Resting-state fMRI

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Section on Functional Imaging Methods

National Institute of Mental Health, NIH, Bethesda, MD

NIMH fMRI Summer Course

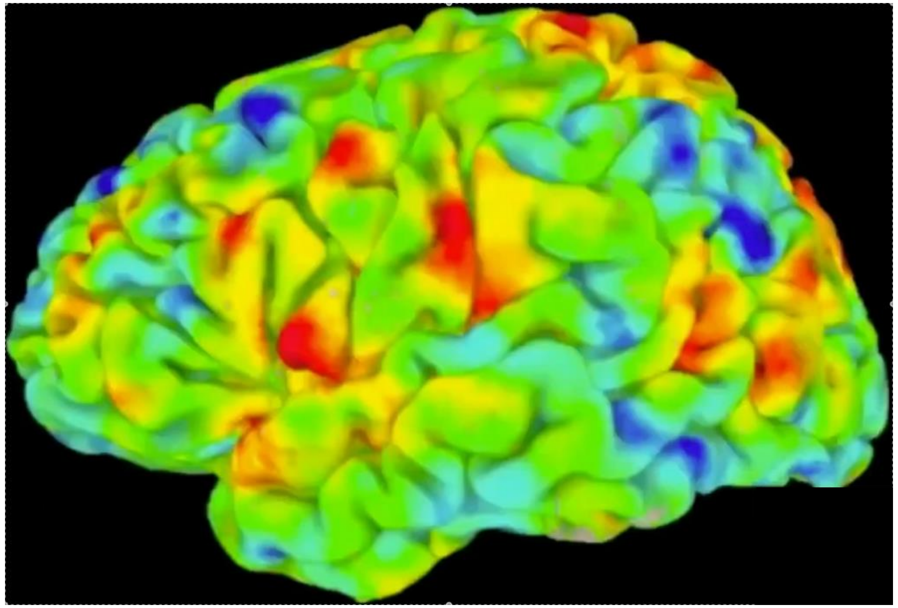
July 16, 2026

NIH National Institute of Mental Health

Agenda

+

"Try not to move, remain awake and let your mind wander freely"



Historical overview of the field of resting-state fMRI

Review — nature

The history and future of resting-state functional magnetic resonance imaging

https://doi.org/10.1038/s41586-025-08953-9

Bharat B. Biswal[1,2] & Lucina Q. Uddin[3,4]

- **Basic description of analytical methods**
- **Emphasis on what rs-fMRI has taught us about functional organizational principles of the brain**
- **Open debates/challenges**
  - Static vs. Dynamic
  - Interpretation

This lecture will not discuss:

- Pre-processing of resting-state data
  → AFNI Bootcamp Lectures
- Functional connectivity methodology
  → Josh's lecture next week

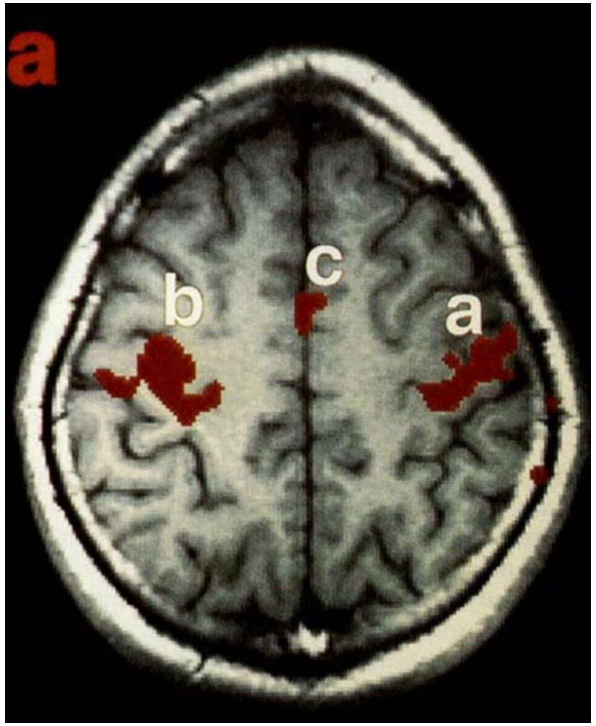
History |

1995	2001	2003	2010	2013	2016	2025
First rsfMRI functional connectivity paper	Default mode hypothesis of brain function	Network analysis of default mode hypothesis	Human Connectome Project and neuroimaging … initiatives begin	rsfMRI is first used to study functional connectivity … fetal brain	Publication of best practices in data analysis and sharing in … using MRI	Multiple ongoing population neuroscience data collection efforts continue to make … researchers

