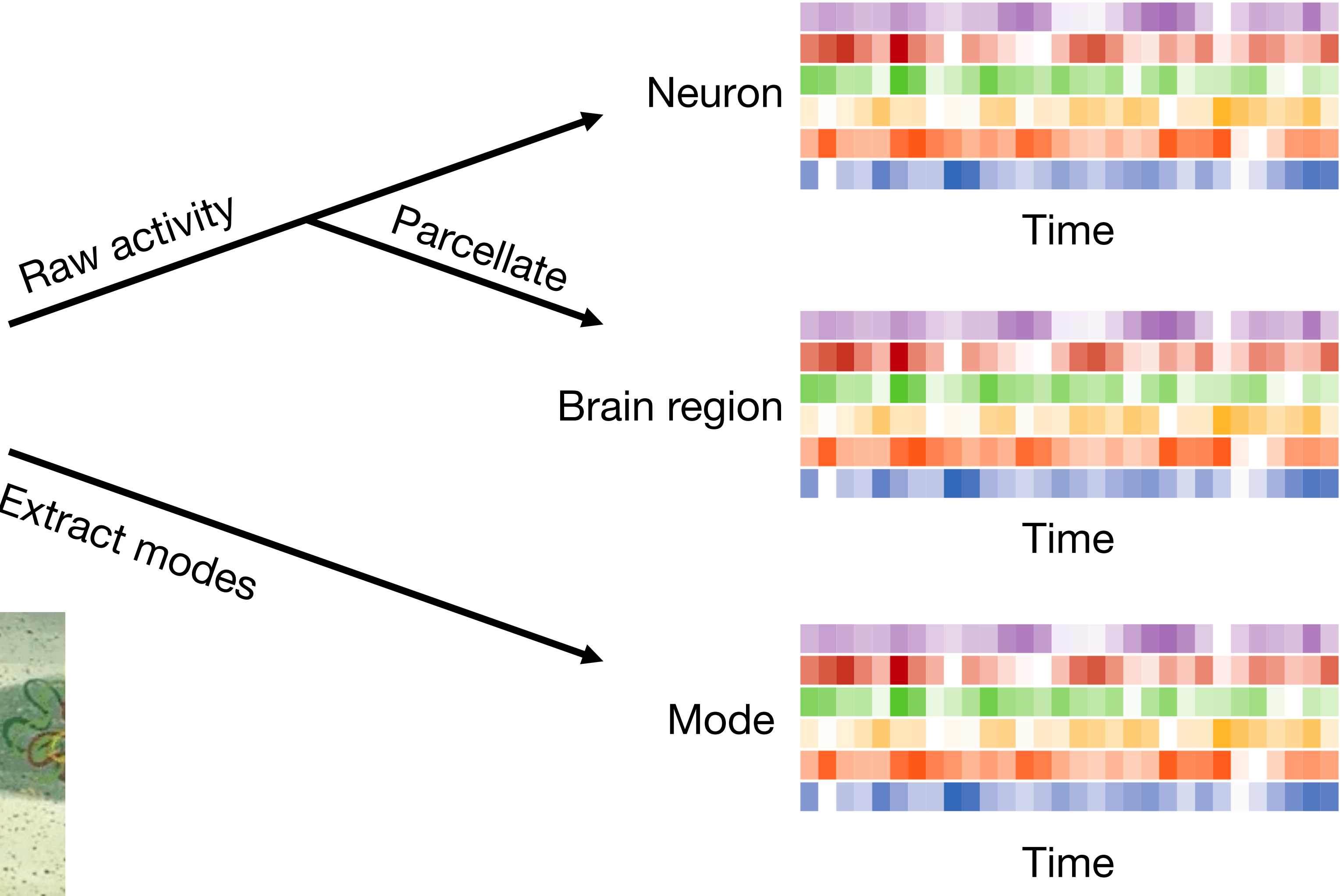
Isotropic propagation across a continuous medium

Pang et al. Geometric constraints on human brain function. *Nature* (2023)

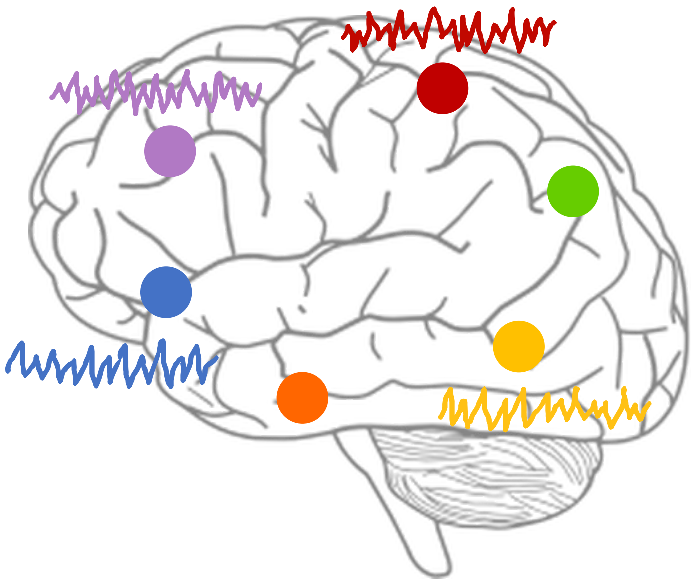
Different ways of **representing brain dynamics**



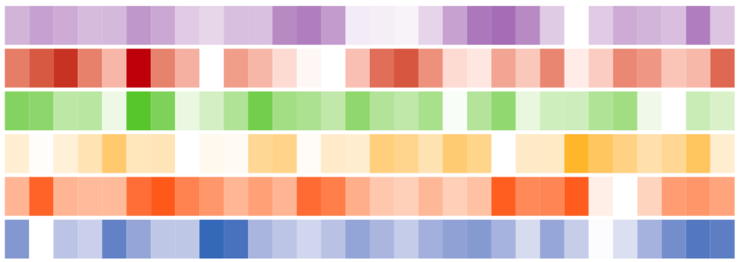


📗 Pang et al. Geometric constraints on human brain function. *Nature* (2023)

Not just the brain: time-varying complex systems are everywhere!



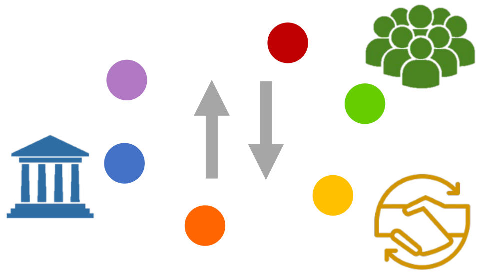
Multivariate time series (**MTS**)



City structure

City properties: density, traffic patterns, crime rates, culture

Economics

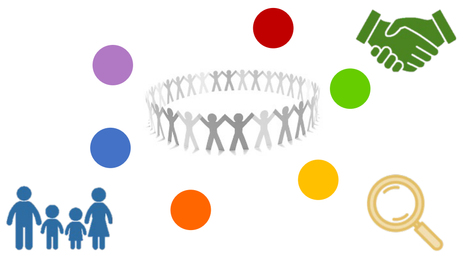


National economy: economic growth, recession

Physics

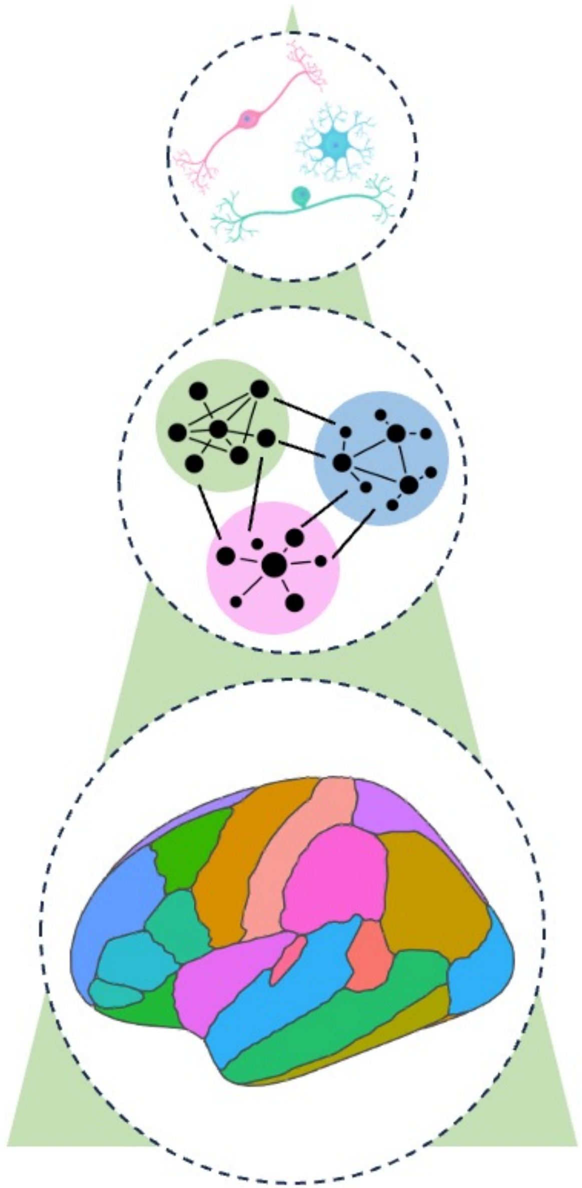
Fluid dynamics: vortices, turbulence

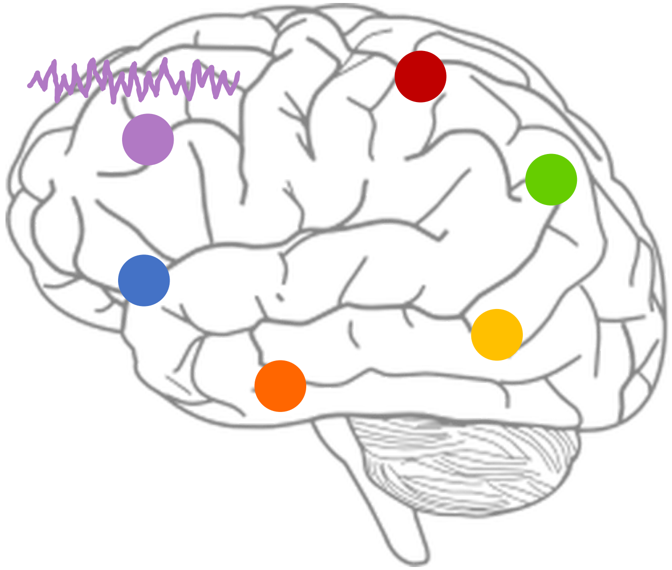
Social networks

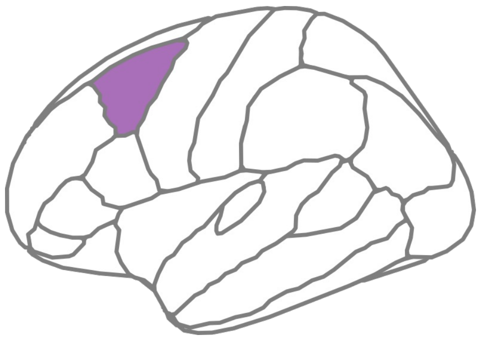


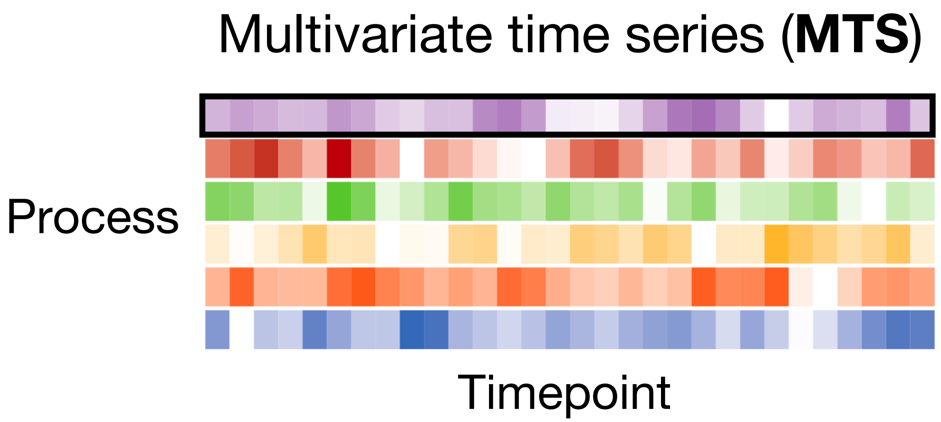
Facebook friends: community formation

Treating the **brain** as a **complex system** of great **biological interest**

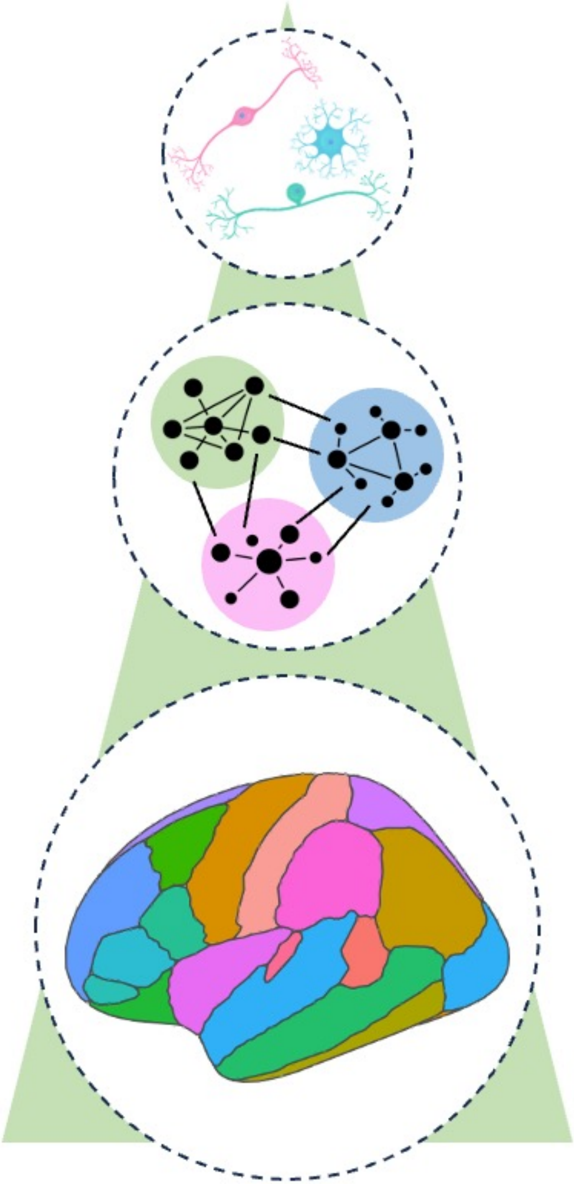


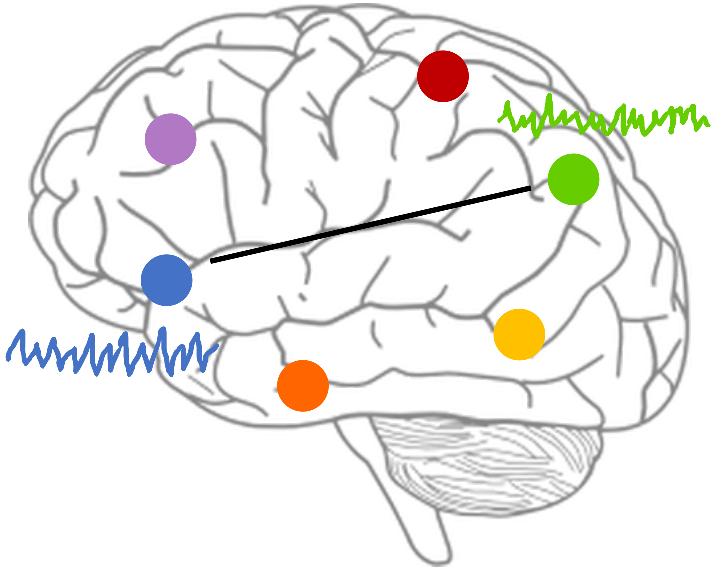


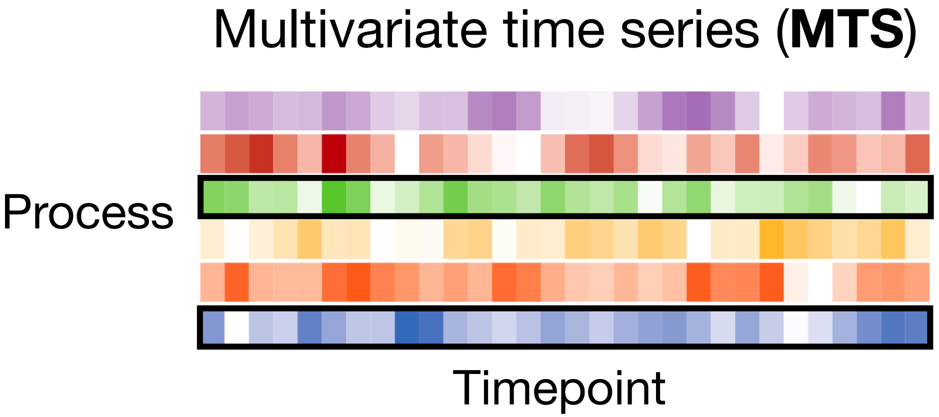


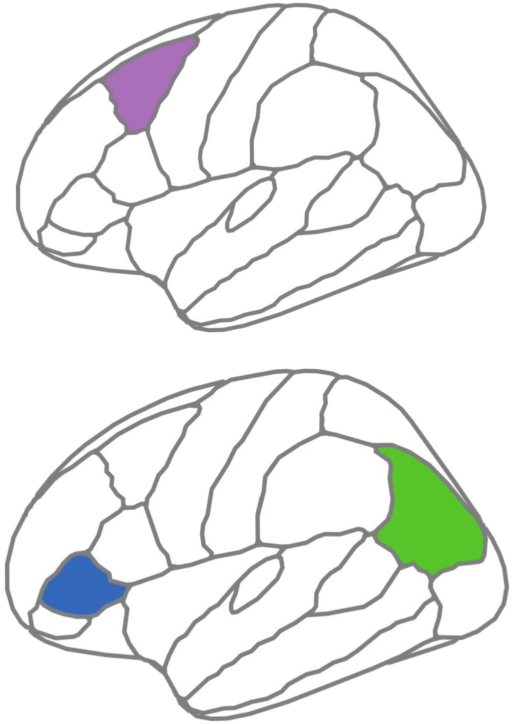


Treating the **brain** as a **complex system** of great **biological interest**

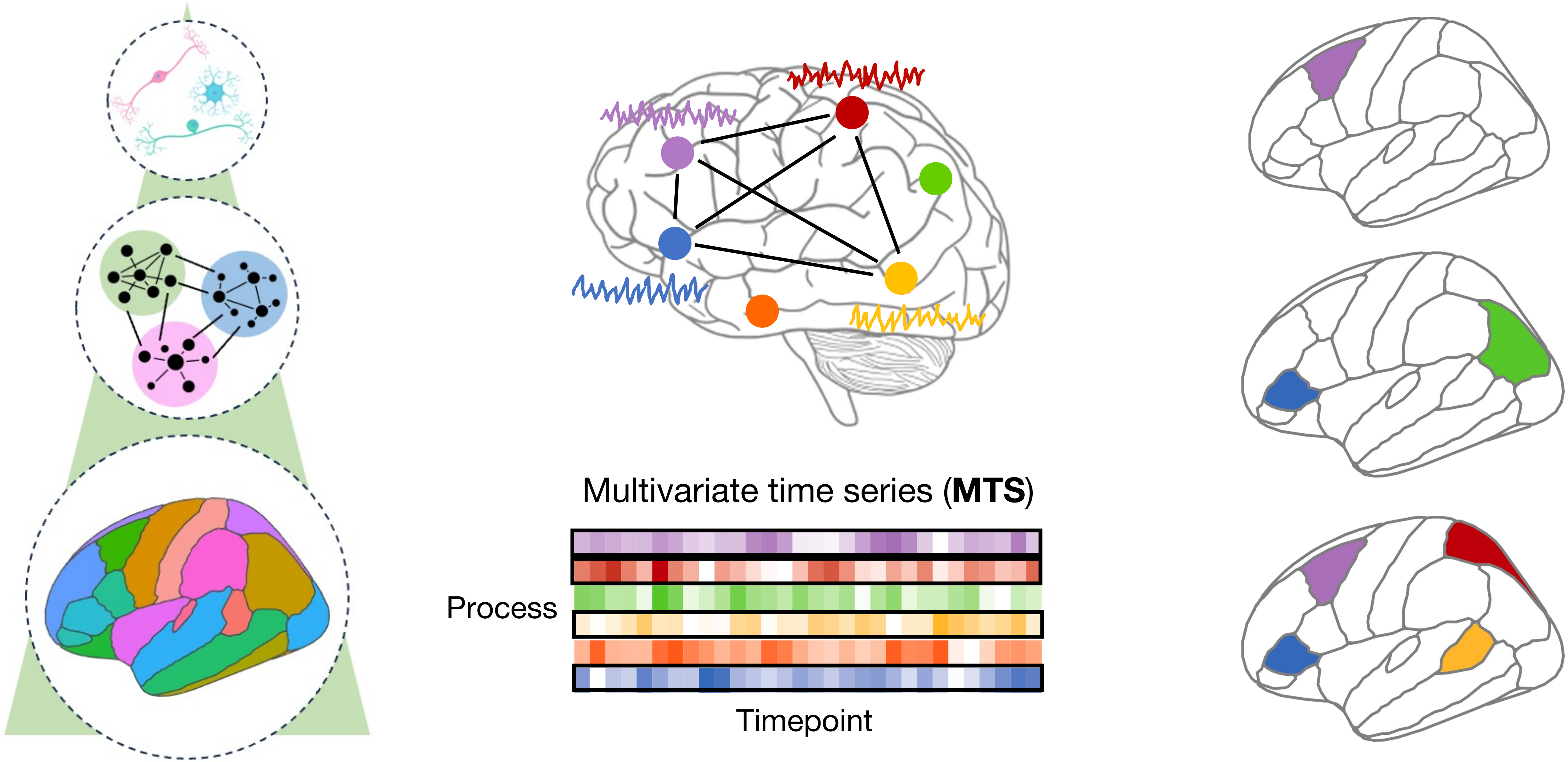




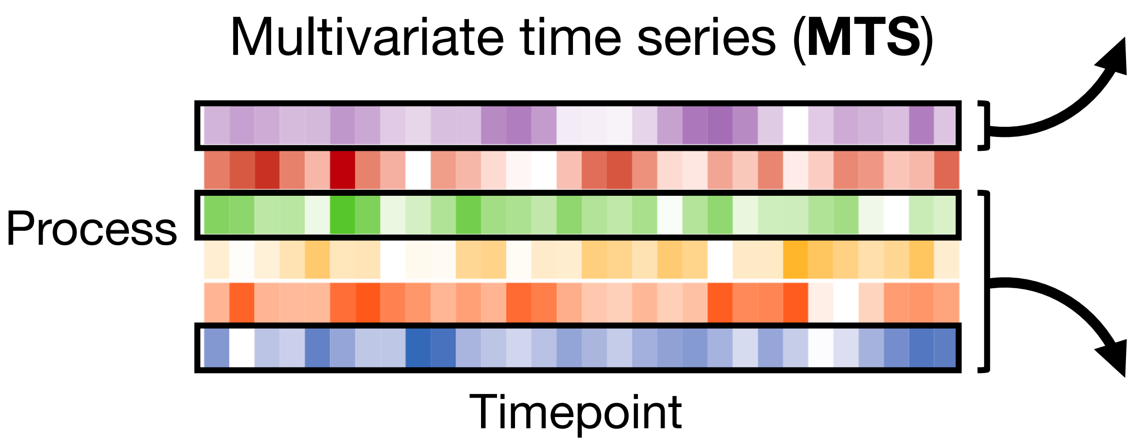




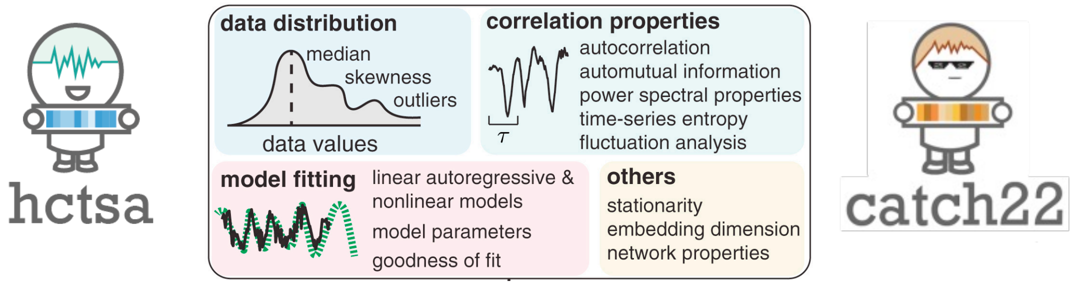
Treating the **brain** as a **complex system** of great **biological interest**



What does this **generalized representation** offer us?