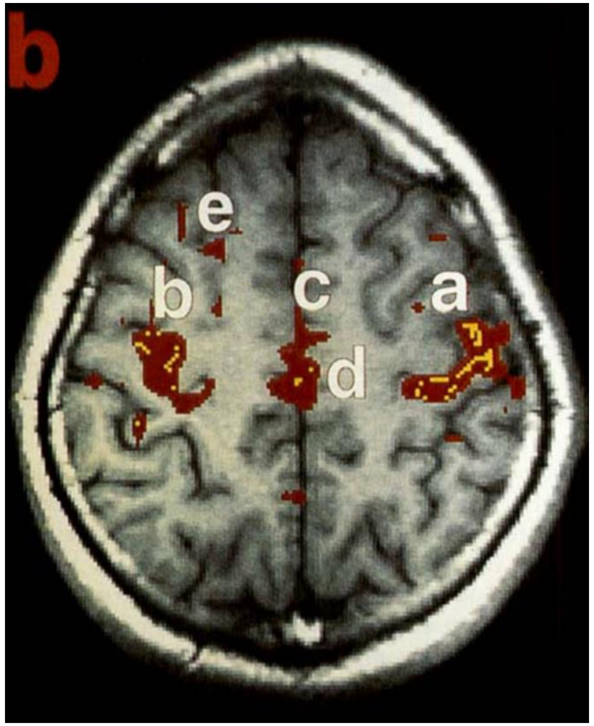
Biswal & Uddin (2025) Nature

Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI

Bharat Biswal, F. Zerrin Yetkin, Victor M. Haughton, James S. Hyde



Bilateral Finger Movement



Resting Brain

"This report demonstrates that functionally related brain regions exhibit correlation of low frequency fluctuations in the resting state… It is concluded that low frequency fluctuation of blood flow and oxygenation is indeed a neurophysiological index."

Biswal et al. (1995) MRM

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Biswal & Uddin (2025) Nature

"unconstrained brain activity can be understood as a 'default mode of brain function' that is temporarily suspended during goal directed behaviors."

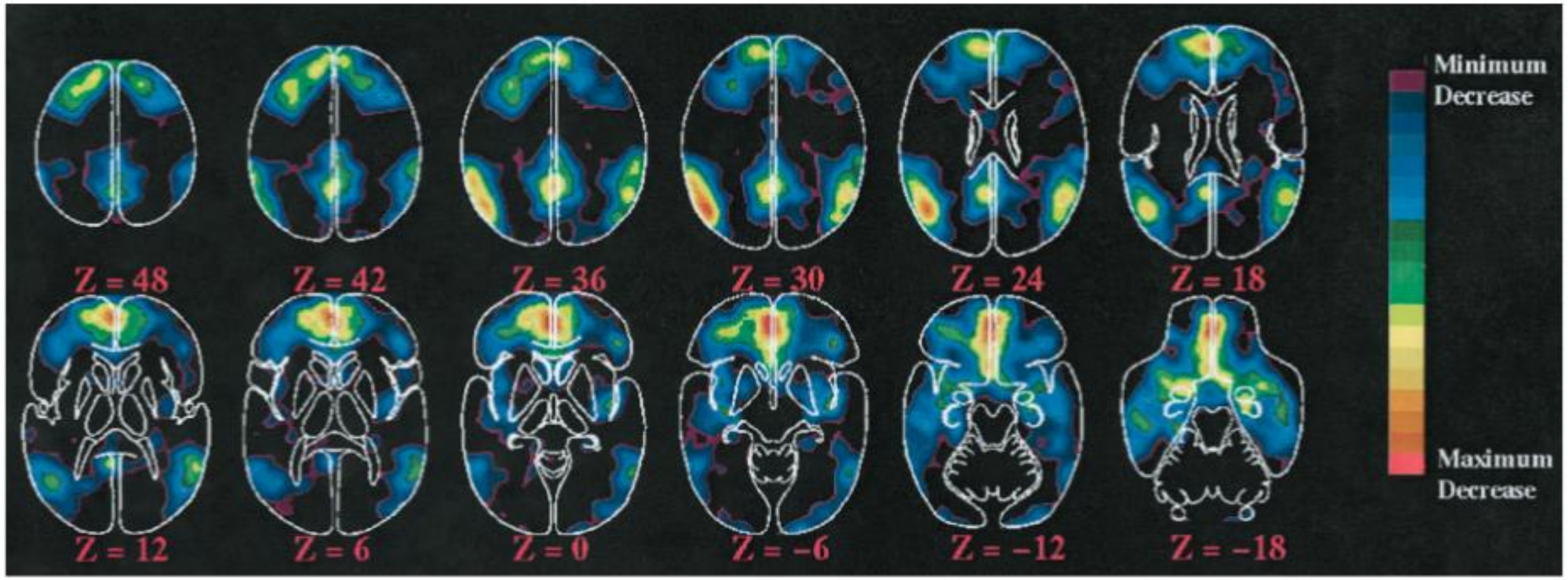

Fig. 1. Regions of the brain regularly observed to decrease their activity during attention demanding cognitive tasks. These data represent a metaanalysis of nine functional brain imaging studies performed with PET and analyzed by Shulman and colleagues (49). In each of the studies included, the subjects processed a particular visual image in the task state and viewed it passively in the control state. One hundred thirty-two individuals contributed to the data in these images. These decreases appear to be largely task independent. The images are oriented with the anterior at the top and the left side to the reader's left. The numbers beneath each image represent the millimeters above or below a transverse plane running through the anterior and posterior commissures (26).