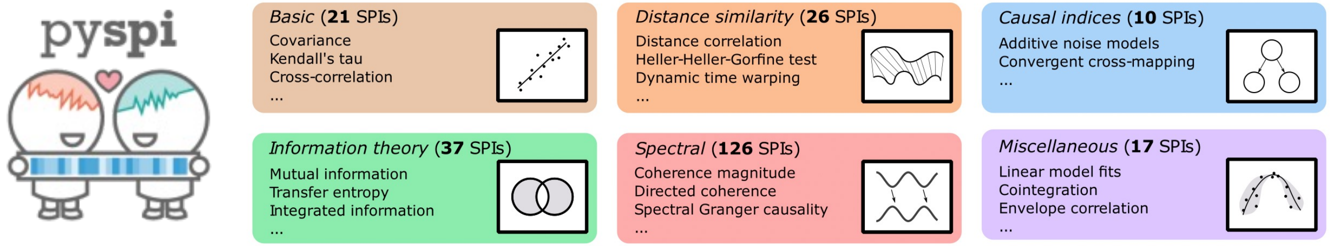
Localized dynamics of one process



Fulcher et al. *J R Soc* (2013), *Cell Systems* (2017)

Lubba et al. *Data Mining and Knowledge Discovery* (2019)

Statistical dependencies between **pairs** of processes



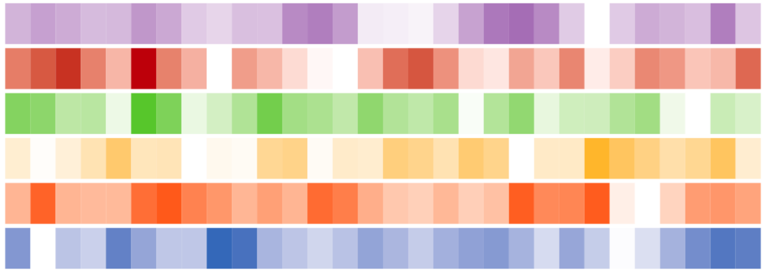
Cliff et al. *Nat Comp Sci* (2023)

This boils down to a **common goal** 🌡️

Quantifying the desired structure in a multivariate time series:

Multivariate time series (**MTS**)

Process

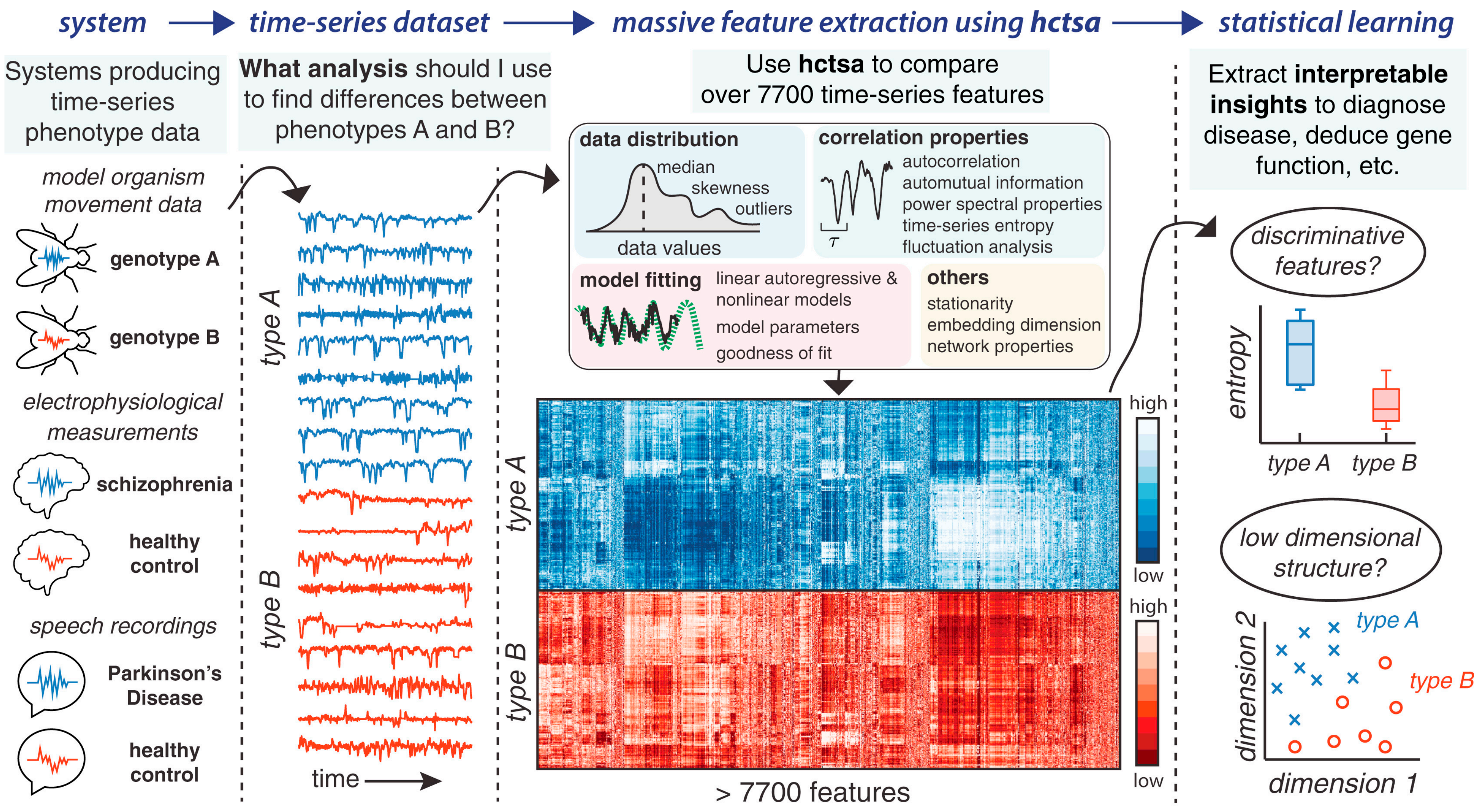


Timepoint

A set of statistical properties based on **clear scientific algorithms** and **interpretable theory**, which are **informative of interesting structure(s)** in our data

The **highly comparative time-series feature analysis** approach compares across a large library of scientific algorithms (spanning a large and interdisciplinary theoretical literature 📕📗📘📙)

This boils down to a **common goal** 🌡️

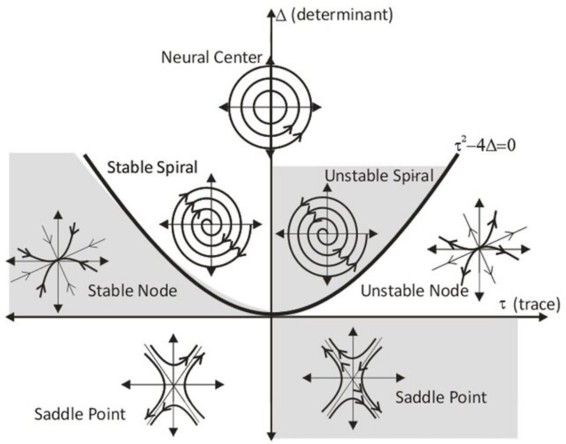


Local dynamics

Pairwise coupling

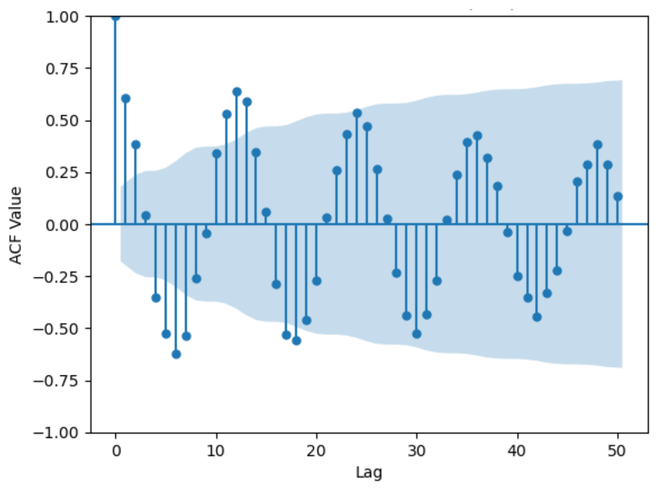
📗 Fulcher & Jones. *hctsa*: A Computational Framework for Automated Time-Series Phenotyping Using Massive Feature Extraction. *Cell Systems* (2017)

hctsa and *pyspi* include both **linear** and **nonlinear features**



The arsenal of **linear time series analysis features** begin by **assuming a system with linear structure**, and we think about what such a linear system would do

A linear system is **fully** captured by its **autocorrelation function (ACF)**



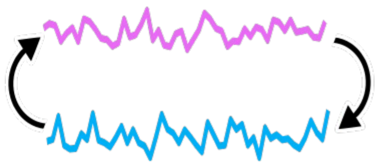
hctsa

Local dynamics

ACF at different lags, local forecast based on rolling average, AR models, basic distributional properties (mean, variance)

pyspi

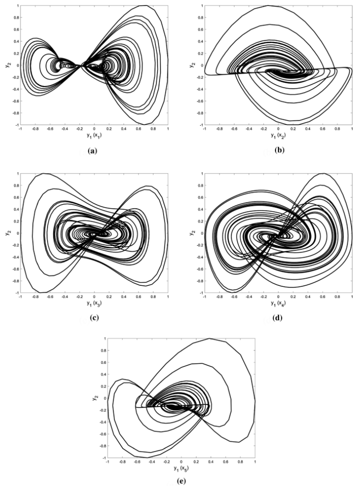
Pairwise coupling



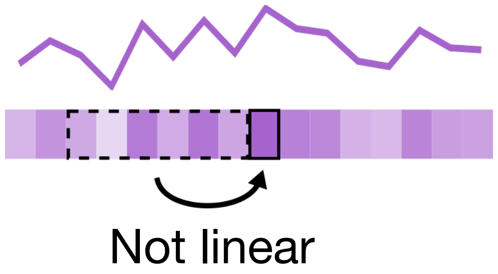
Pearson correlation, Granger causality, Euclidean distance, linear model fits, power envelope correlation

Erbaş *Chaos Theory and Applications* (2022); Li et al. *Nonlinear Dynamics* (2021)

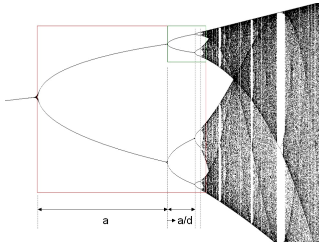
hctsa and *pyspi* include both **linear** and **nonlinear features**



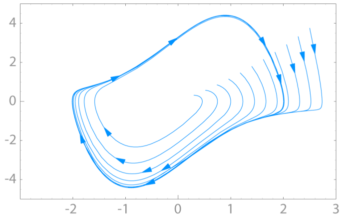
Nonlinear time series analysis features do not make assumptions about the structure of the system, which can be additionally summarized by e.g., polynomial functions



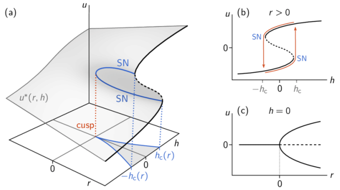
Small changes to the input can give rise to:



Chaos



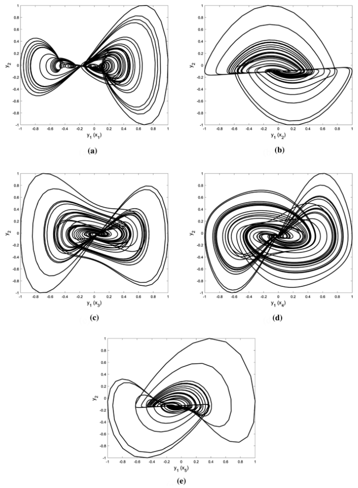
Oscillations



Bifurcations

Li et al. *Nonlinear Dynamics* (2021); Wikipedia; PhysicsOpenLab; Frey & Brauns *arXiv* (2021)

hctsa and *pyspi* include both **linear** and **nonlinear features**



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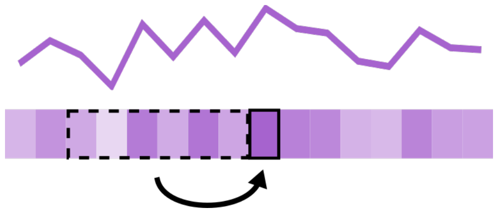
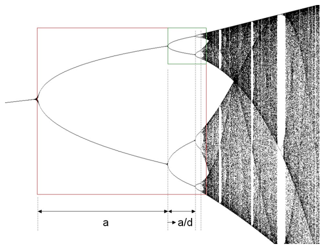
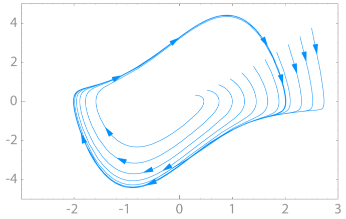


Not linear

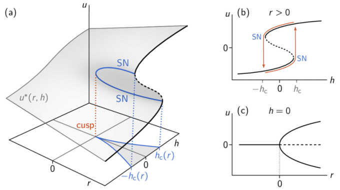
Small changes to the input can give rise to:



Chaos



Oscillations



Bifurcations

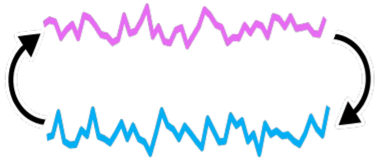
hctsa

Local dynamics

Automutual information, Lyapunov exponent, fractional dimensionality, phase-space entropies, embedding distance

pyspi

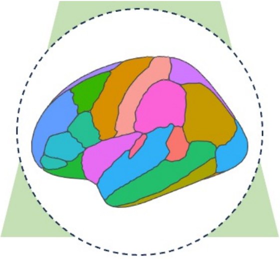
Pairwise coupling



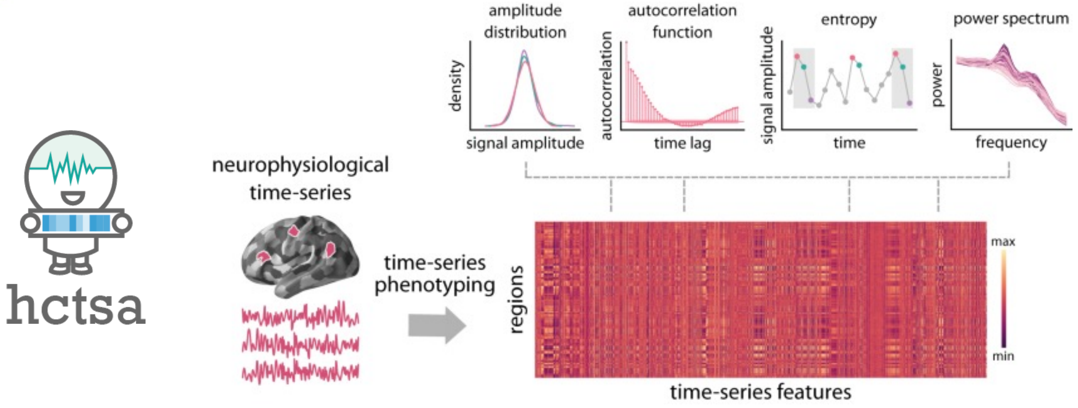
Transfer entropy, dynamic time warping, additive noise modelling, phase lag index

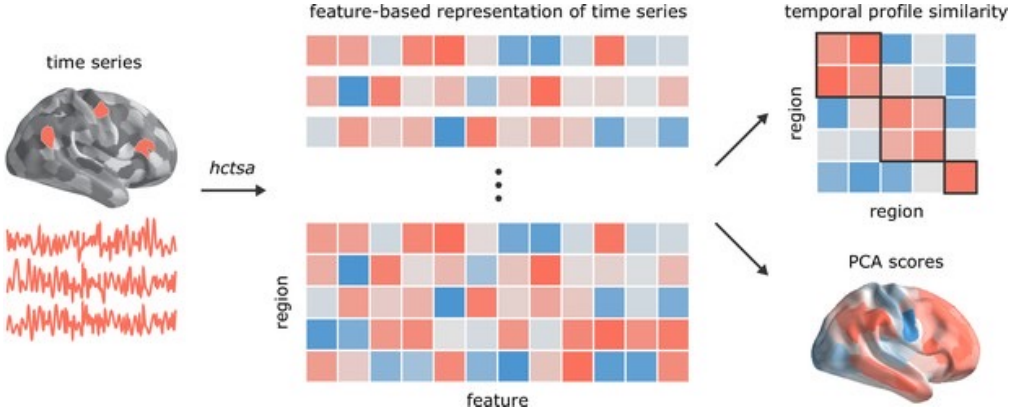
📷 Li et al. *Nonlinear Dynamics* (2021); Wikipedia; PhysicsOpenLab; Frey & Brauns *arXiv* (2021)

Nonlinearity in brain dynamics (?)



Real-world systems that we study, like the **brain**, extend **beyond** the behaviors that a linear system can exhibit; we therefore define them as **nonlinear.**



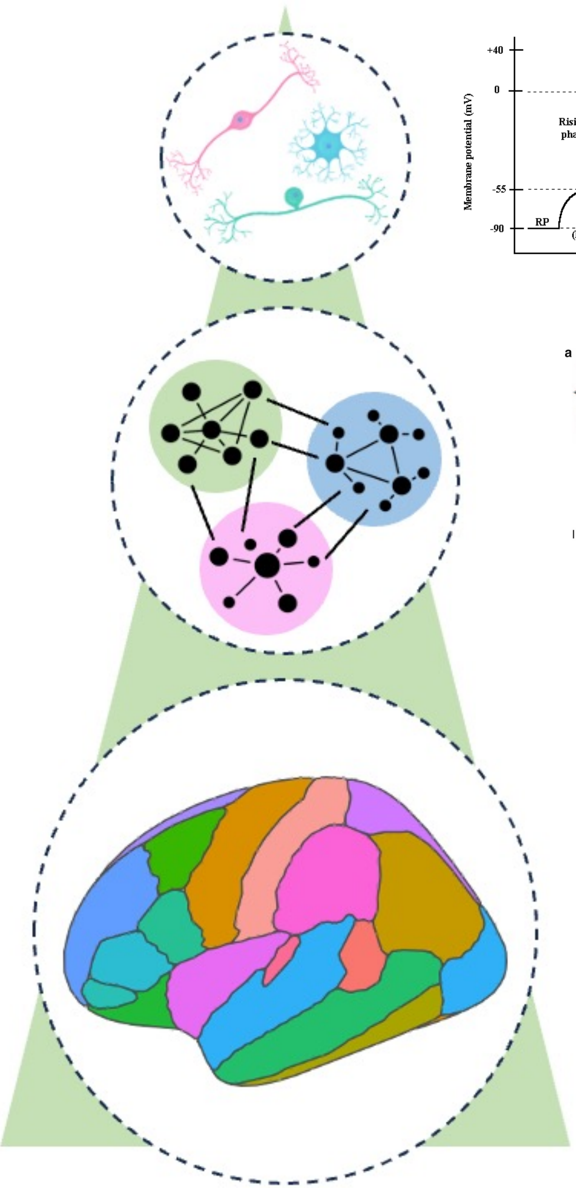


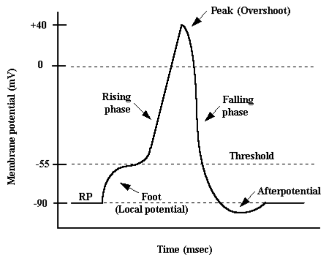
Applications of *hctsa* to **MEG (left)** and **fMRI (right)** data have shown that **linear properties** of local dynamics tend to dominate the **principal brain-wide axes of temporal variation** of the brain at rest.