Raichle et al. (2001) PNAS

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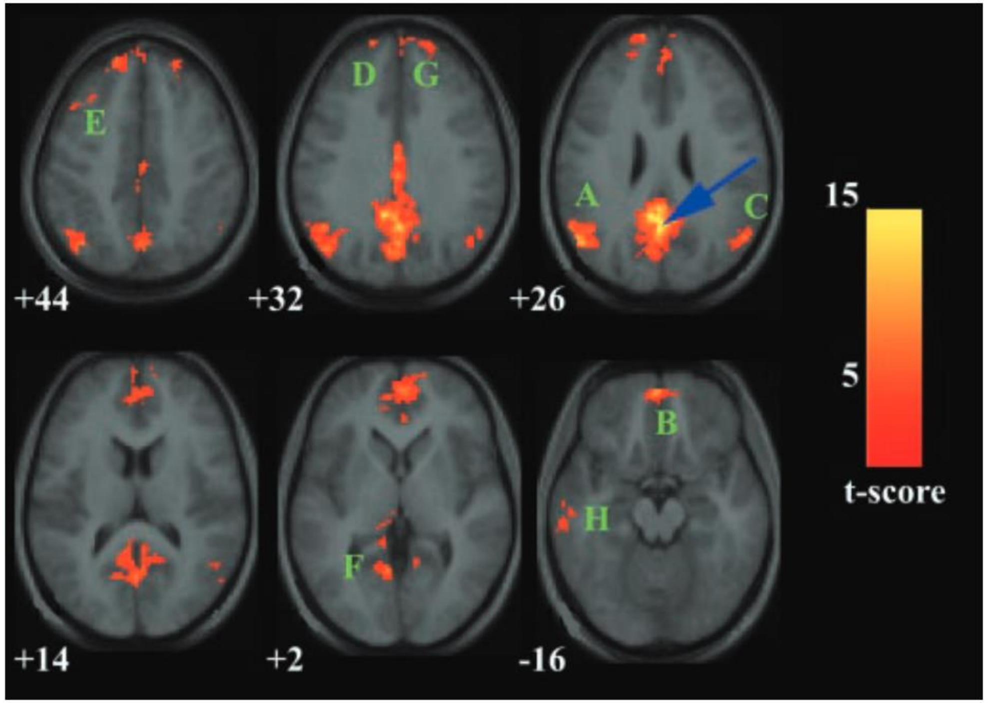
Biswal & Uddin (2025) Nature



"In summary, we have provided compelling evidence for the existence of a default mode network in the resting state.

Greicius et al. (2003) PNAS

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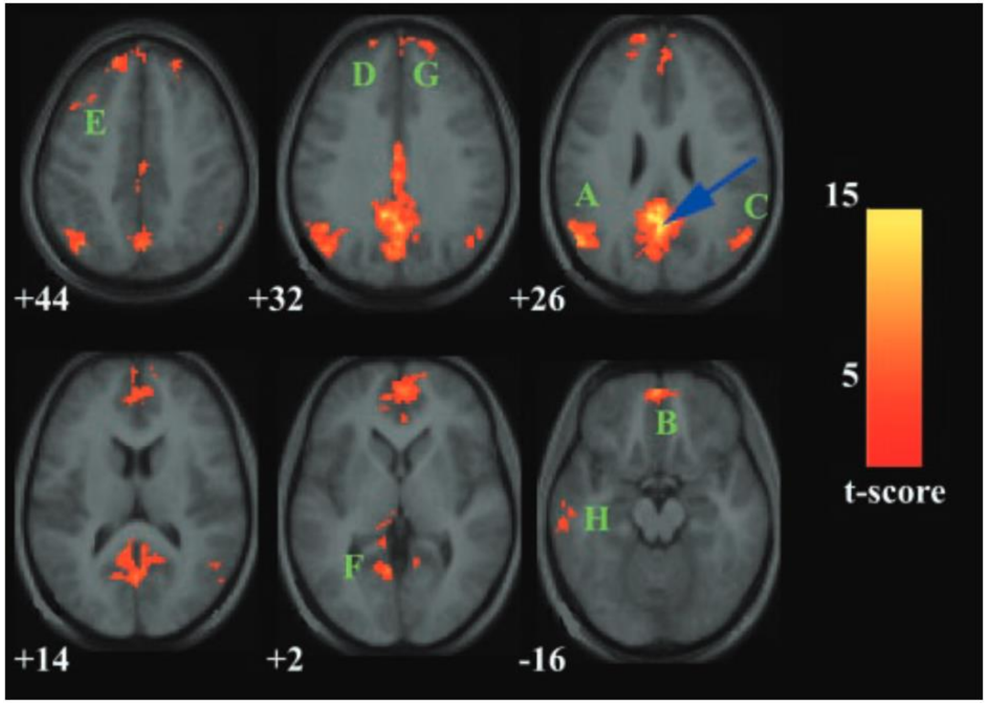

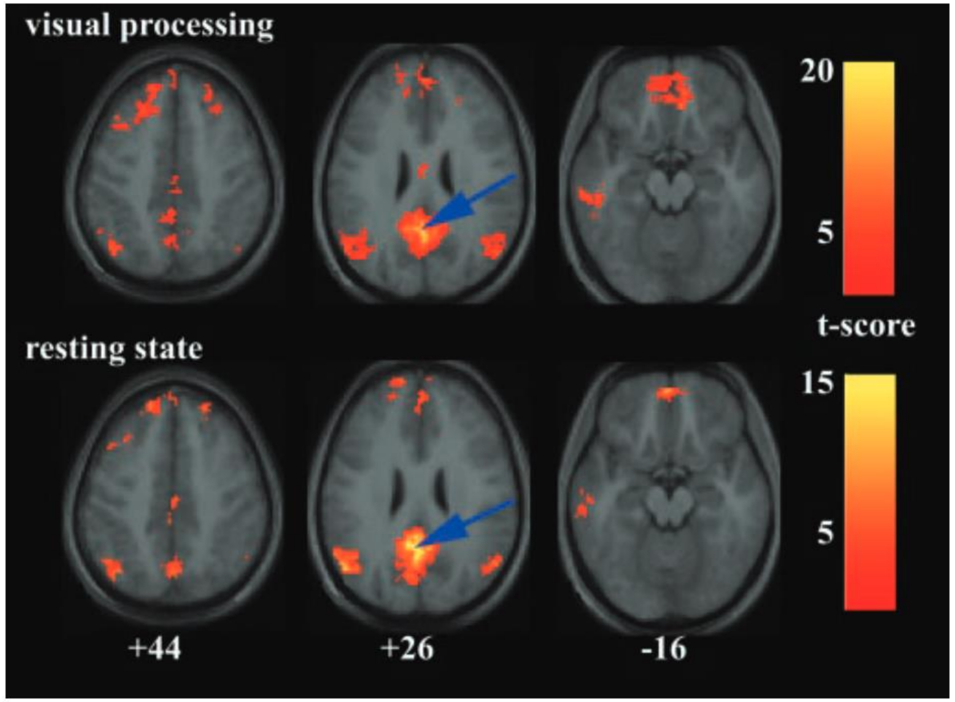

"In summary, we have provided compelling evidence for the existence of a default mode network in the resting state. We have also shown that this network is minimally disrupted during a visual processing task..."

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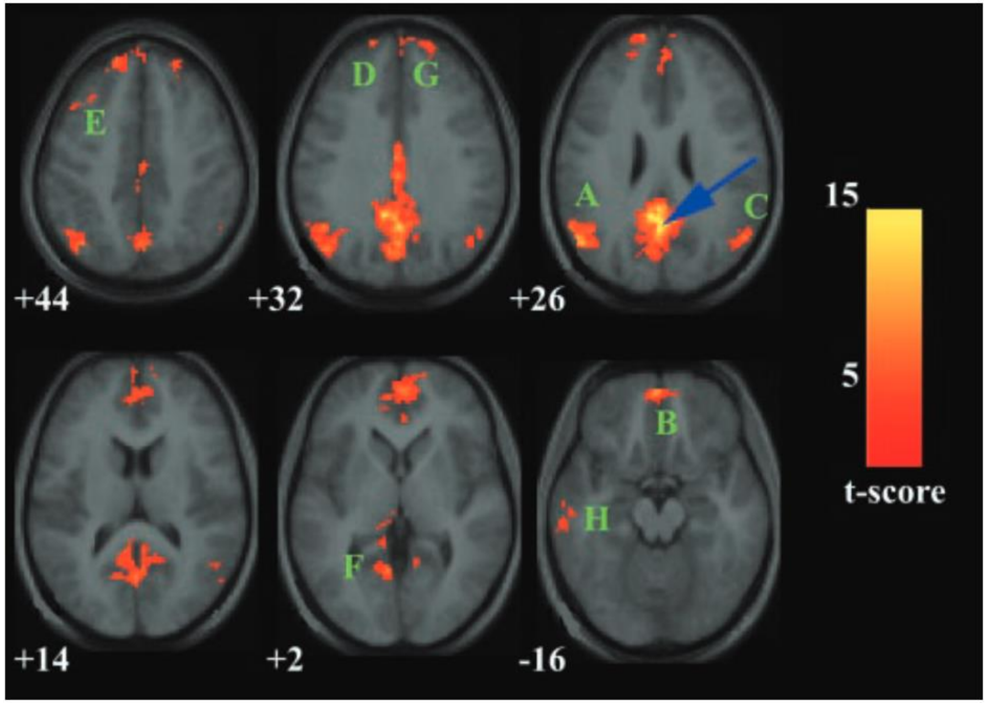
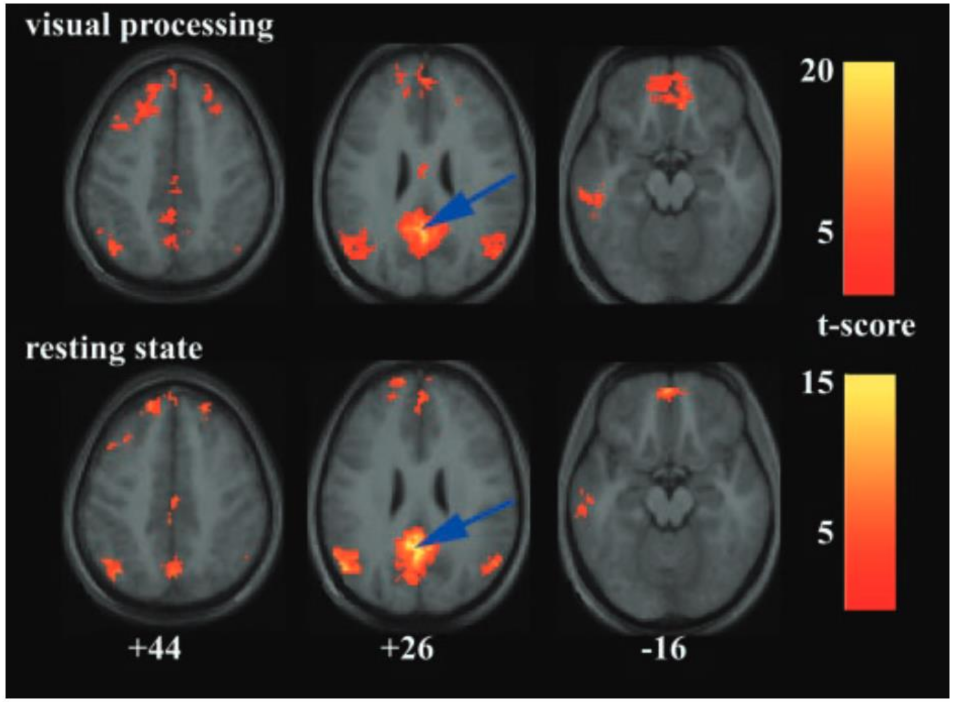
Biswal & Uddin (2025) Nature