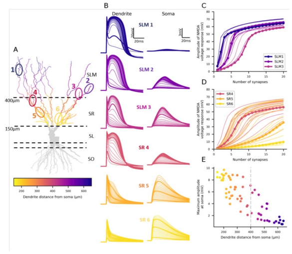
When your brain is at rest – as in not actively performing a cognitive task – it is sitting close to an equilibrium, where the **governing dynamics are approximately linear**. To detect nonlinear dynamics with **functional neuroimaging**, do we need to increase the **temporal precision** and/or **perturb** the brain away from resting equilibrium?

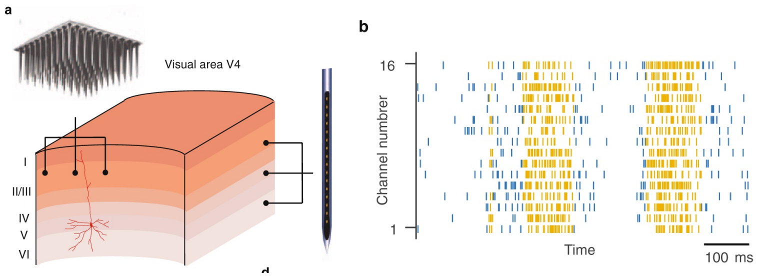
Shafiei et al. *Nature Comms* (2023); *eLife* 2020)

Do we still see **nonlinearity** at the **macroscale**?









?

Article | Open access | Published: 11 December 2023

Macroscopic resting-state brain dynamics are best described by linear models

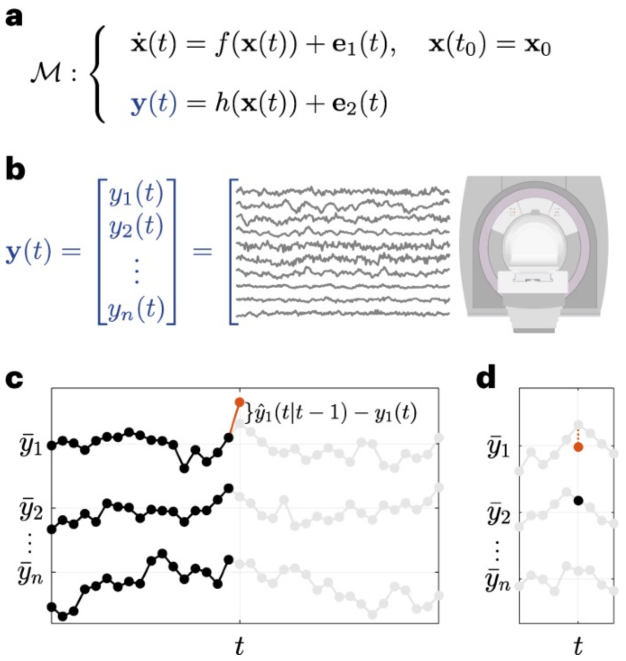
Erfan Nozari, Maxwell A. Bertolero, Jennifer Stiso, Lorenzo Caciagli, Eli J. Cornblath, Xiaosong He, Arun S. Mahadevan, George J. Pappas & Dani S. Bassett

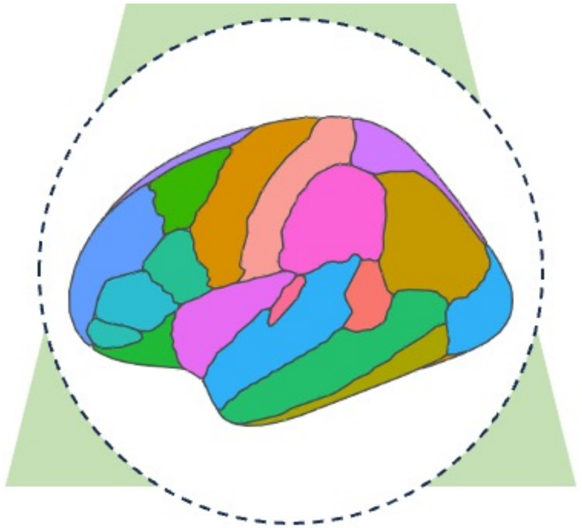
Nature Biomedical Engineering 8, 68–84 (2024) | Cite this article

8010 Accesses | 12 Citations | 18 Altmetric | Metrics

https://www-archiv.fdm.uni-hamburg.de/b-online/library/crone/3028/membrane/mempot.html;
Humphries et al. *Neuroscience* (2023); Shi et al. *Nat Comms* (2022)

Do we still see **nonlinearity** at the **macroscale**?





With an AR(1) process:
$x_{t+1} = f(x_t)$ with a linear function, fully specified by the **autocorrelation function** at lag 1

AC(1) is a "**sufficient statistic**" here – the summary of past observations that contains info needed to predict the future values of x

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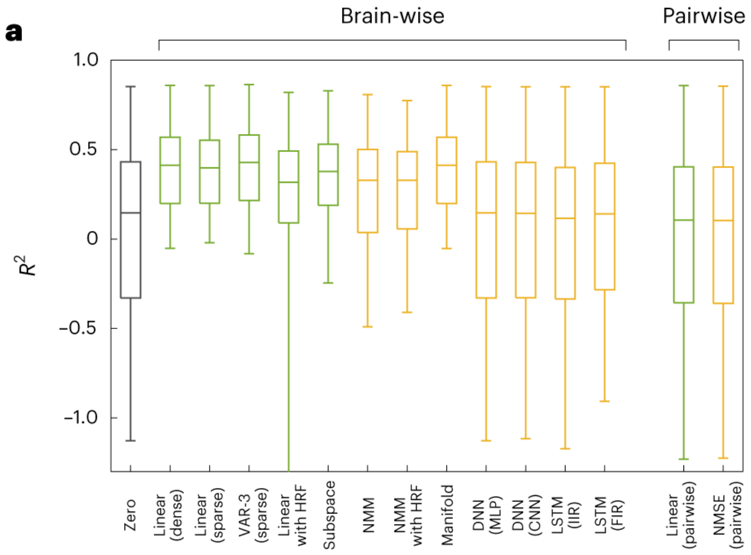
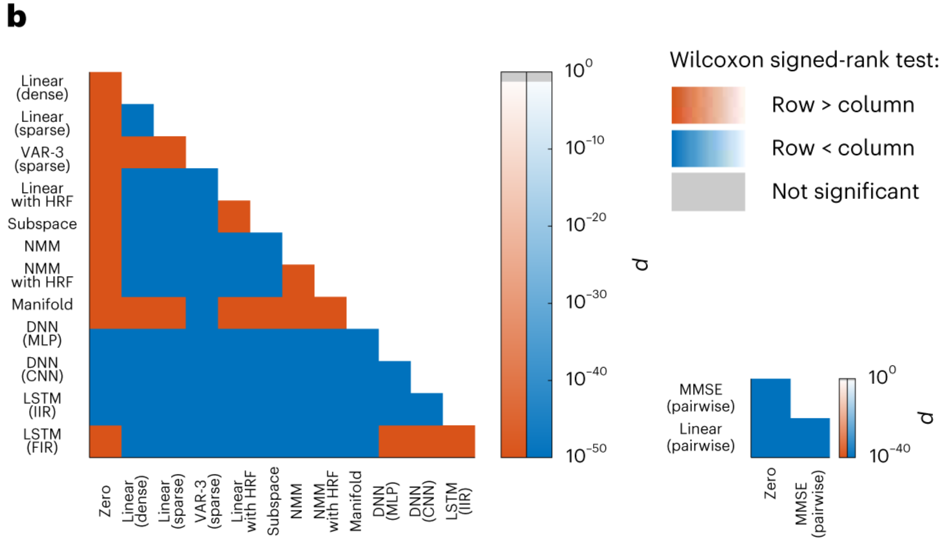
🏆 Linear autoregressive (AR) models

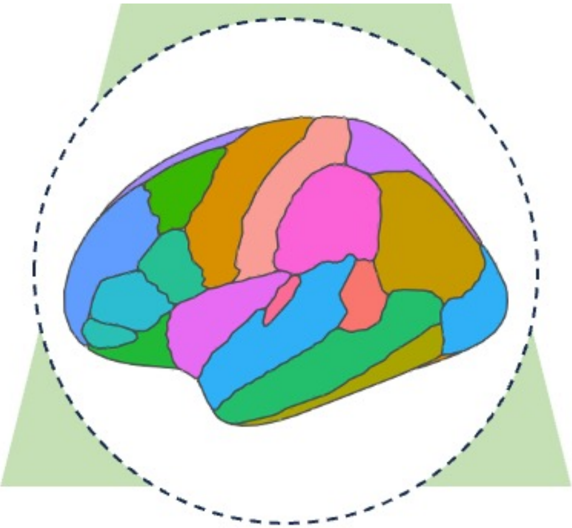


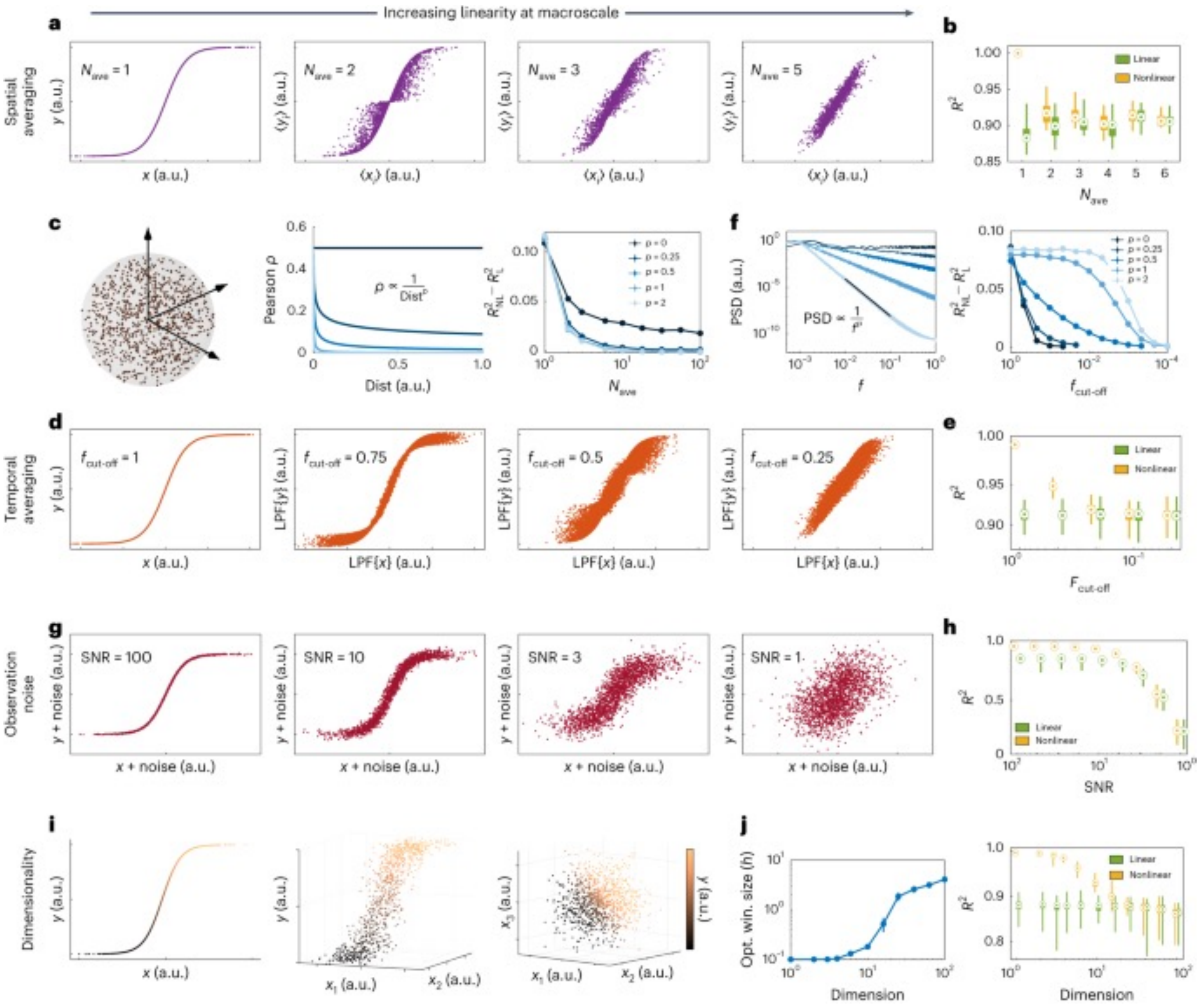


Do we still see **nonlinearity** at the **macroscale**?

4 “**linearizing effects**” that we can observe with **functional neuroimaging** at the **whole-brain scale**:

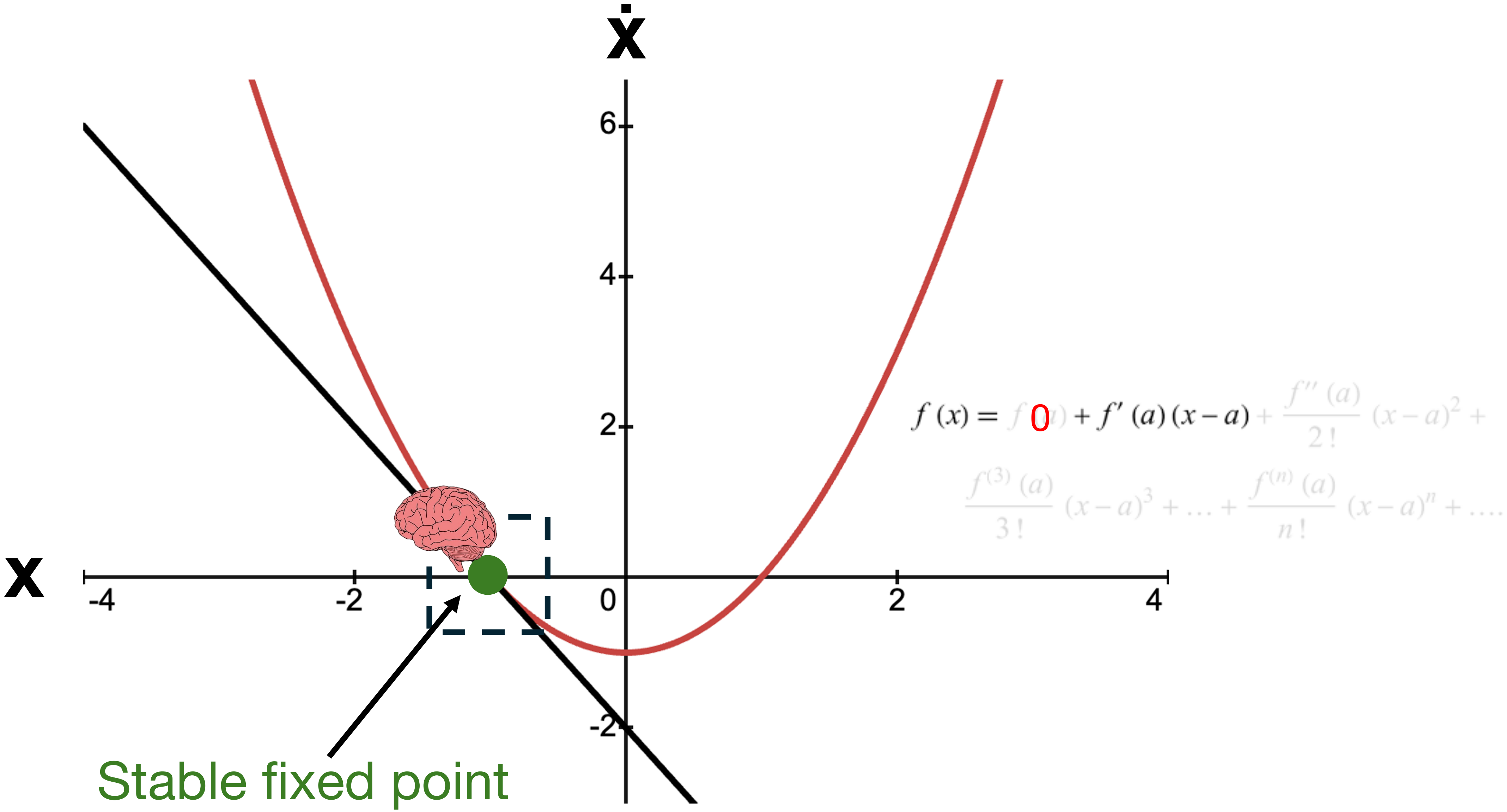
1. Spatial averaging
2. Temporal averaging
3. Observational noise
4. Dimensionality





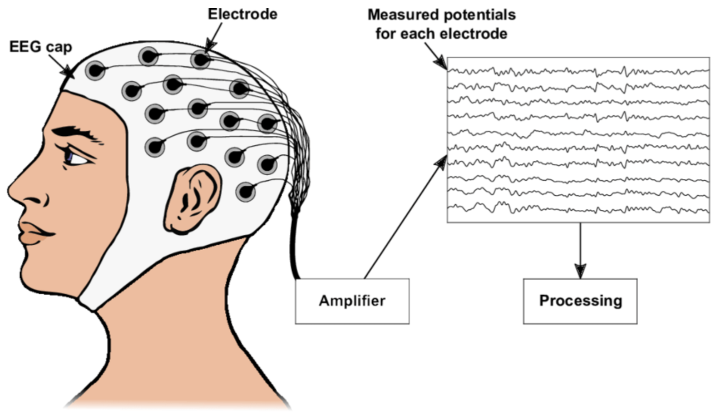
Nozari et al. Macroscopic resting-state brain dynamics are best described by linear models. *Nat Biomed Eng* (2024)

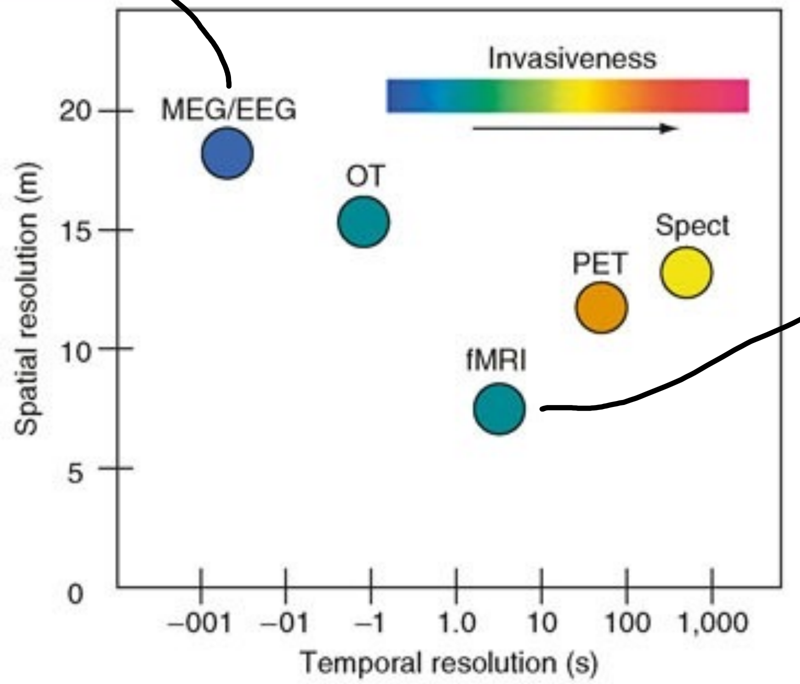
Nonlinear systems can be **locally linear**

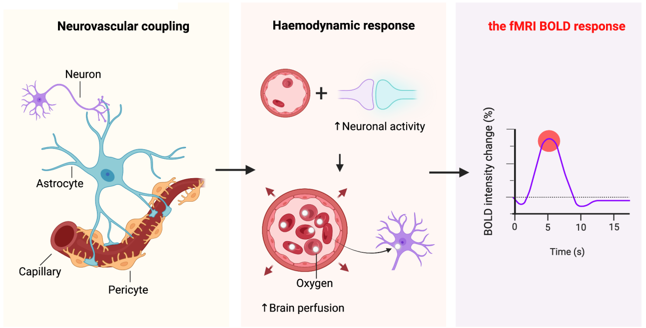


📷 https://www.desmos.com/calculator

Brain imaging modalities exhibit a **spatial/temporal resolution tradeoff**







Electroencephalography (**EEG**) **directly** measures **activity of neural masses** (populations of neurons) at **high temporal precision**, but spatial resolution is **limited to the cortical surface**

Functional magnetic resonance imaging (**fMRI**) **indirectly** measures neural activity from the **cortex down to deep gray matter nuclei** via **hemodynamic coupling**

↑ Temporal ↓ Spatial

↓ Temporal ↑ Spatial

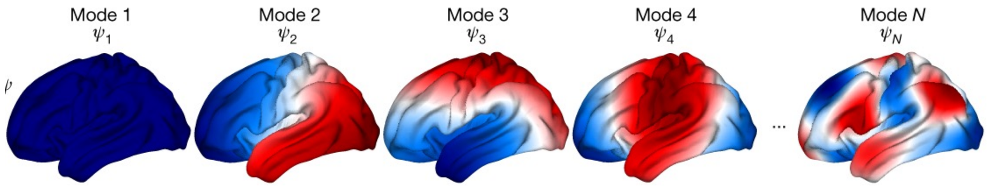
Image sources: Nagel S, Doctoral dissertation, Universität Tübingen (2019); Tachtsidis I, *Atlas of Epilepsies* (2010); Adobe Stock; BioRender

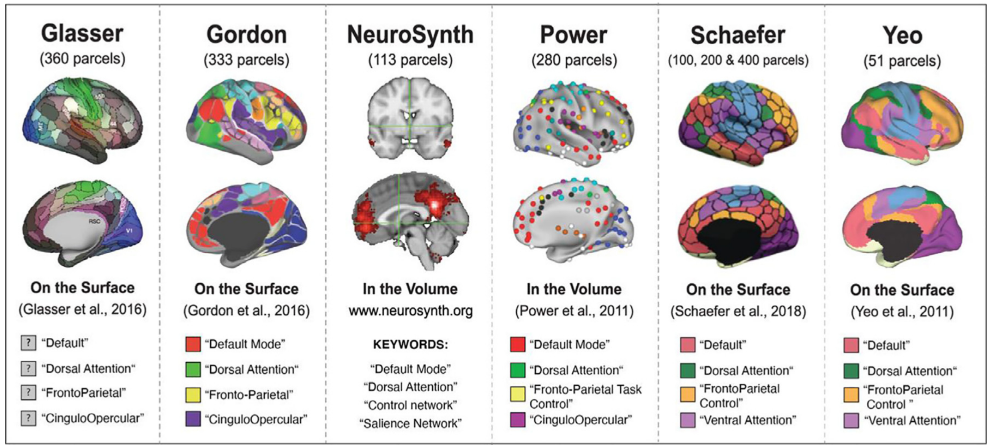
Time-series analysis with **realistic brain activity datasets**

>7,000 features

hctsa

×





Tens to hundreds of modes or parcels

Sample sizes of a few hundred at the most in neuroimaging studies in general

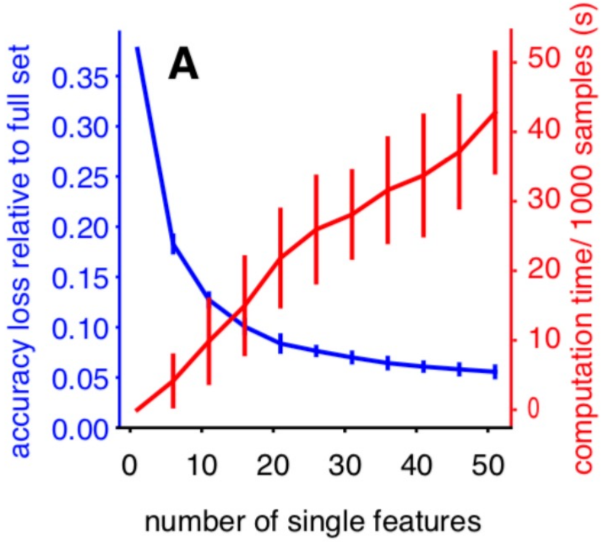
Bryce et al. Brain parcellation selection: An overlooked decision point with meaningful effects on individual differences in resting-state functional connectivity. *Neuroimage* (2021).