“In summary, we have provided compelling evidence for the existence of a default mode network in the resting state. We have also shown that this network is minimally disrupted during a visual processing task... Although the precise mental processes supported by the default mode network remain to be elucidated, we suggest that the retrieval and manipulation of episodic memories and semantic knowledge are likely candidates”

Greicius et al. (2003) PNAS

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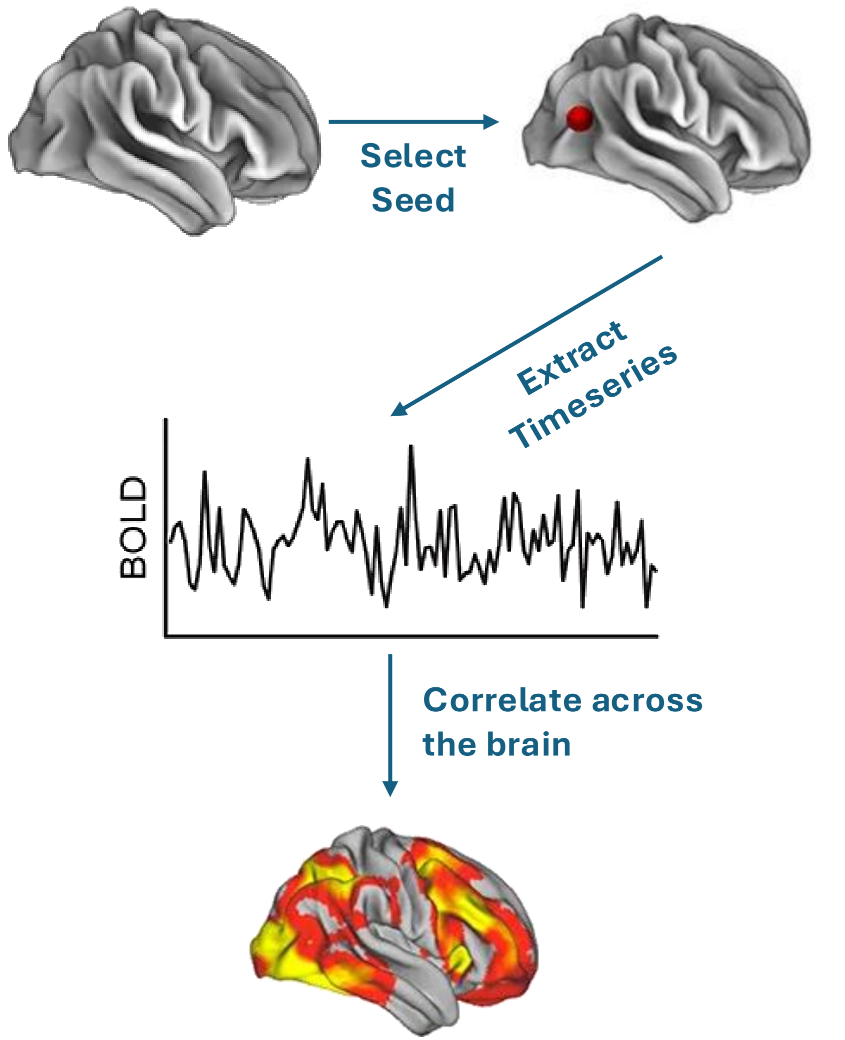
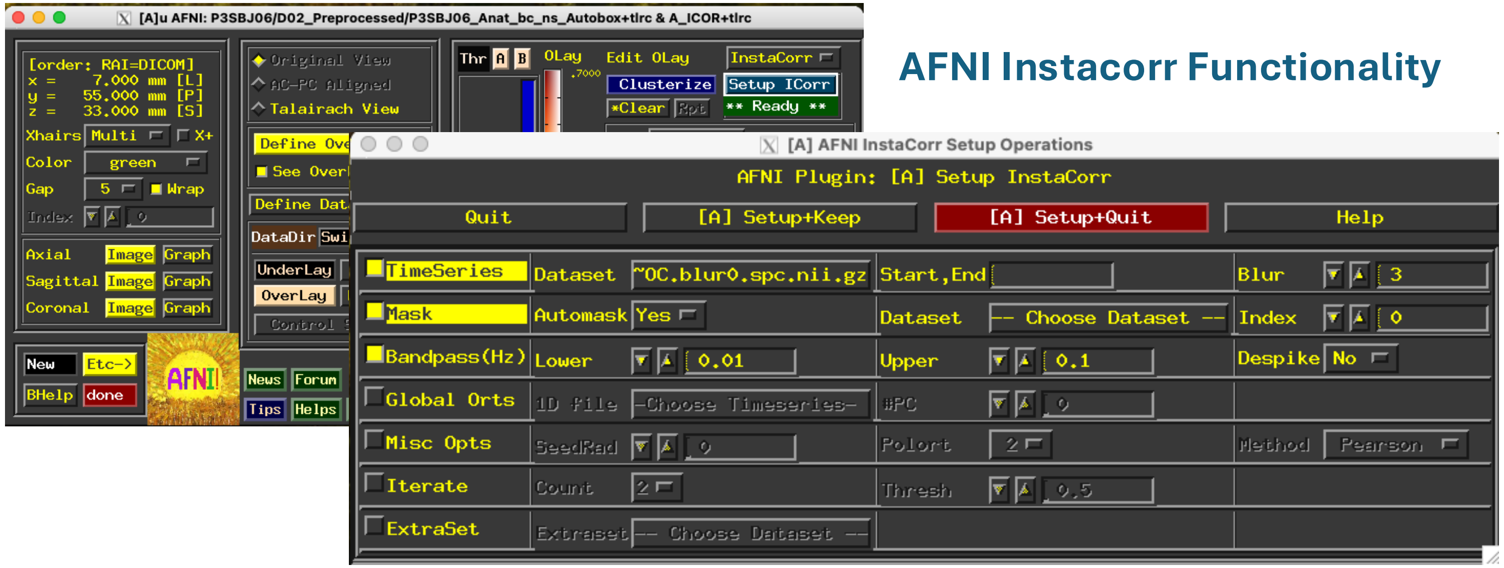
Biswal & Uddin (2025) Nature