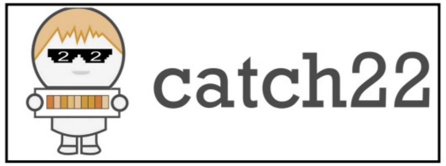
Time-series analysis with **realistic brain activity datasets**

catch22

Evaluate features across **93 diverse time-series classification tasks**

We can usually get away with using **just 22 features**.



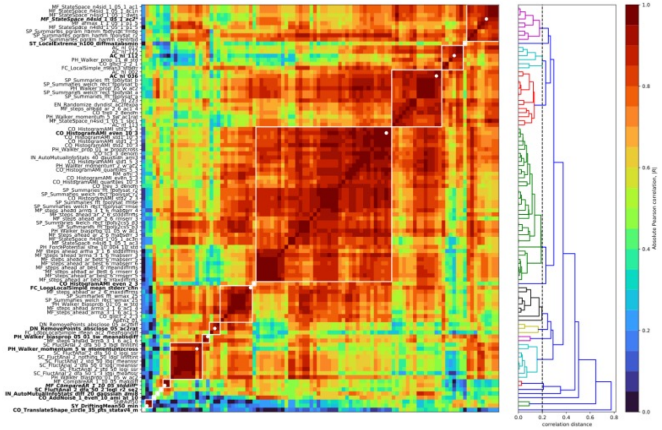


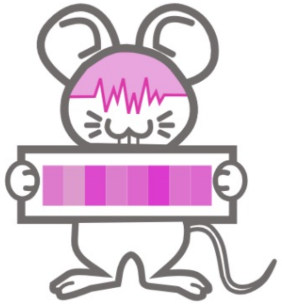
Lubba et al. *catch22*: CAnonical Time-series CHaracteristics. *Data Min Knowl Disc* (2019).

catchaMouse16

Feature evaluation across **12 mouse fMRI classification tasks**

We can usually get away with using **just 16 features**.

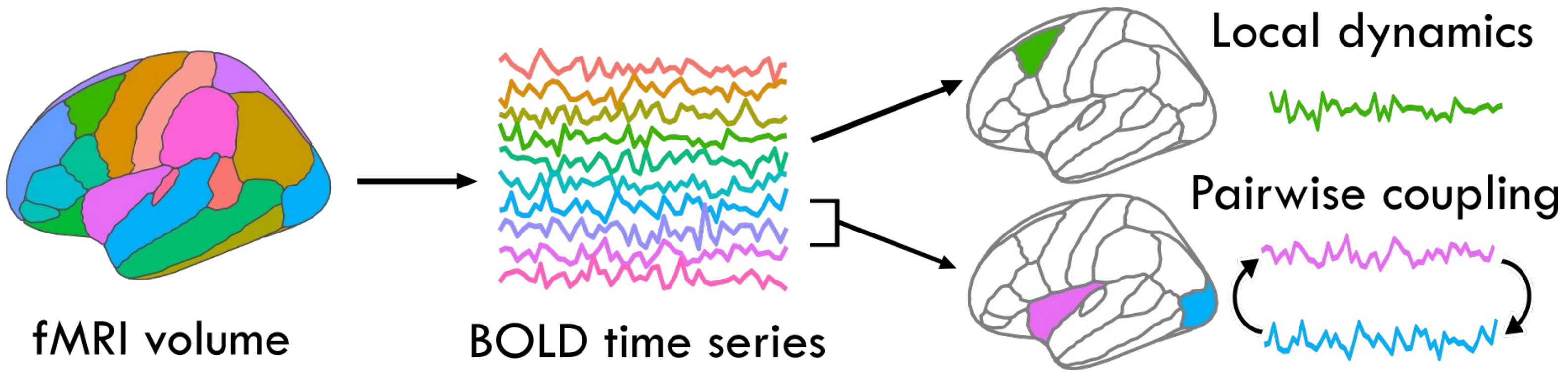




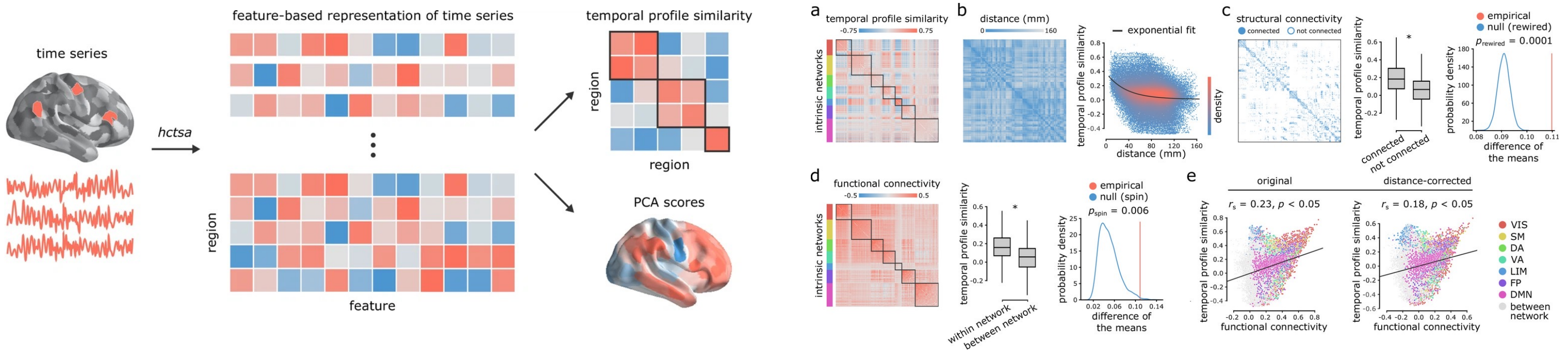
Alam et al. Canonical time-series features for characterizing biologically informative dynamical patterns in fMRI. *bioRxiv* (2024).

Slide courtesy of Dr Ben Fulcher

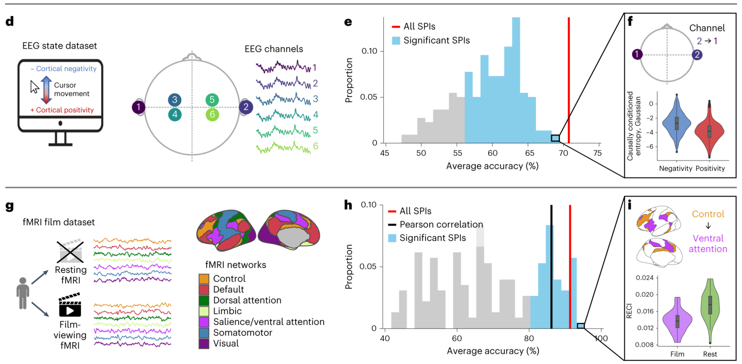
A ~~shameless plug~~ case study on **time-series analysis for fMRI**

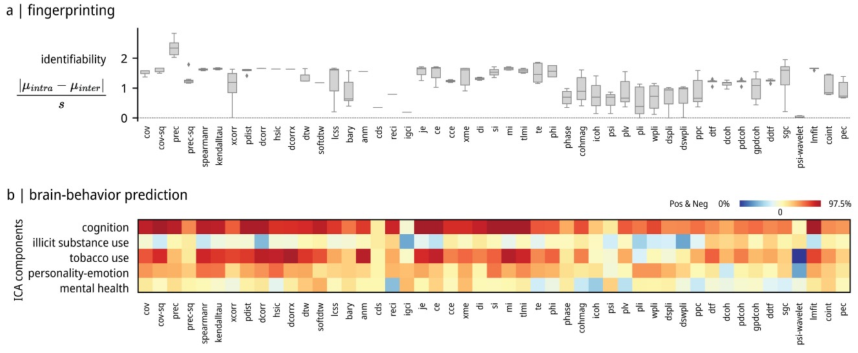


Shafiei et al. *eLife* 2020 (pictured), *Nat Comms* 2023

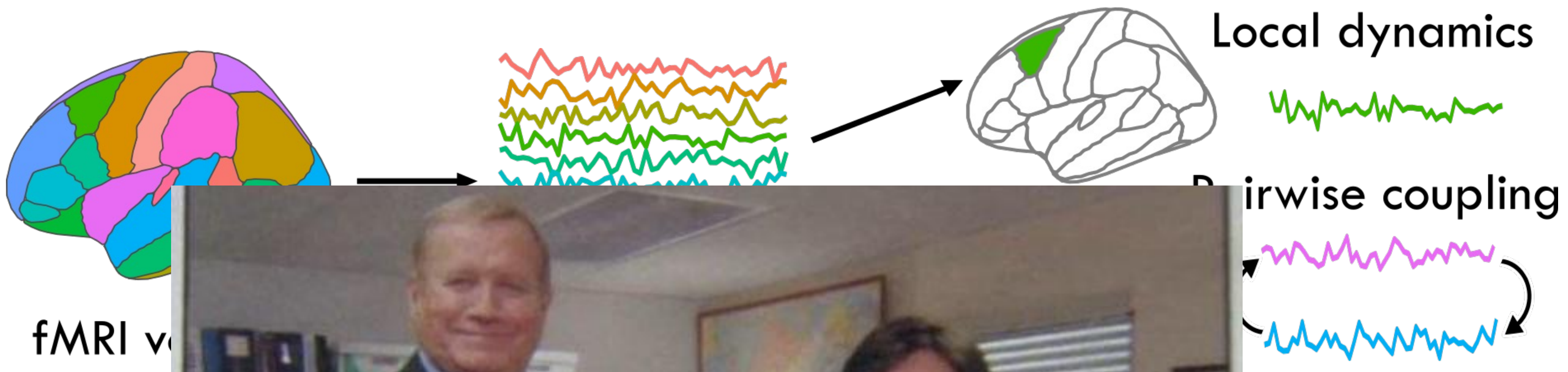


Cliff et al. *Nat Comp Sci* 2023 (left)
Liu et al. *bioRxiv* 2024 (right)

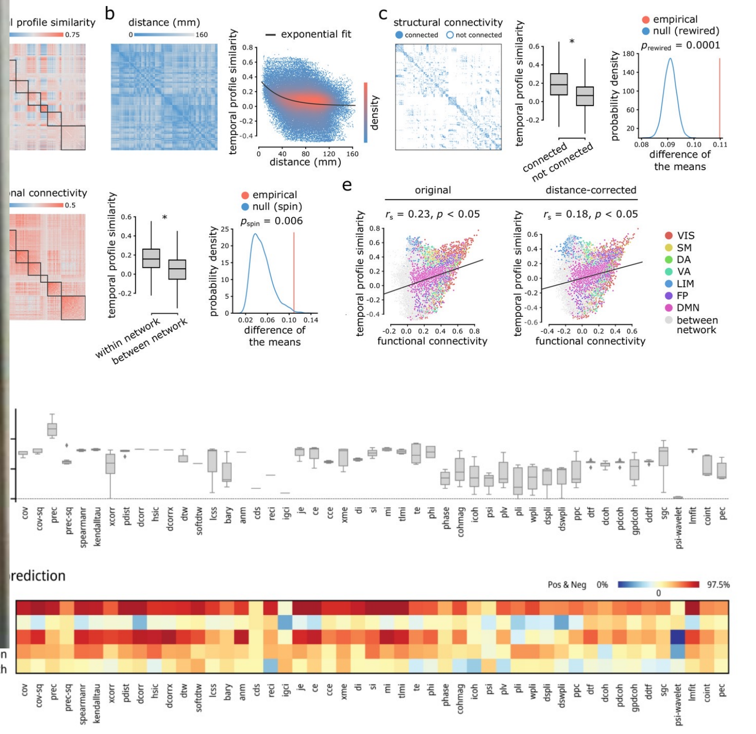




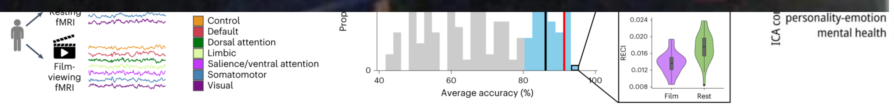
A ~~shameless plug~~ case study on **time-series analysis for fMRI**



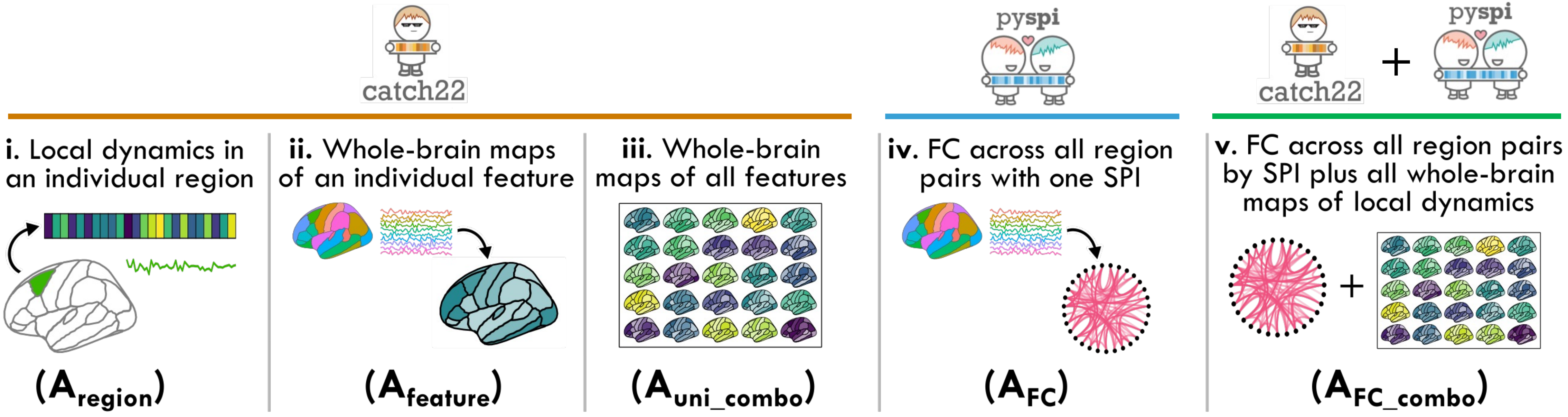
Shafiei et al. *eLife* 2020 (pictu
Nat Comms 2023

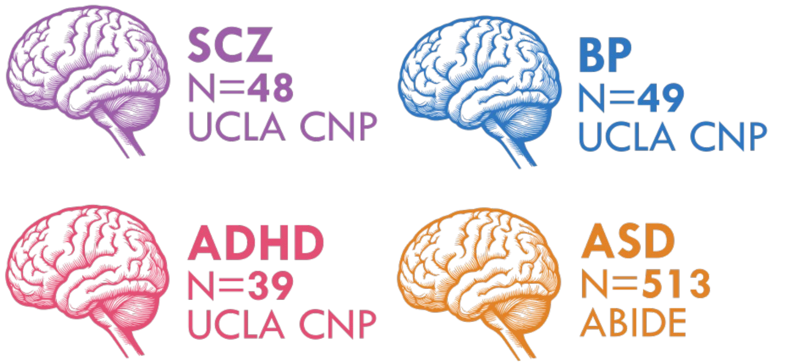


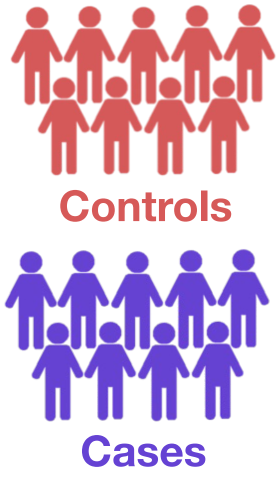
Cliff et al. *Nat Comp Sci* 2023
Liu et al. *bioRxiv* 2024 (right)

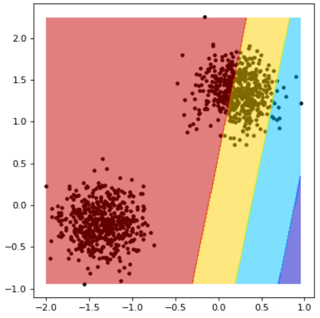


Classifying **neuropsychiatric disorder** cases vs. **healthy controls**








Source: scikit-learn

Linear support vector machine (SVM)
- Balanced accuracy
- Inverse probability weighting

× 10-fold CV
× 10 repeats

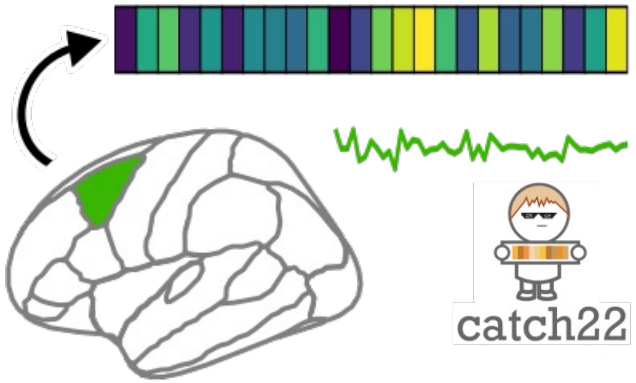
ABIDE Data preprocessed by Traut et al. *NeuroImage* (2022)

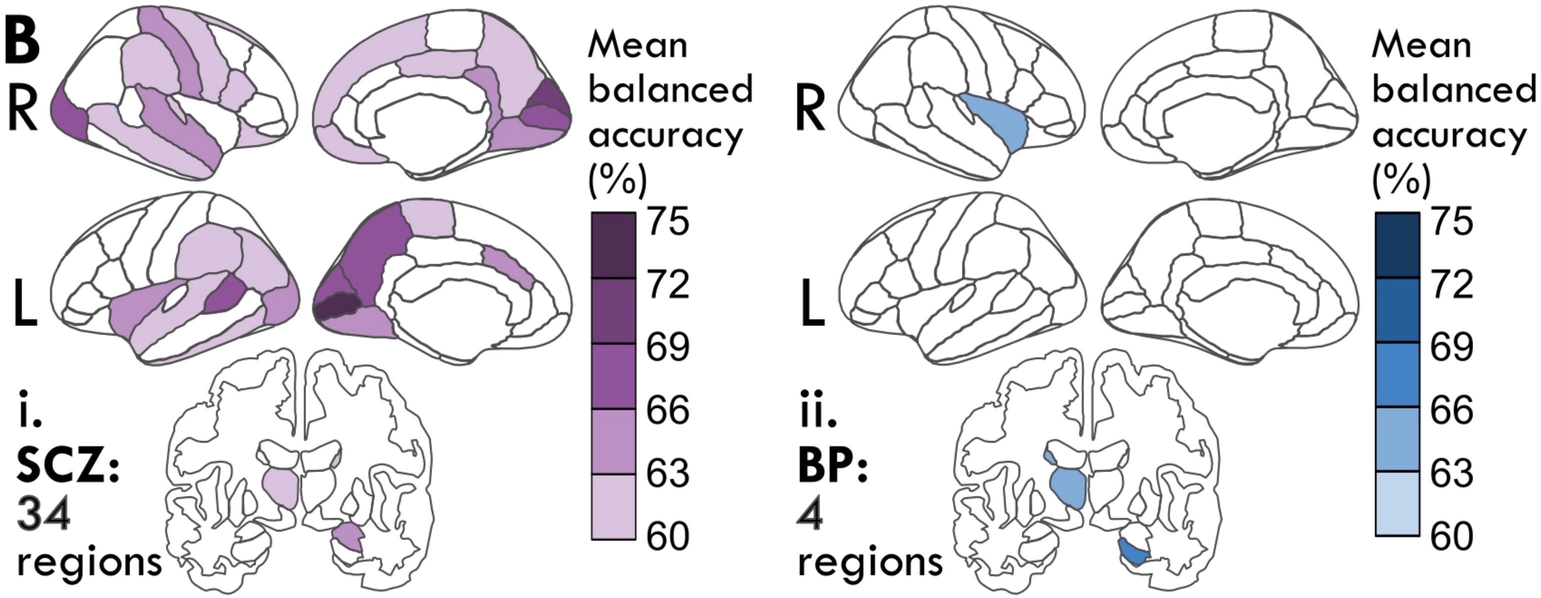
Ucla Data preprocessed by Dr Kevin Aquino

Bryant et al. Extracting interpretable signatures of whole-brain dynamics through systematic comparison. *bioRxiv* (2024)

Interpretable **spatial maps** of **region-specific dysfunction**

Dynamical signatures of resting-state activity in **individual brain regions** can distinguish patients from controls in schizophrenia and bipolar disorder





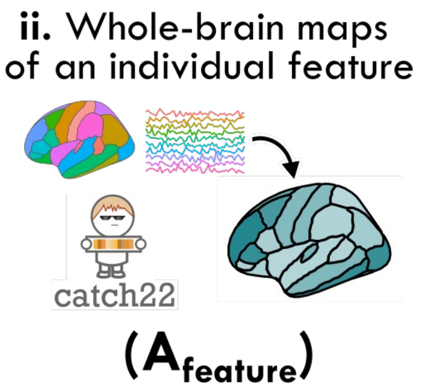
Gene expression 🧬

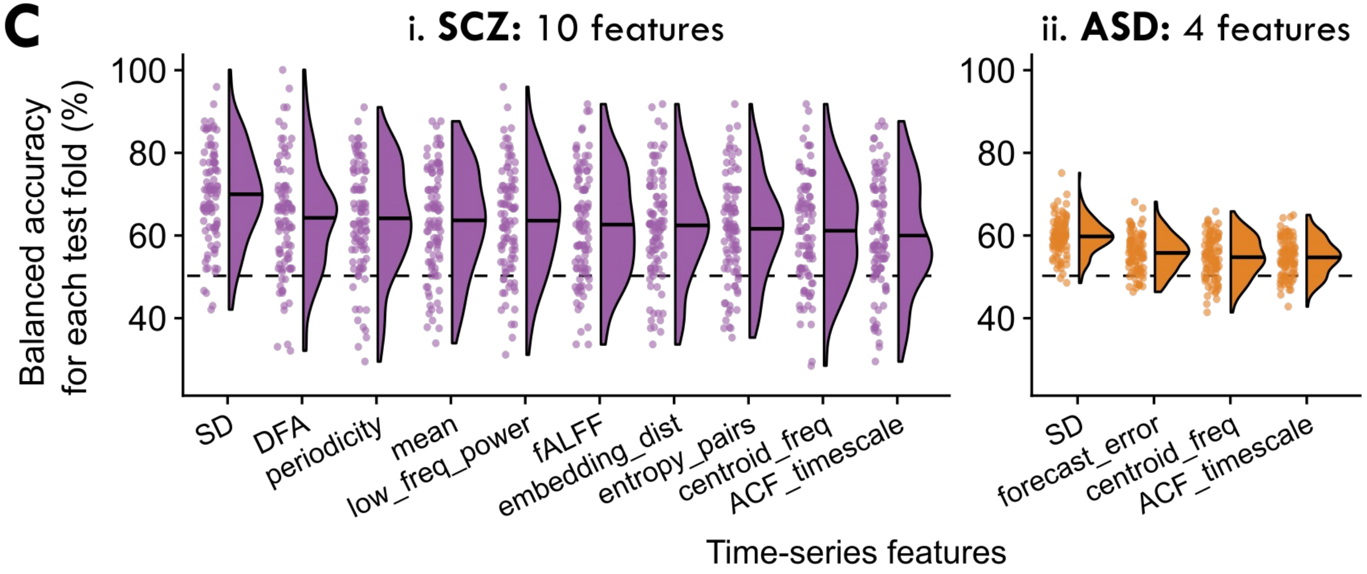
Anatomical changes 🧠

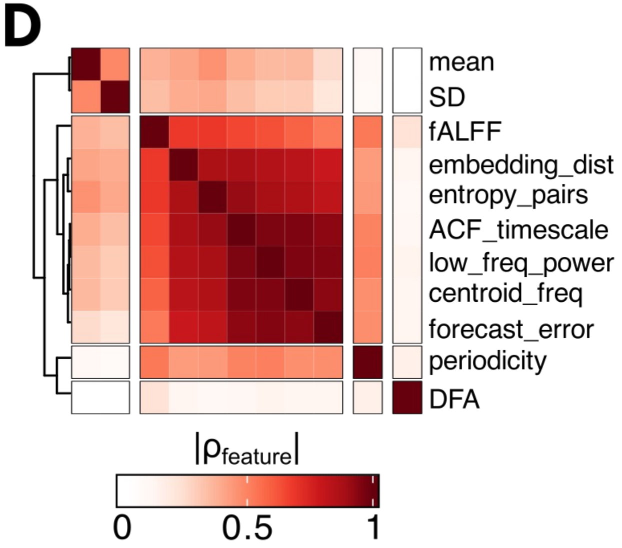
Stimulation analysis ⚡

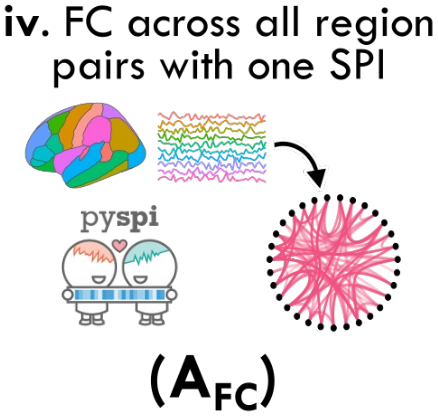
📗 Bryant et al. Extracting interpretable signatures of whole-brain dynamics through systematic comparison. *bioRxiv* (2024)

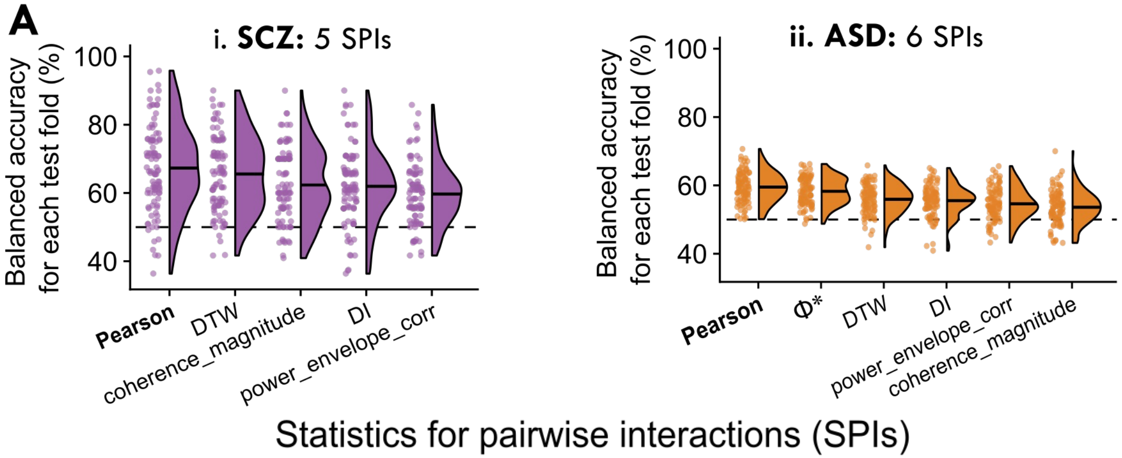
Highlighting **linear features** for **resting-state fMRI** analysis

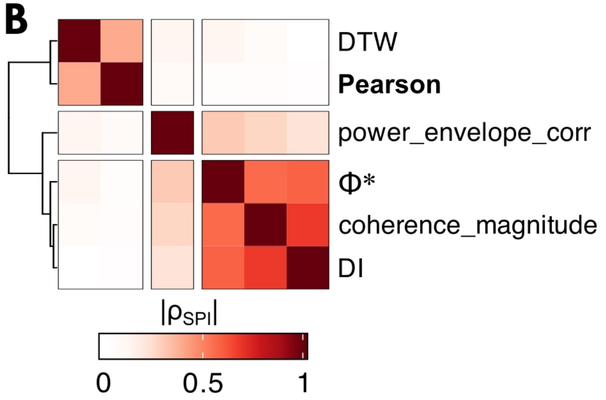






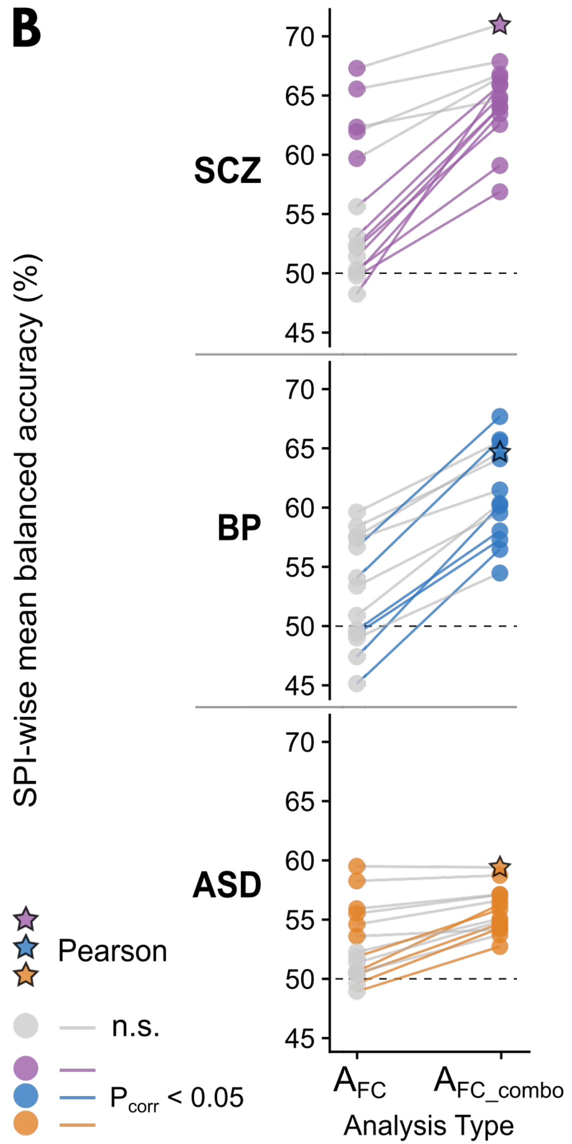


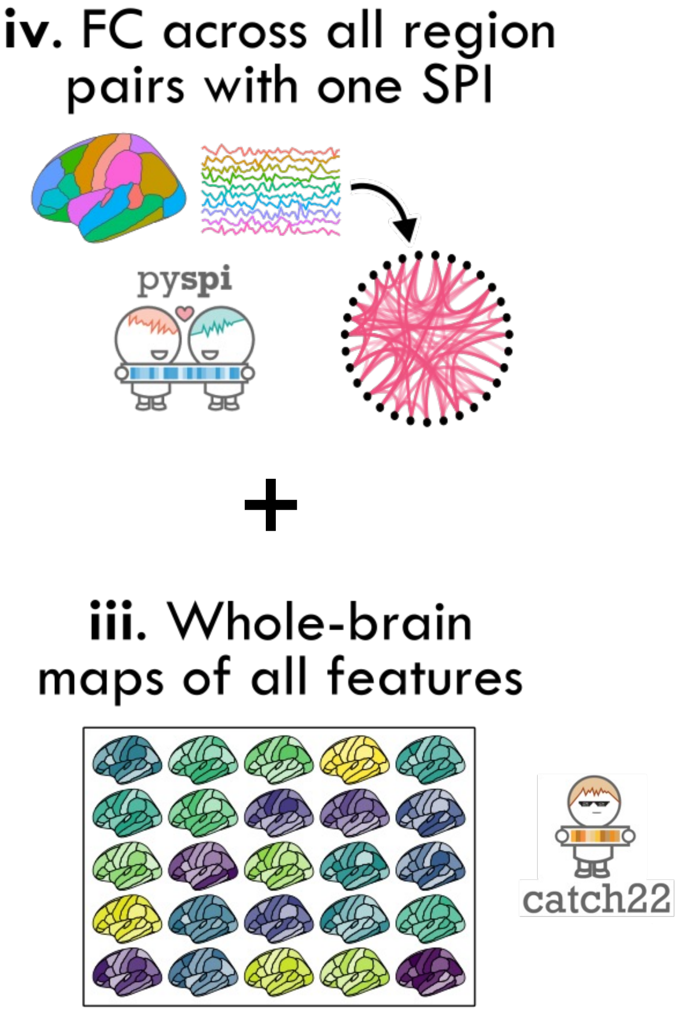




Bryant et al. Extracting interpretable signatures of whole-brain dynamics through systematic comparison. *bioRxiv* (2024)

The benefit of **integrating** local dynamics **and** pairwise coupling

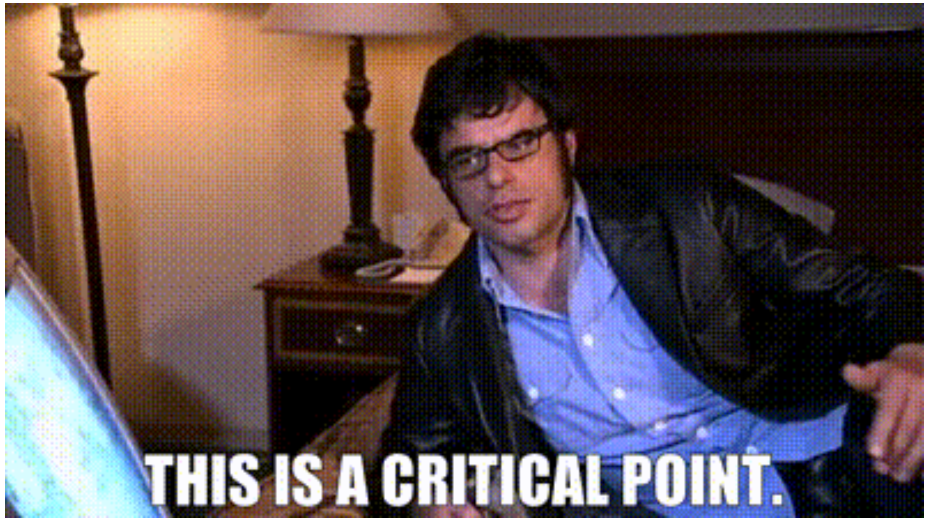




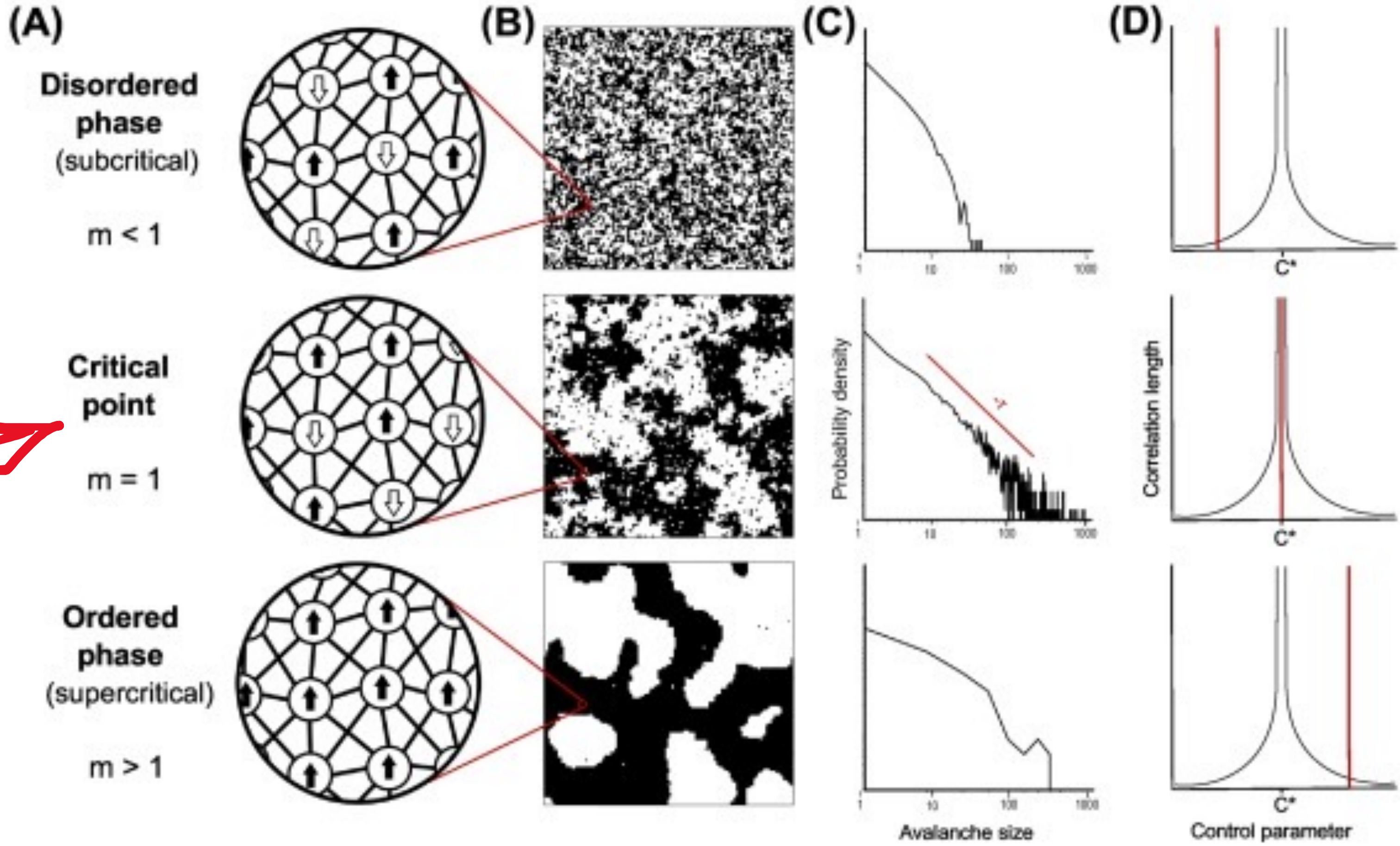
Most **functional connectivity** metrics are more informative with the inclusion of **brain-wide maps** of **local regional dynamics**

Bryant et al. Extracting interpretable signatures of whole-brain dynamics through systematic comparison. *bioRxiv* (2024)

Segue to: Tracking the **distance to criticality**

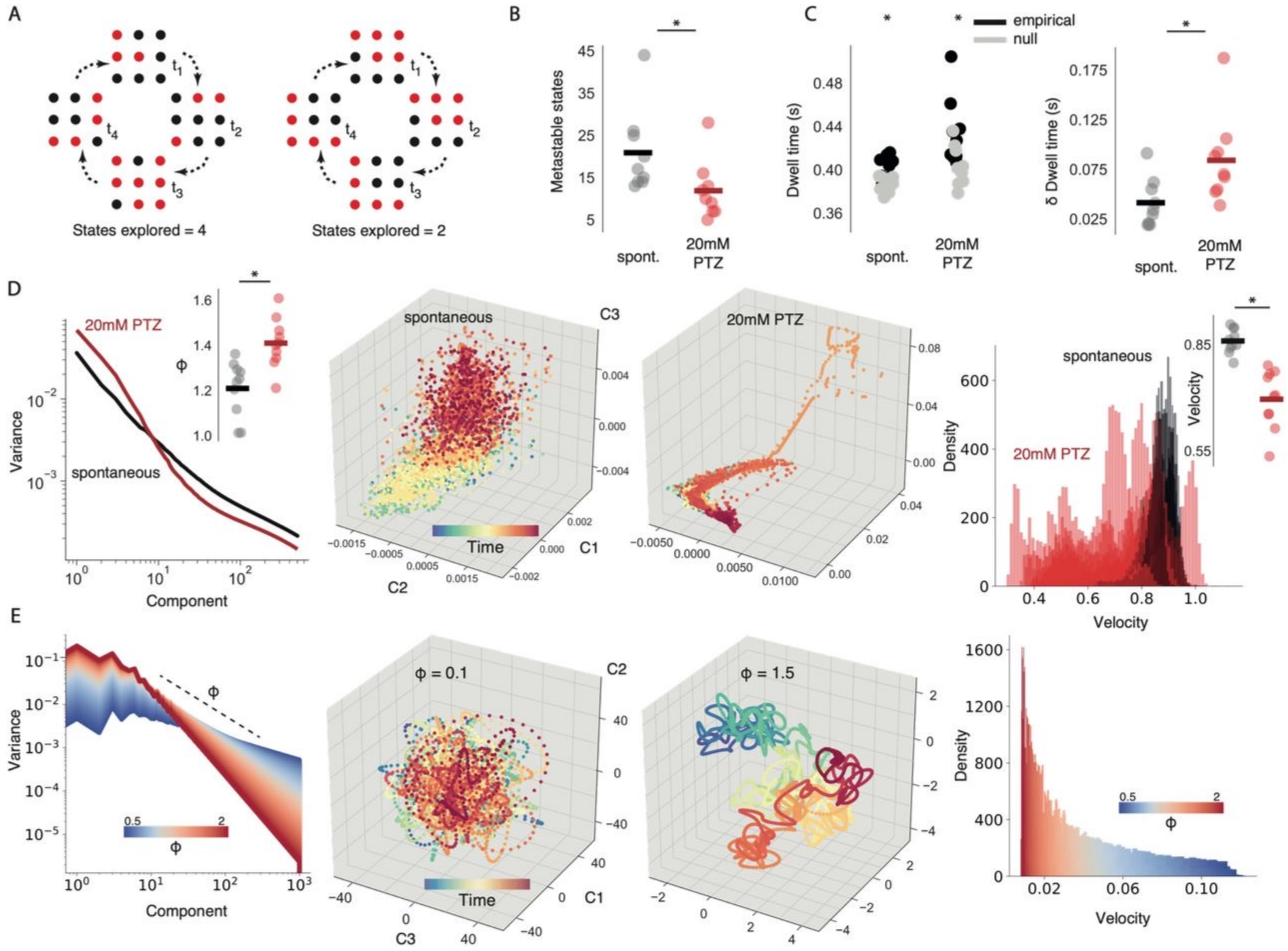


Ising model: nodes of the lattice can be thought of as individual neurons/neuronal ensembles 🧠