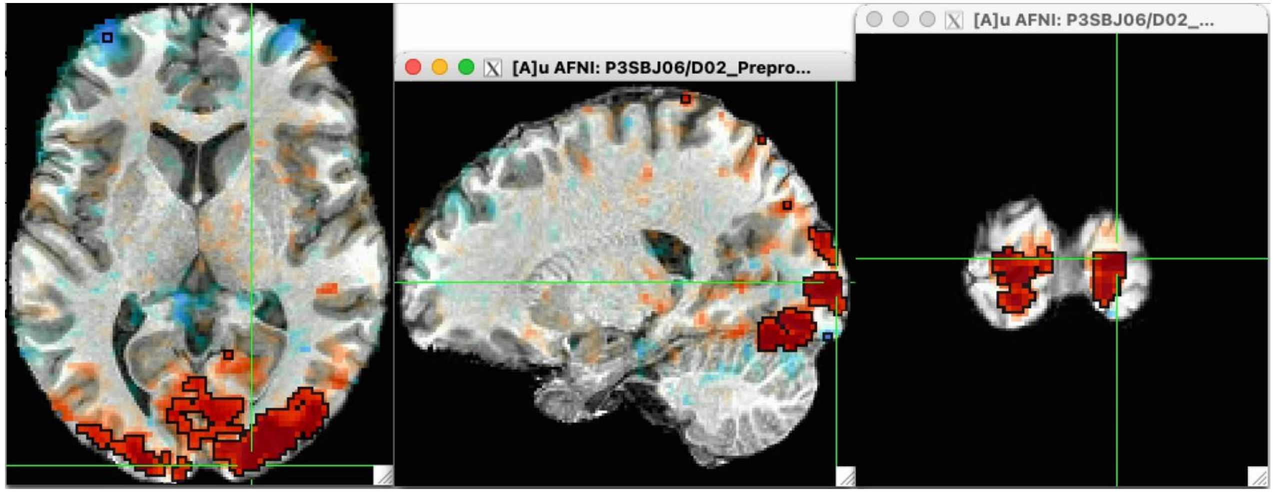
SEED-BASED FUNCTIONAL CONNECTIVITY



https://anastasija-v-petrovic.medium.com/an-overview-of-functional-connectomics-resting-state-fmri-8aca8b2446cb