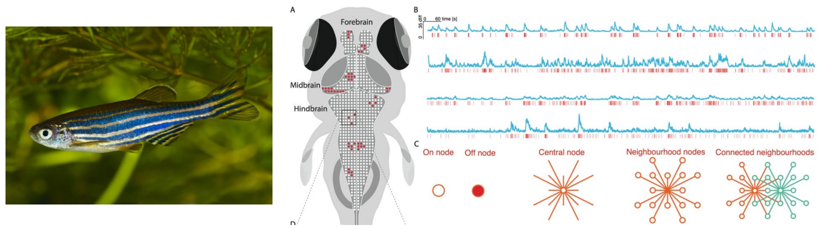


📗 O'Byrne & Jerbi. How critical is brain criticality? *Trends in Neuroscience* (2022)

We see patterns of **criticality** in **brain dynamics**



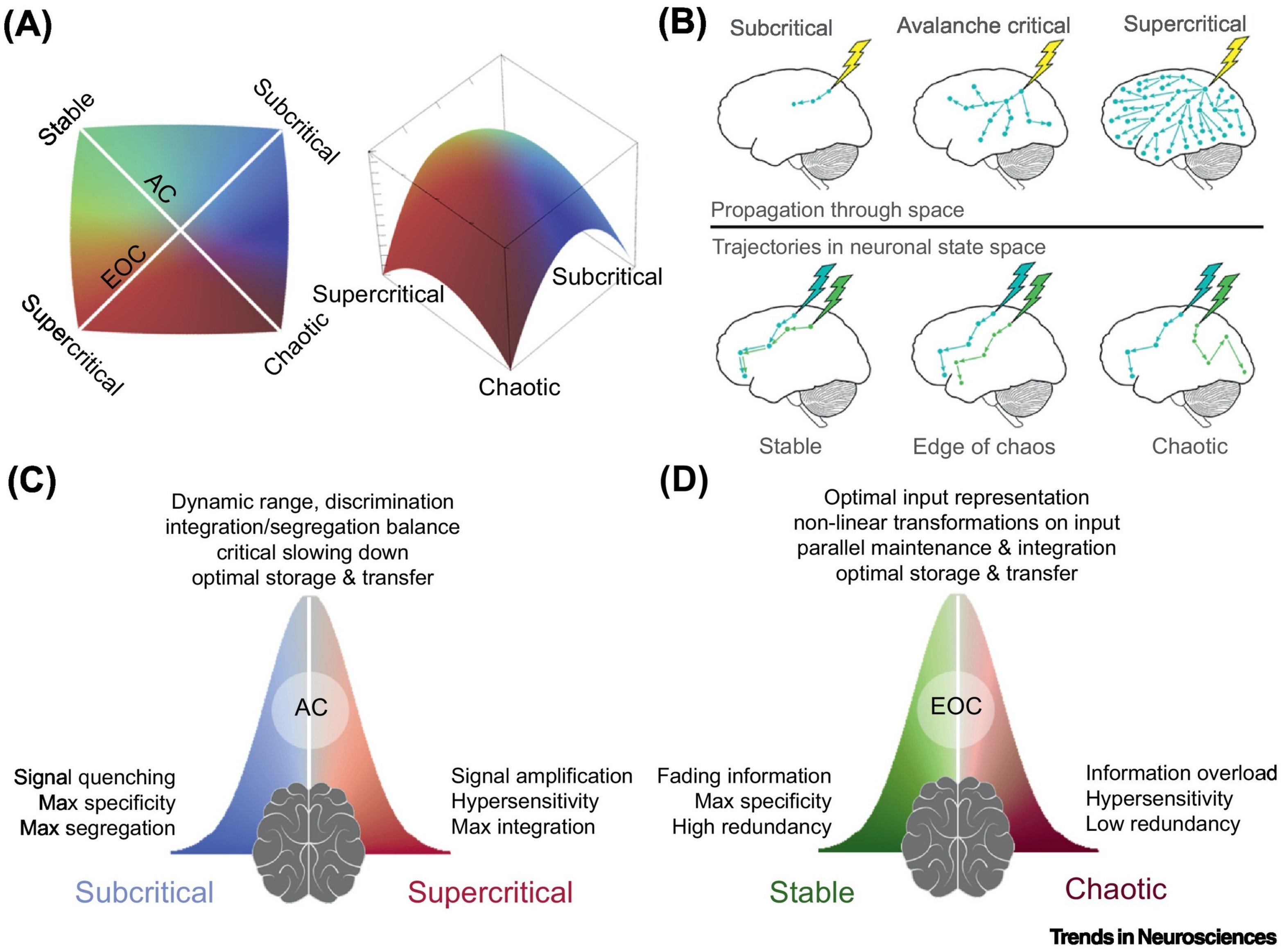
"(A) A **critical system** can explore a **greater subset of its possible brain states** … while a non-critical system will explore a more limited subset."



Zebrafish models are used to study how **epilepsy** induces changes to **excitation/inhibition balances** that push the brain **away from criticality**.

Burrows et al. Single-cell Networks Reorganise to Facilitate Whole-brain Supercritical Dynamics During Epileptic Seizures. *bioRxiv* (2021)

We see patterns of **criticality** in **brain dynamics**

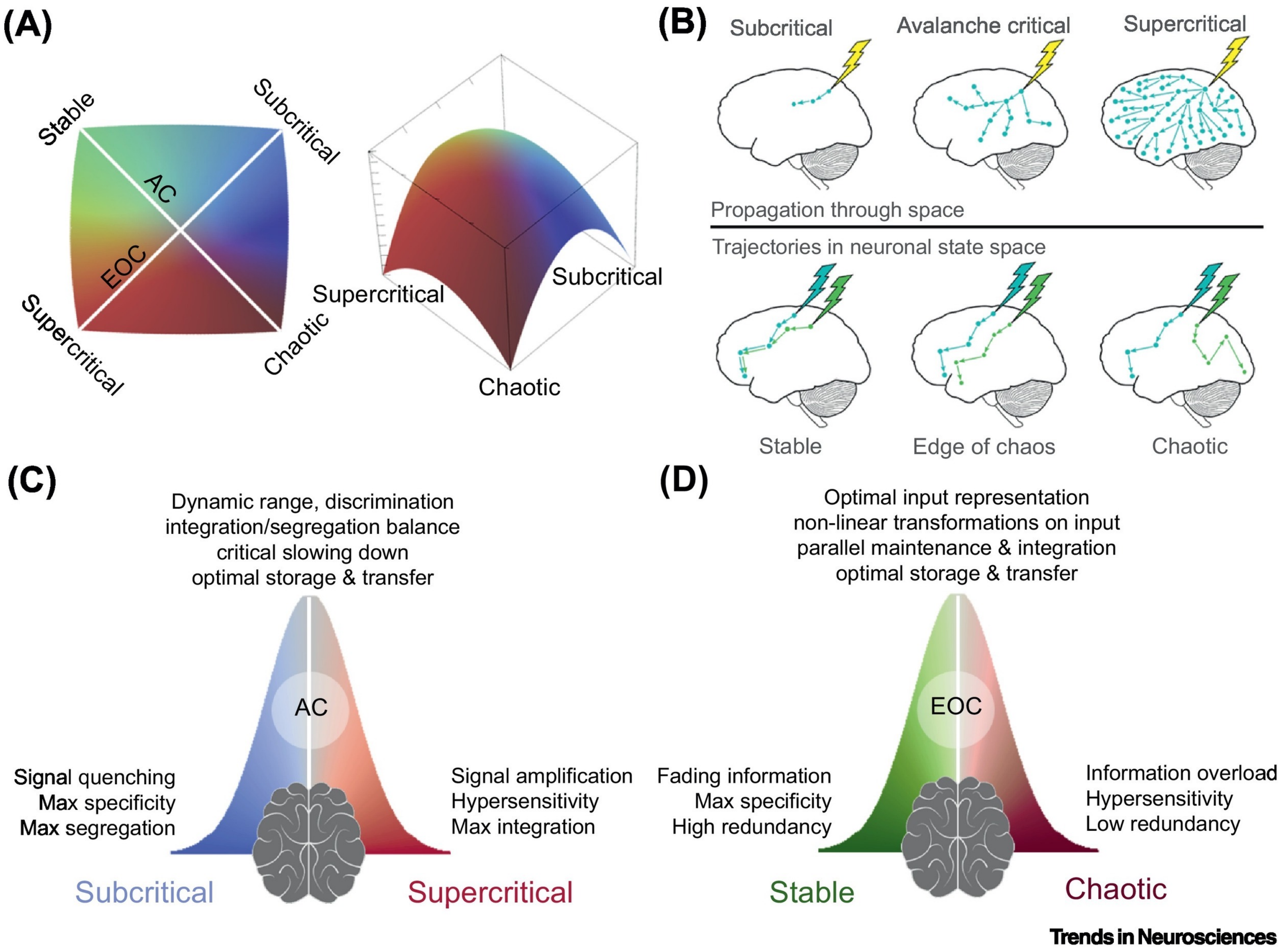


"The **distance to criticality** presents a **promising and underexploited** biological parameter for characterizing **cognitive differences** and **mental illness**."

"…these ideas underscore the relevance of the **distance to criticality** for **cognition**: this distance may be **dynamically varied** at a moment-to-moment timescale in order to **flexibly adapt** to task requirements."

O'Byrne & Jerbi. How critical is brain criticality? *Trends in Neuroscience* (2022)

We see patterns of **criticality** in **brain dynamics**

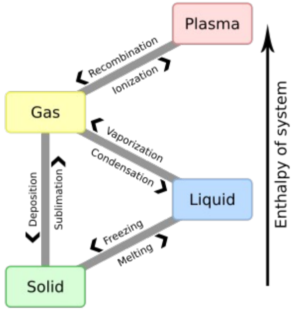


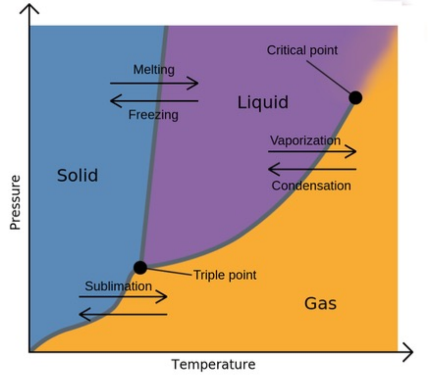
"[T]he distance to criticality may constitute a well-placed biological variable for understanding both **healthy** and **pathological changes** in cognition and behavior, one that forms a **direct mechanistic link** between **neurons and neuronal ensembles at the micro scale** and **computation at the macro scale.**"

O'Byrne & Jerbi. How critical is brain criticality? *Trends in Neuroscience* (2022)

Distance to criticality is relevant **beyond the brain**

Physics

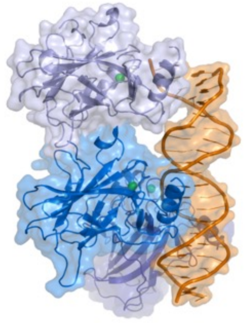


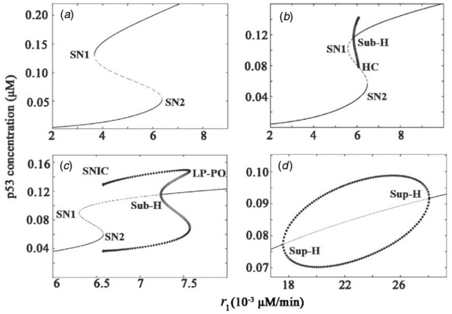


Phase transitions

Wikiepdia; Labster.com

Medicine

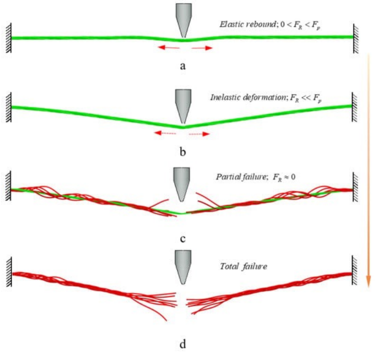


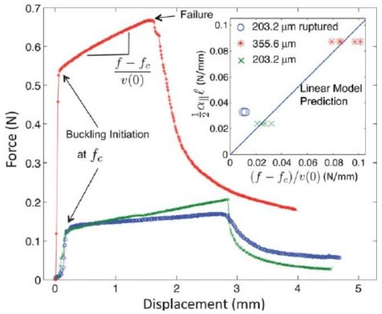


Tumor metabolism

Wikipedia; Tingzhe Sun et al. *Phys Biol* (2010)

Engineering

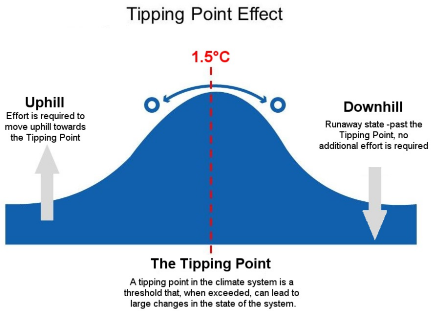


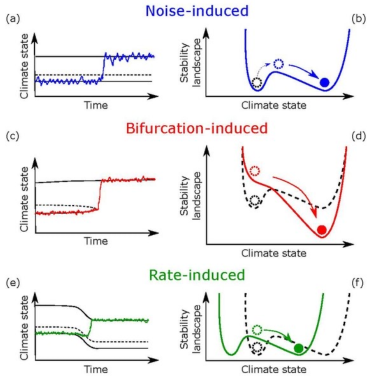


Wire buckling events

Wu et al. *Buildings* (2023); Shan et al. *Soft Matter* (2013)

Climate science

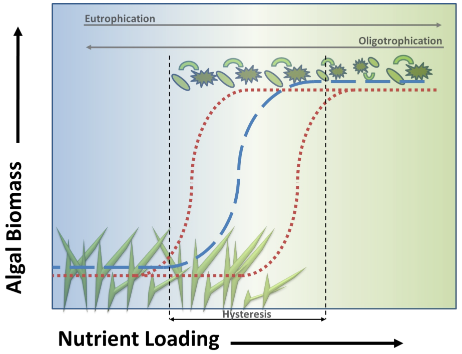




Temperature tipping points

ClimateAtAGlance.com; Wikipedia

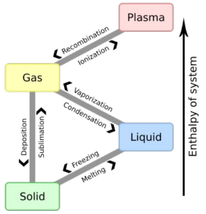
Ecology

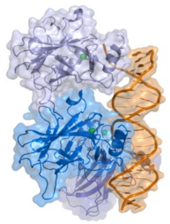


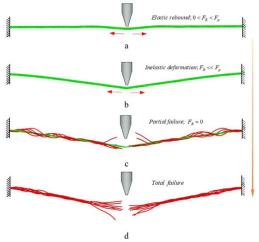
Chlorophyll in lake ecosystems

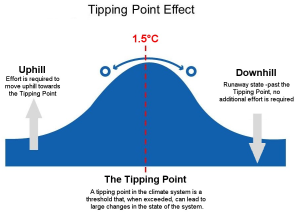
LakeScientist.com; Earth.com

How is the distance to criticality **typically measured**?







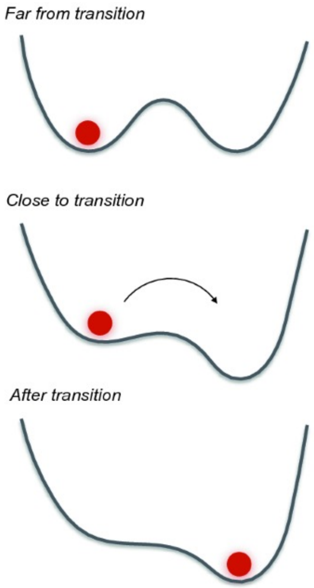


Critical slowing down

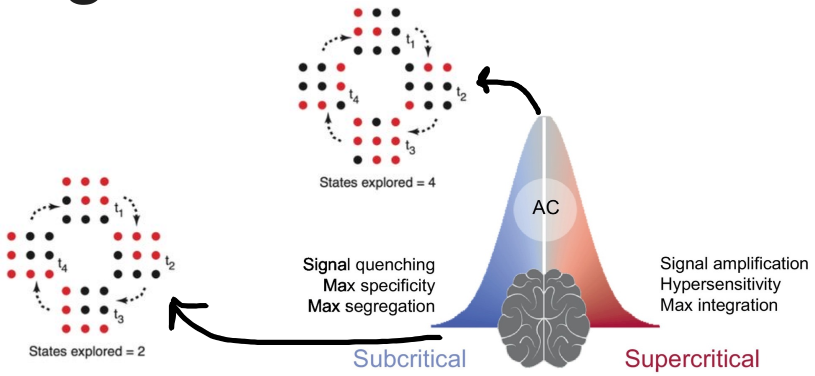
Dynamics are:

More variable

Evolving on a slower timescale



As you get closer to the critical point:



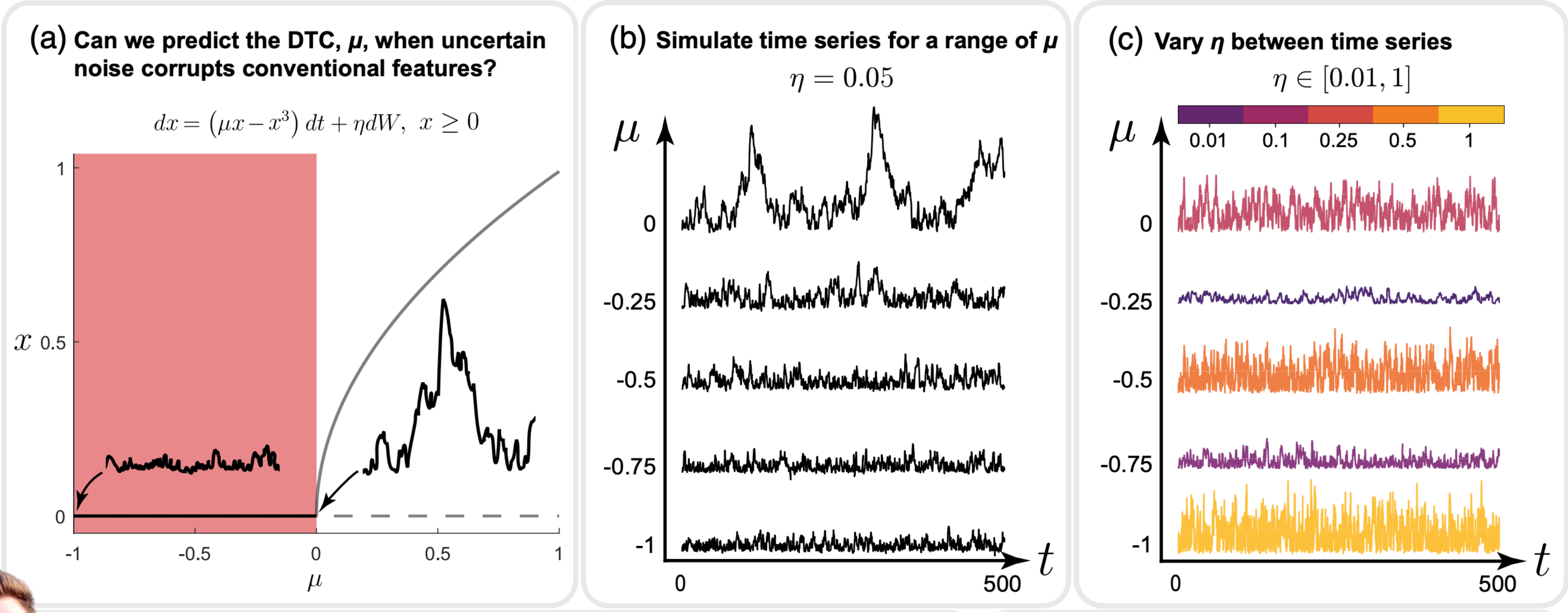
The system will explore a greater state domain closer to the critical point, which generally manifests as increase in the **standard deviation (SD) of the time series**.

Properties of the potential function naturally motivate time-series features like the **SD or lag-1 autocorrelation** to track distance to the critical point, but both these measurements are **biased by noise**.

Physical systems like the brain exhibit noise that is **not trivial** relative to the scale of their **deterministic dynamics**.