AFNI Instacorr Functionality





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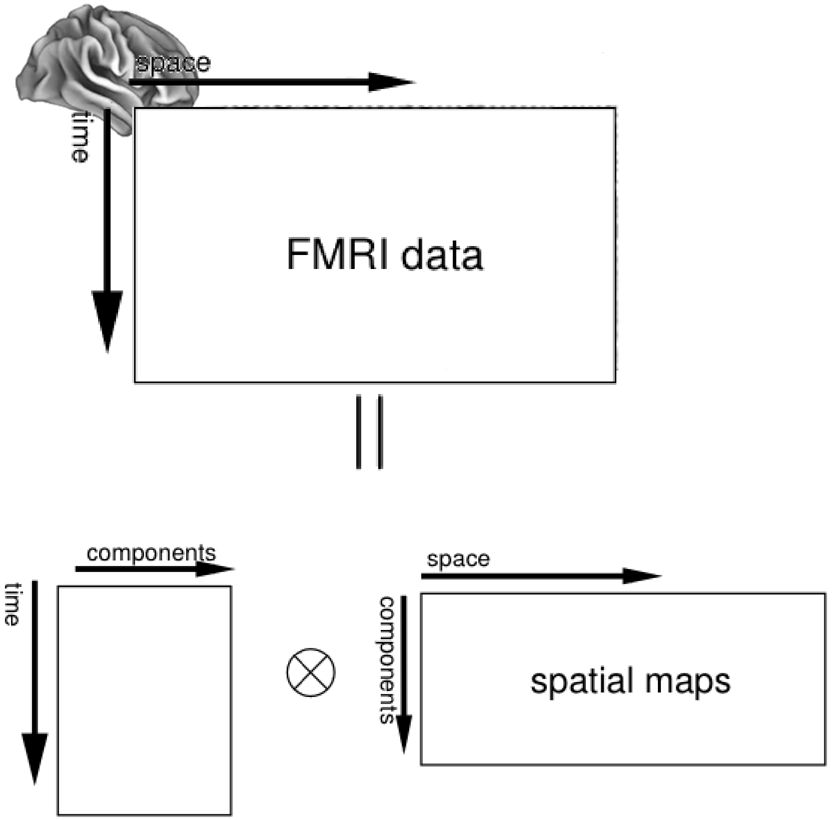
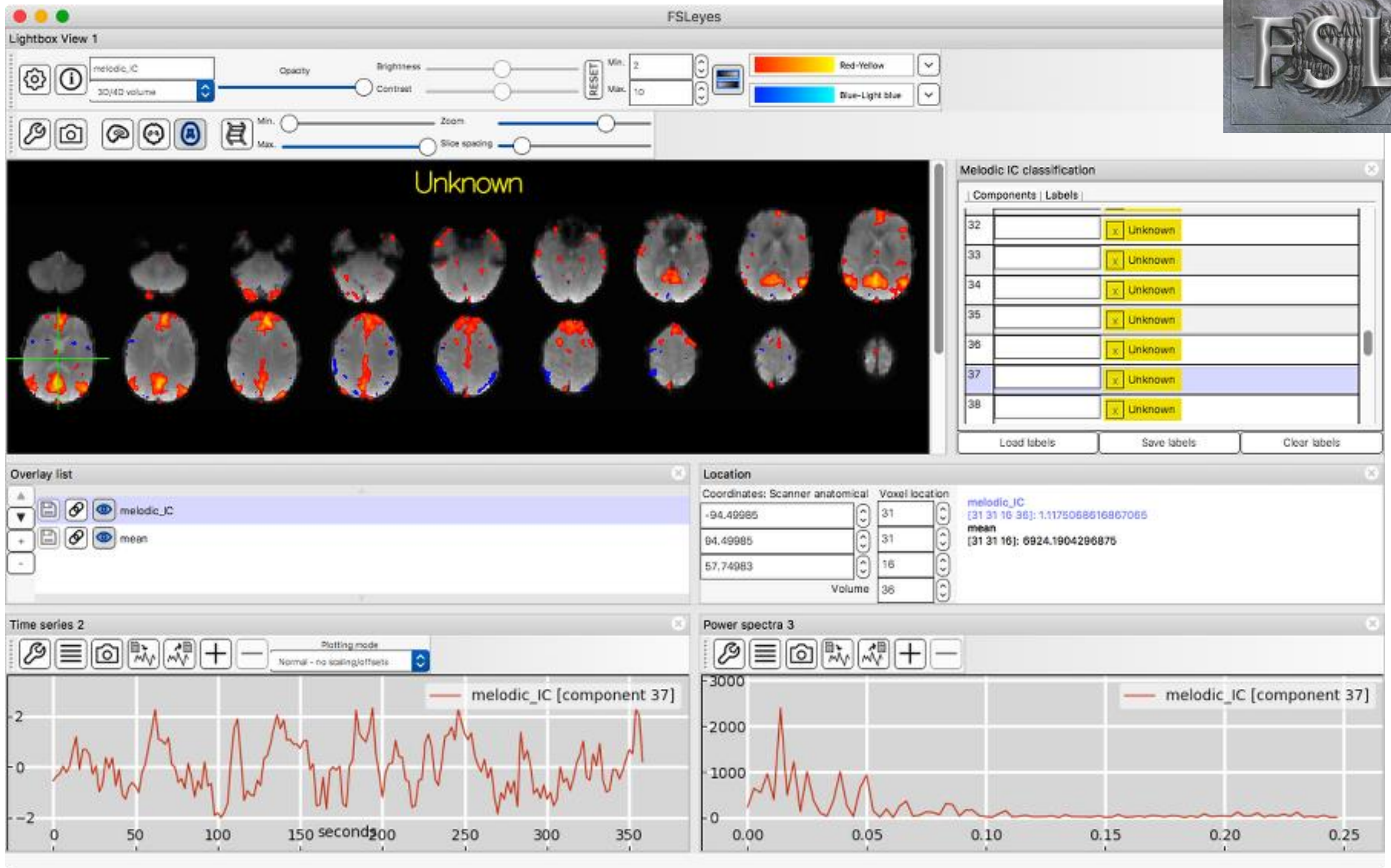
Biswal & Uddin (2025) Nature