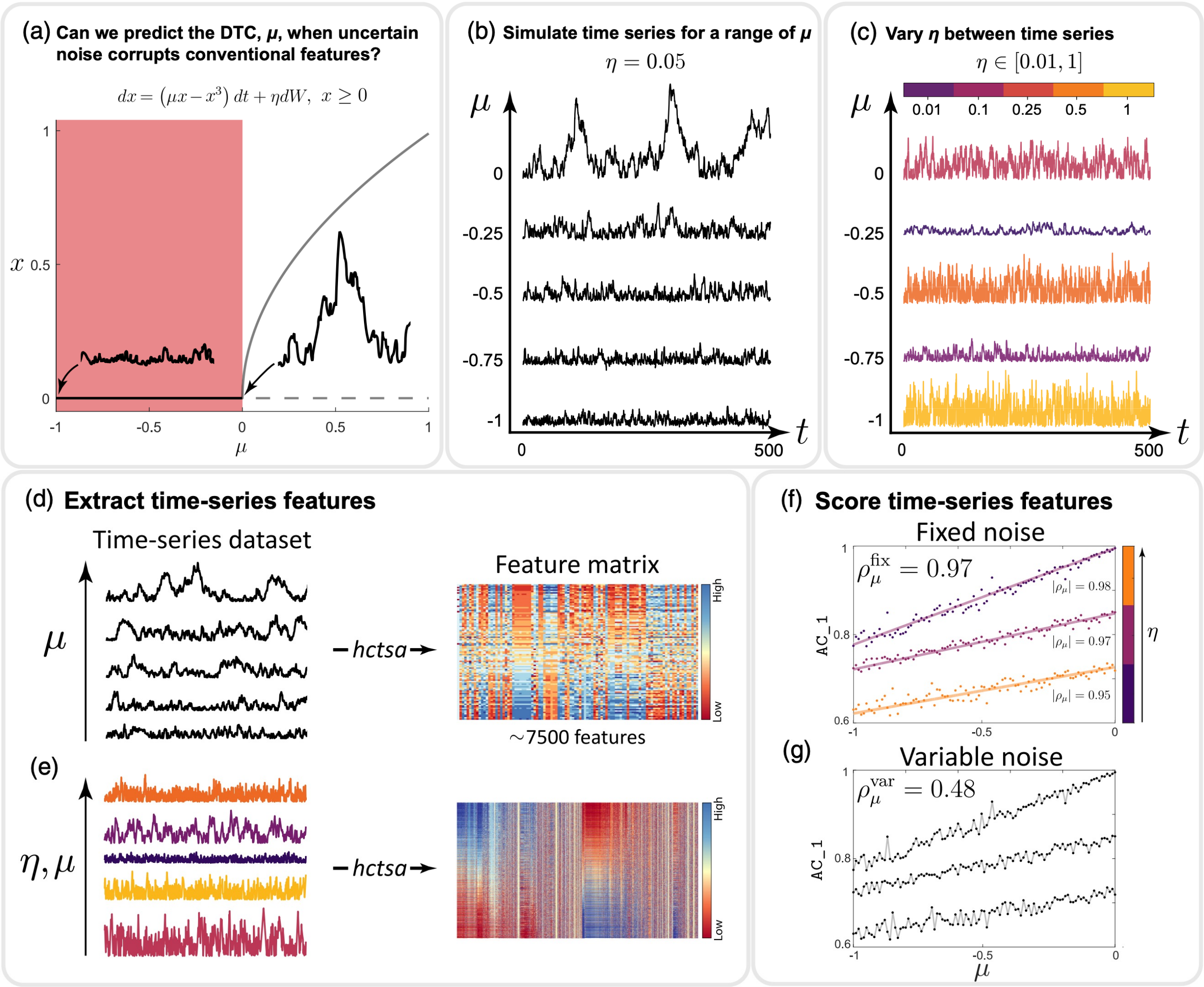
Meisel. From Neurons to Networks: Critical Slowing Down Governs Information Processing Across Vigilance States. (2022)

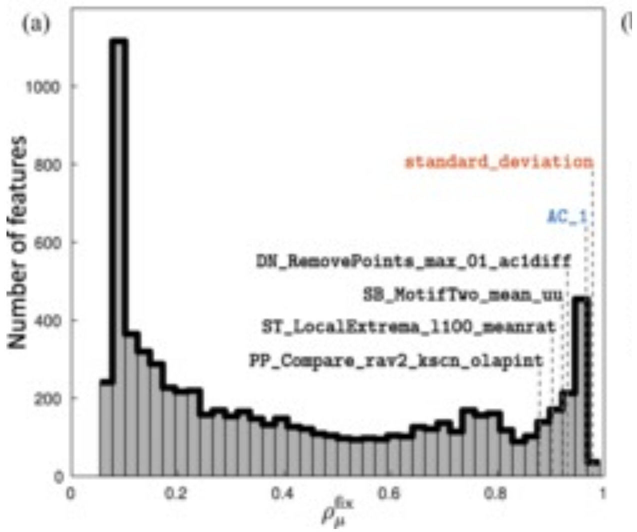
The search for a **DTC measure** that is **robust** across levels of **dynamical noise**

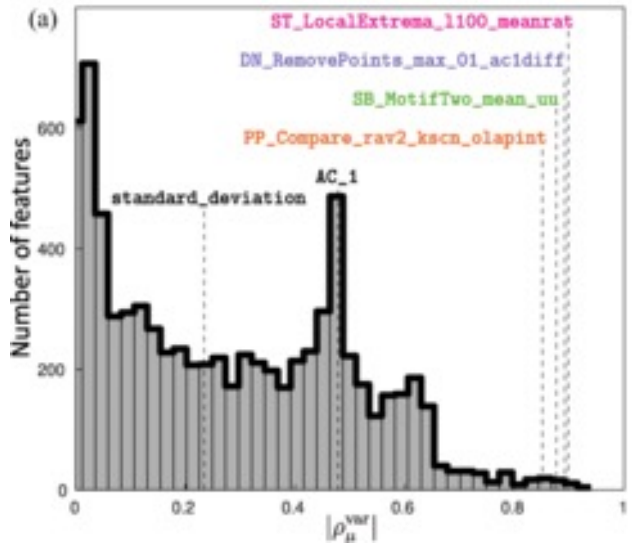


Harris, Gollo & Fulcher. Tracking the Distance to Criticality in Systems with Unknown Noise. *Phys Rev X* (2024)

The search for a **DTC measure** that is **robust** across levels of **dynamical noise**



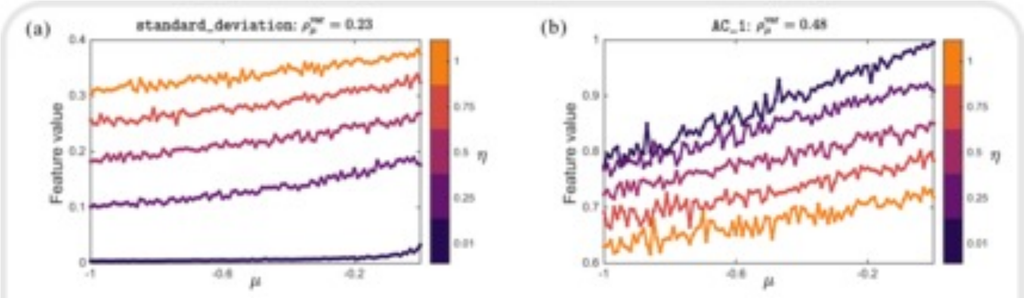




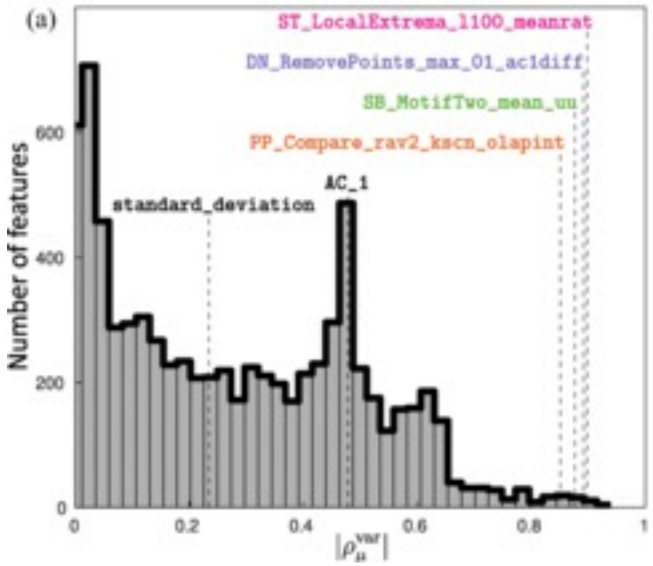
Harris, Gollo & Fulcher. Tracking the Distance to Criticality in Systems with Unknown Noise. *Phys Rev X* (2024)

Conventional DTC measures are **sensitive to noise**

SD



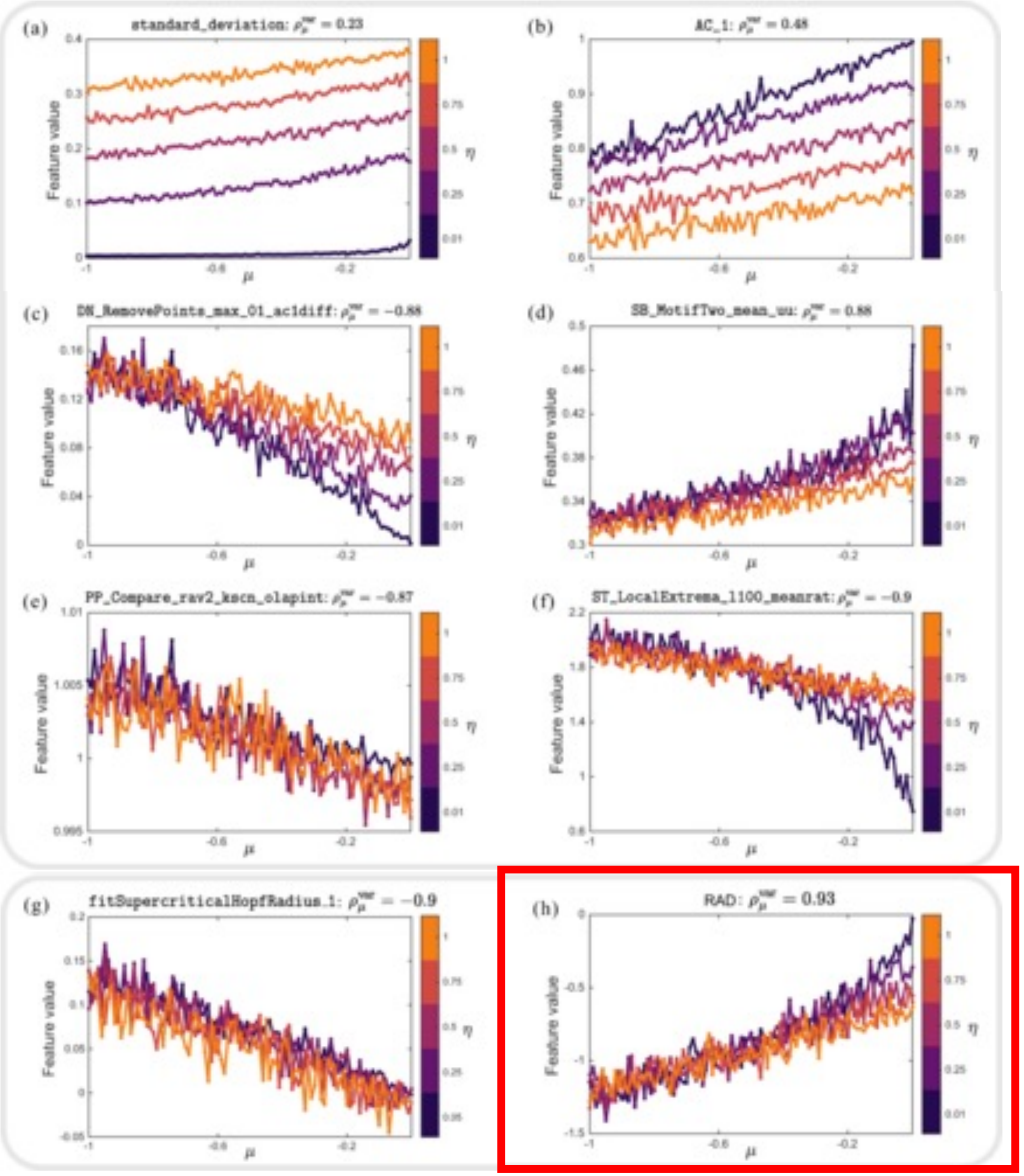
AC1



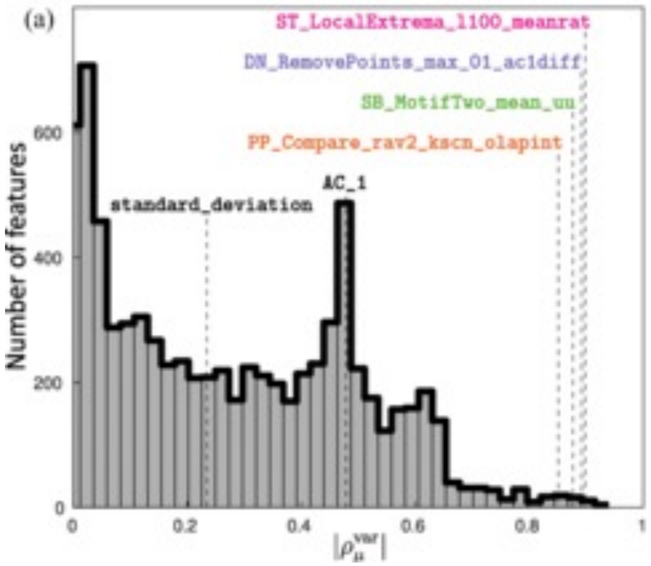
📗 Harris, Gollo & Fulcher. Tracking the Distance to Criticality in Systems with Unknown Noise. *Phys Rev X* (2024)

…but new **noise-robust time-series features** enter the villa

SD



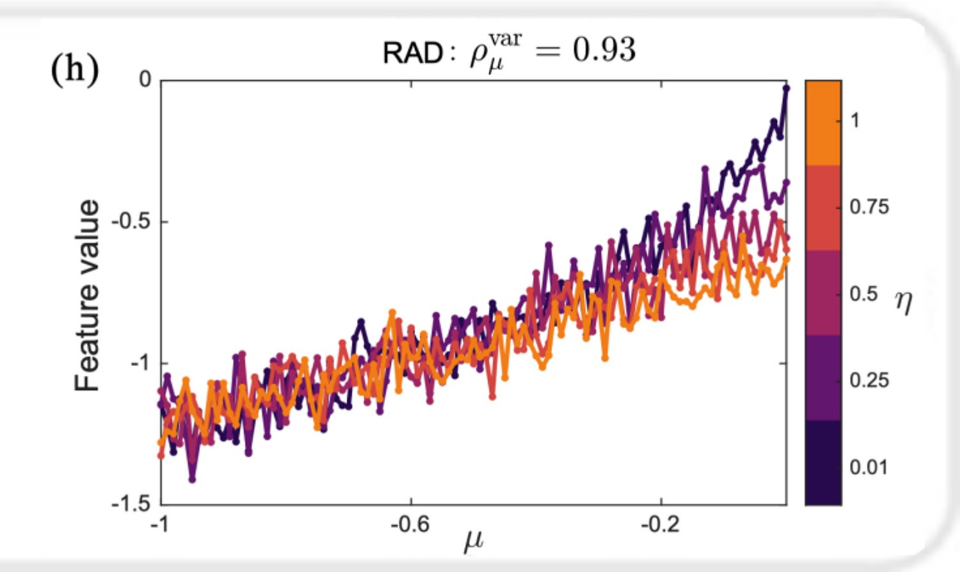
AC1

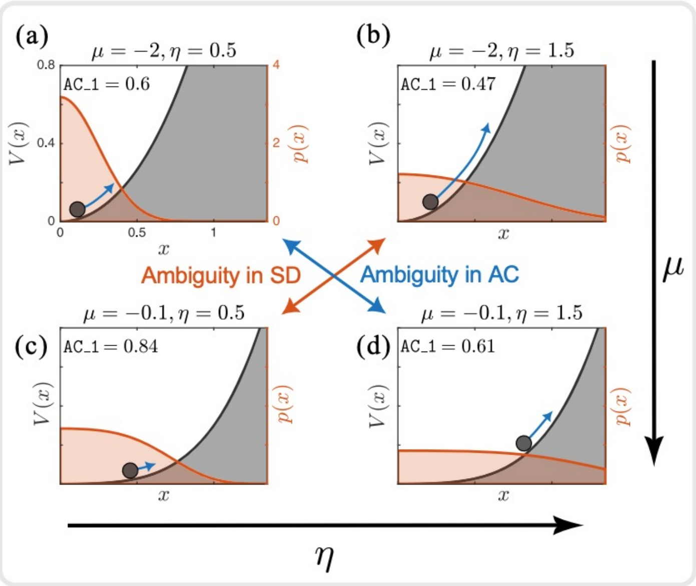


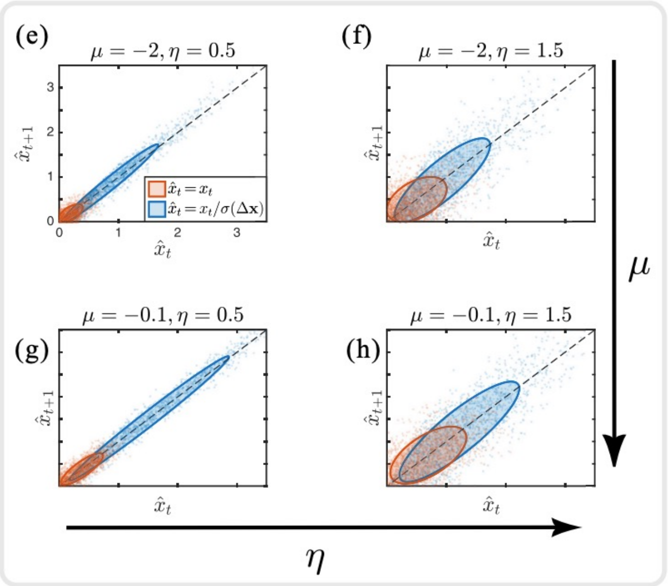
Brendan & co inspected properties of these noise-robust algorithms (identified via **data-driven analysis**!) to propose a new noise-robust index of the distance to criticality:
Rescaled autodensity

Harris, Gollo & Fulcher. Tracking the Distance to Criticality in Systems with Unknown Noise. *Phys Rev X* (2024)

…but new **noise-robust time-series features** enter the villa



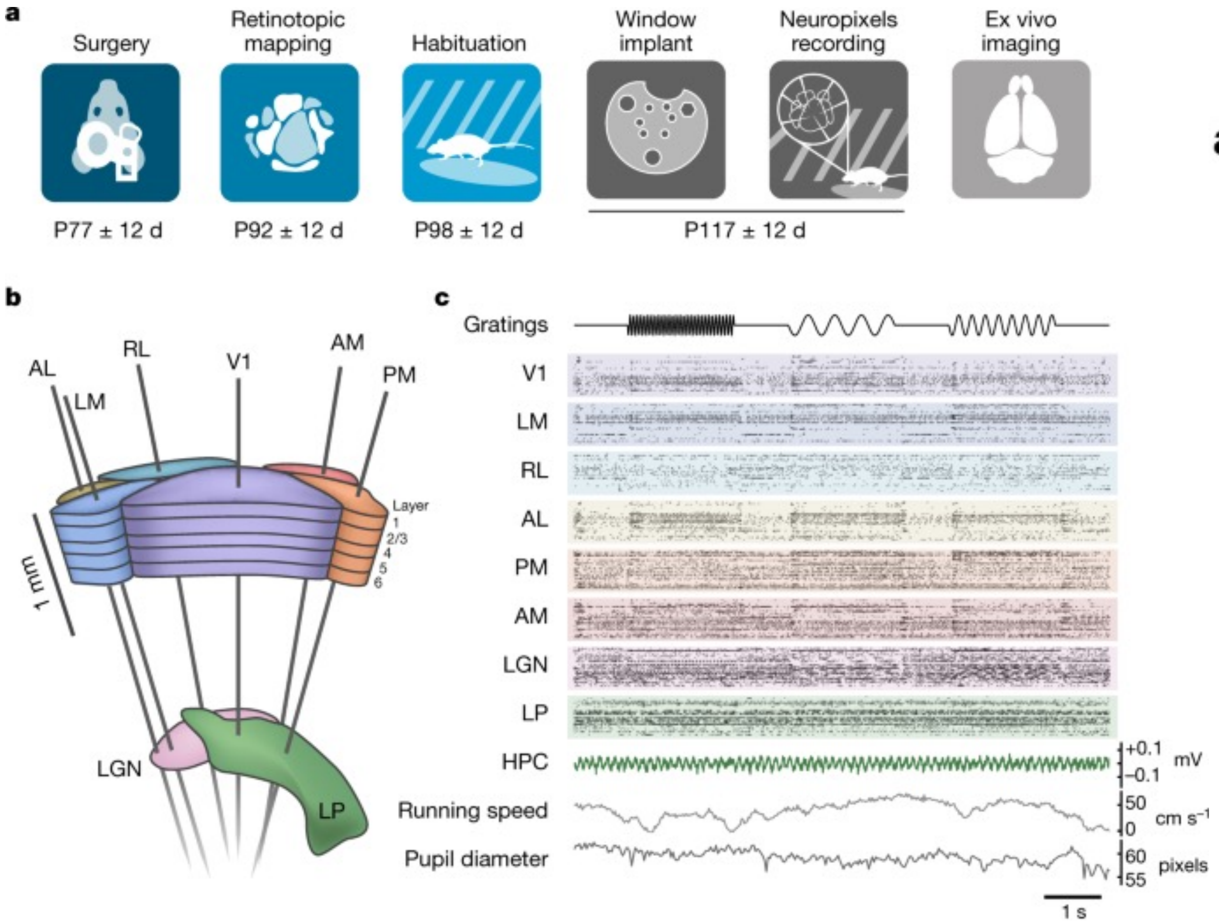


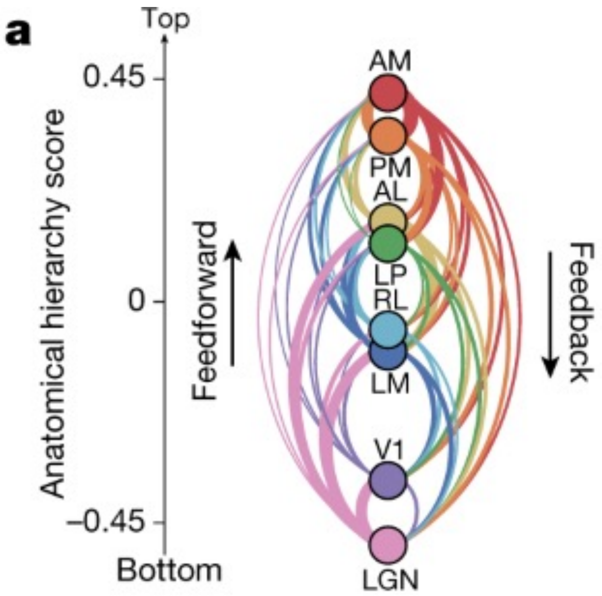


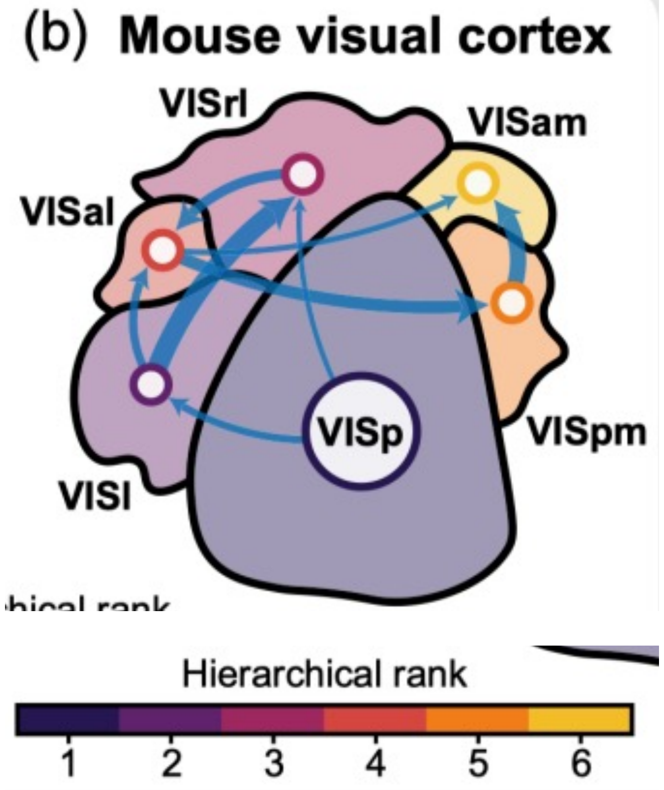
Rescaling time-series values by the spread of differenced values corrects for the confounding effect of a **variable-noise amplitude**, by capturing the **shape of the invariant density** (which depends on both the DTC and the noise amplitude) relative to the **spread of fast fluctuations** (which depends only on the noise amplitude)

Harris, Gollo & Fulcher. Tracking the Distance to Criticality in Systems with Unknown Noise. *Phys Rev X* (2024)

Application: Does **distance to criticality** vary across the **visual hierarchy**?



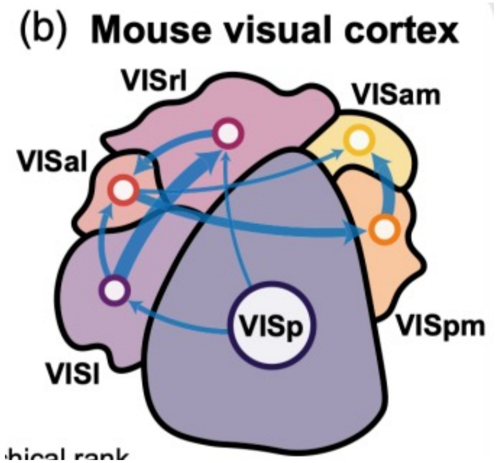


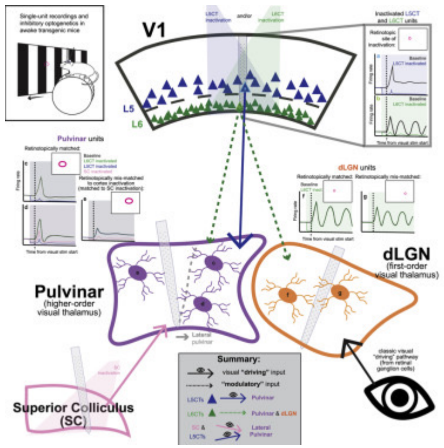


Siegle et al. *Nature* (2021); Harris, Gollo & Fulcher. *Phys Rev X* (2024)

Application: Does **distance to criticality** vary across the **visual hierarchy**?

Hypothesis: **higher-order** regions exhibit **longer timescales** of neuronal activity because they are **closer to the critical point**





This is a good setting to test the noise robustness of RAD because we see variable noise levels across brain regions, attributable to:

- Differences in **thalamic drives**

Kirchgessner et al. *Current Biology (2021);* Harris, Gollo & Fulcher. *Phys Rev X* (2024)

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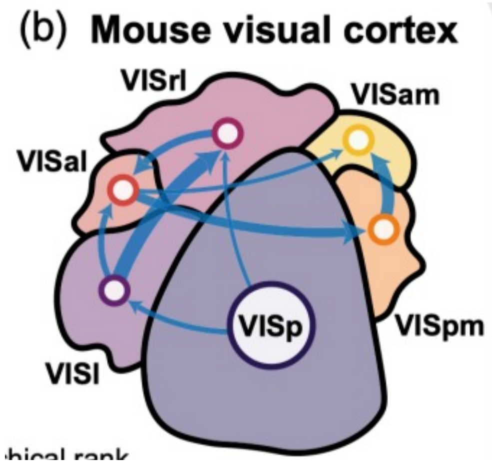

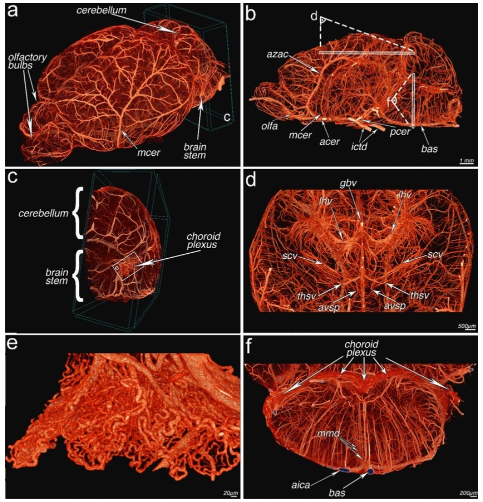

This is a good setting to test the noise robustness of RAD because we see variable noise levels across brain regions, attributable to:

- Differences in thalamic drives
- Differences in **adjacent vasculature**

📗 Hluschuk et al. *Brain Structure and Function* (2020); Harris, Gollo & Fulcher. *Phys Rev X* (2024)

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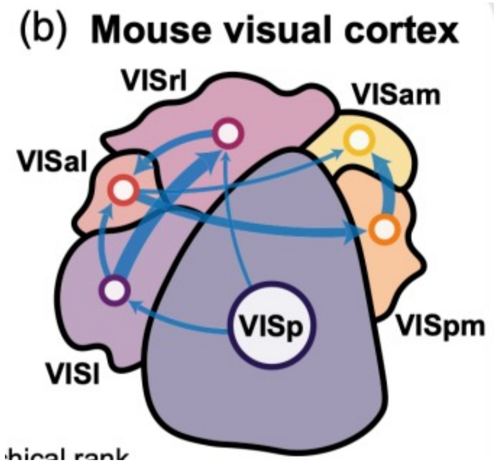

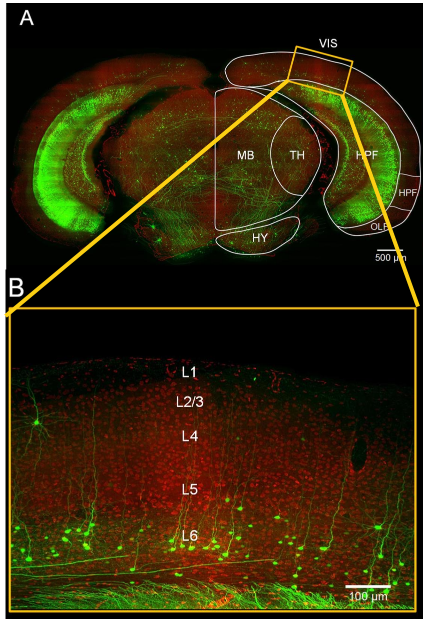

This is a good setting to test the noise robustness of RAD because we see variable noise levels across brain regions, attributable to:

- Differences in thalamic drives
- Differences in adjacent vasculature
- Differences in **cytoarchitecture**

Zhang et al. *Front Neurosci* (2019); Harris, Gollo & Fulcher. *Phys Rev X* (2024)

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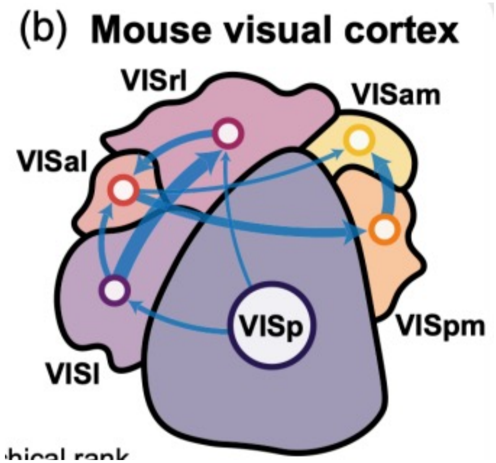
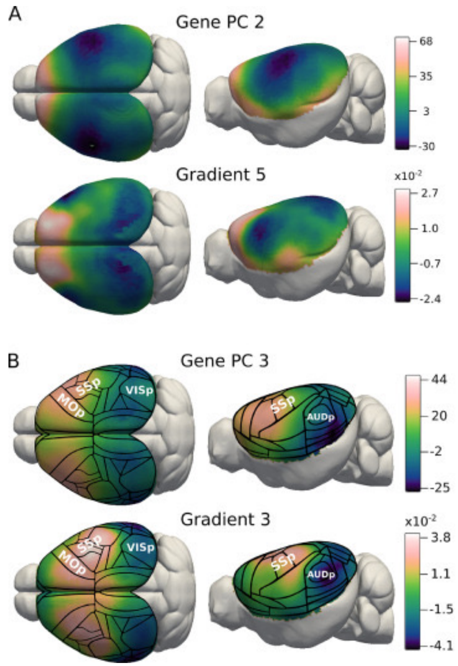


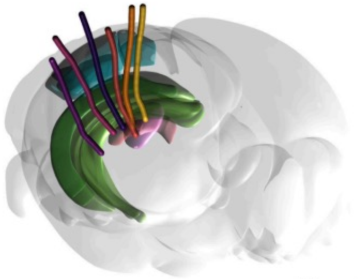


This is a good setting to test the noise robustness of RAD because we see variable noise levels across brain regions, attributable to:

- Differences in thalamic drives
- Differences in adjacent vasculature
- Differences in cytoarchitecture
- Differences in **transcriptomic and neuromodulatory gradients**

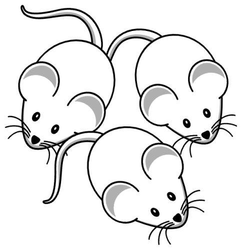
📗 Huntenberg et al. *NeuroImage* (2021); Harris, Gollo & Fulcher. *Phys Rev X* (2024)

Application: Does **distance to criticality** vary across the **visual hierarchy**?



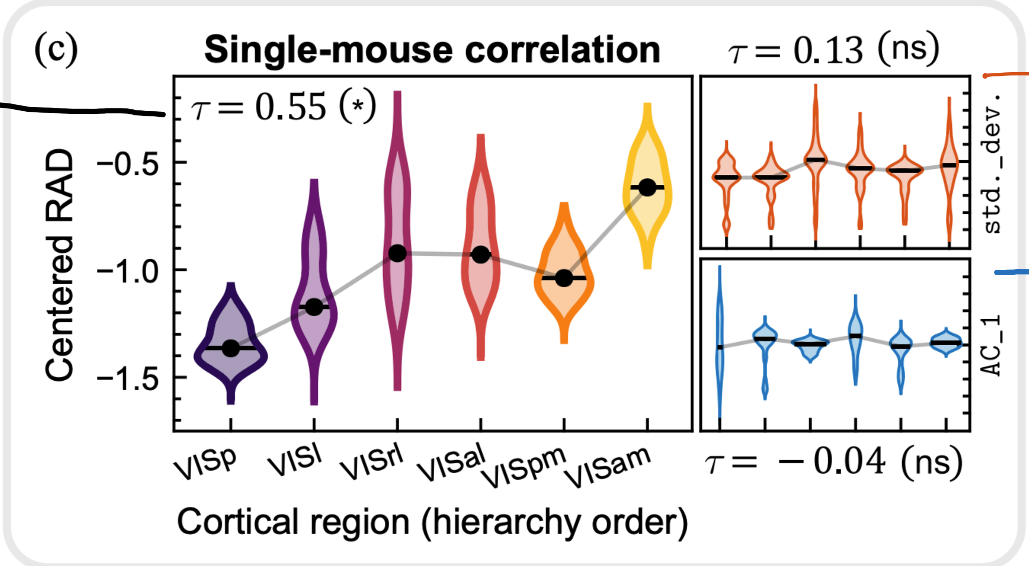
6 NeuroPixels probes

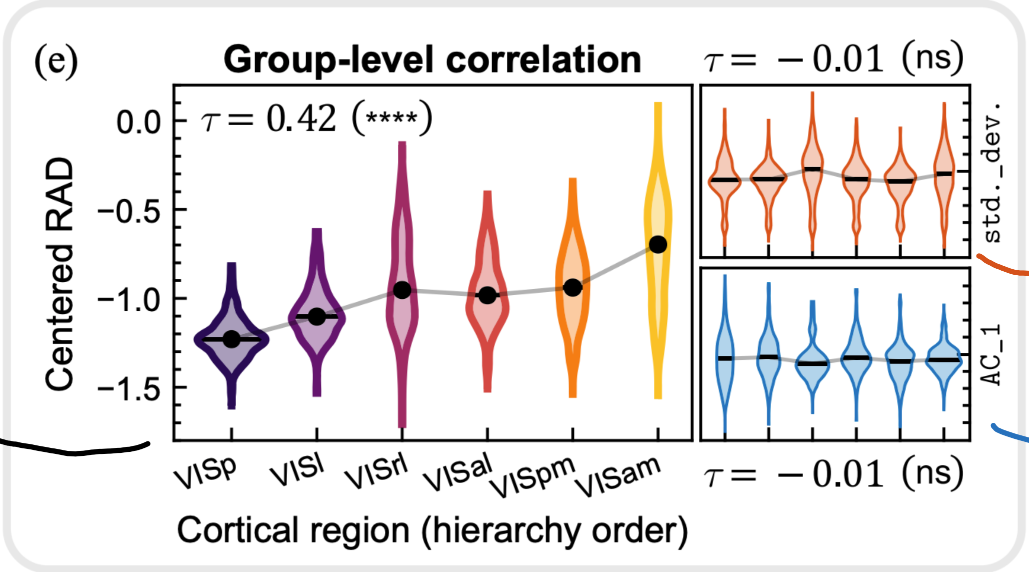
×



39 mice

Across mice, RAD **successfully captures** the variation in **visual cortex hierarchy**



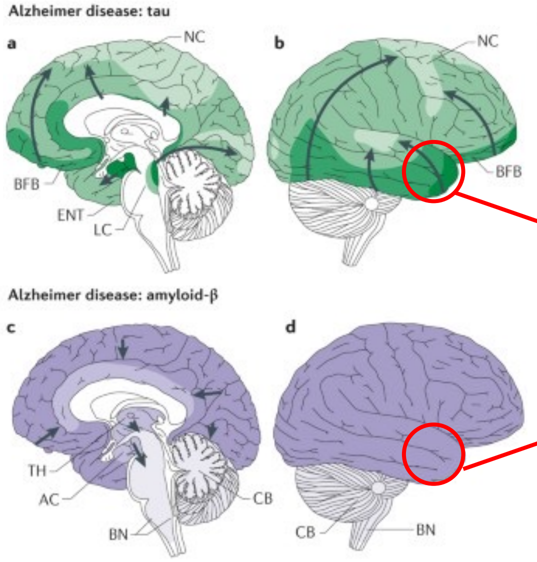


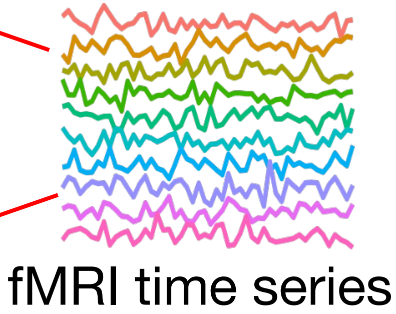
Traditional criticality metrics, SD and AC1, **fail to track** this hierarchical structure

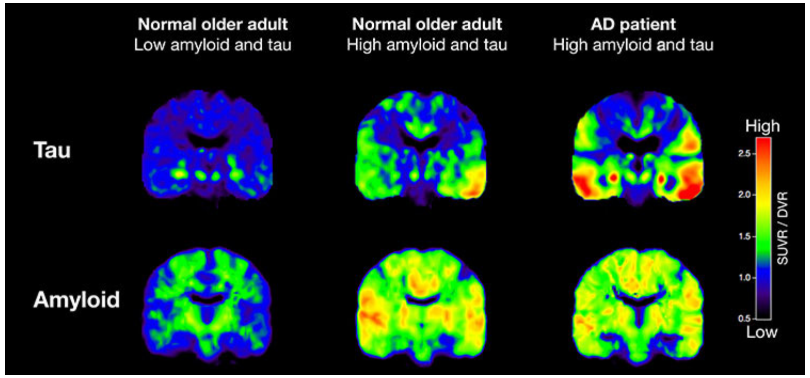
Harris, Gollo & Fulcher. Tracking the Distance to Criticality in Systems with Unknown Noise. *Phys Rev X* (2024)

My **final PhD projects** with hctsa + pyspi

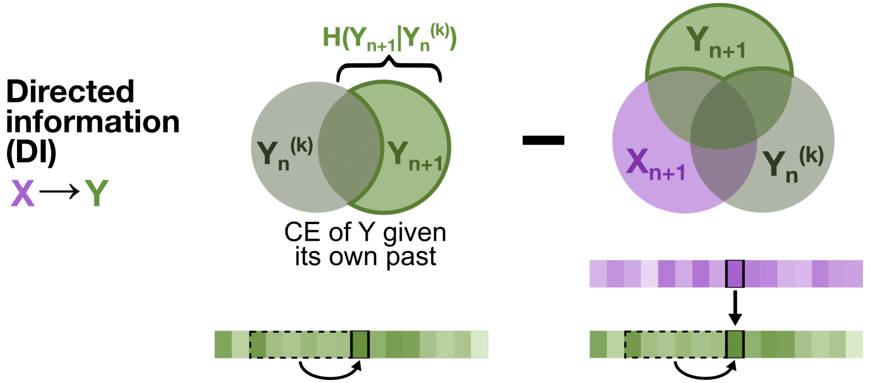
Project #1: Characterizing the effects of **Alzheimer's disease pathology** on **localized region-specific dynamics**

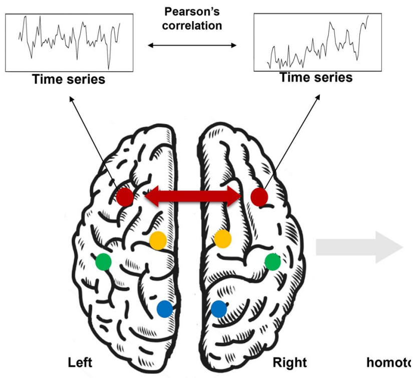


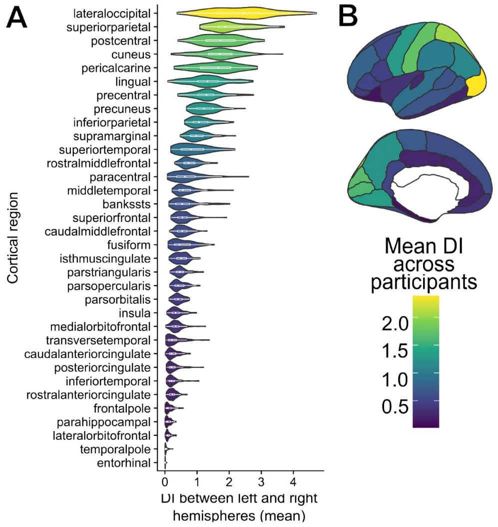




Project #2: **Directed information** flow between the left and right hemispheres in health and disease

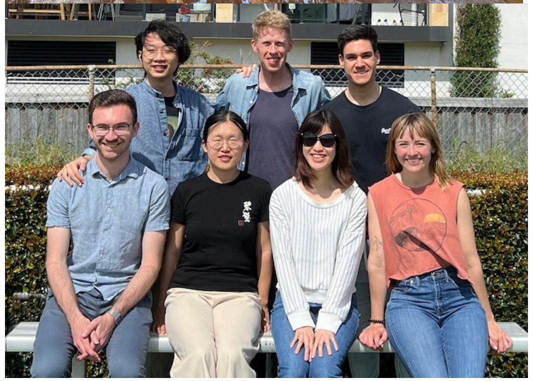






Brettschneider et al. *Nat Rev Neuro,* 2015; Jin et al. *Front Neurosci* (2020)

Thanks to my research groups as always 😊



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THE UNIVERSITY OF SYDNEY

shinelab

github.com/anniegbryant/CSYS5040_Demo

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