MATRIX DECOMPOSITION / ICA





Beckmann et al. (2004) IEEE Trans. Med.

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Biswal & Uddin (2025) Nature

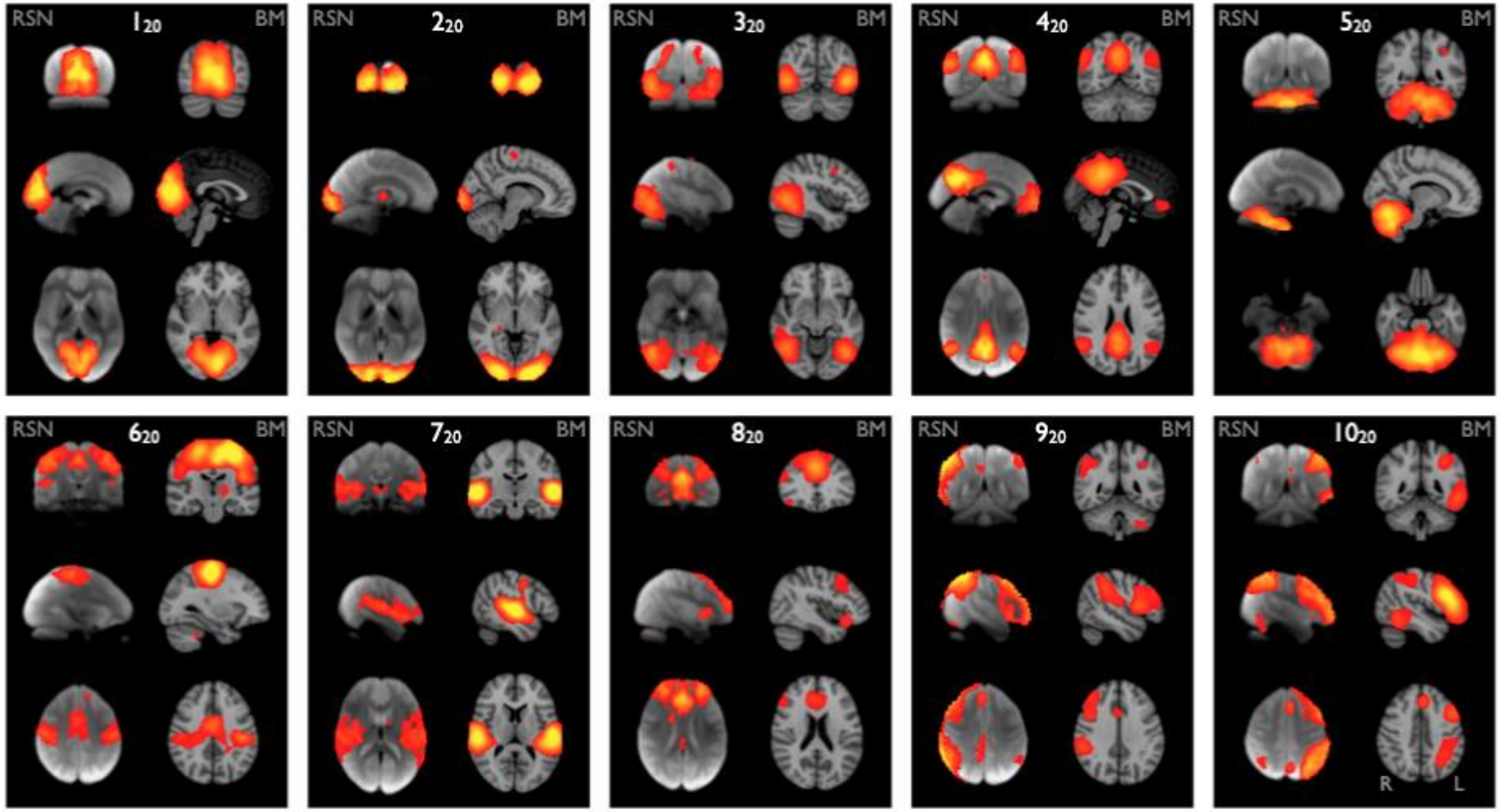

Fig. 1. Ten well-matched pairs of networks from the 20-component analysis of the 29,671-subject BrainMap activation database and (a completely separate analysis of) the 36-subject resting FMRI dataset. This figure shows the 3 most informative orthogonal slices for each pair. (Left column of each pair) Resting FMRI data, shown superimposed on the mean FMRI image from all subjects. (Right column of each pair) Corresponding network from BrainMap, shown superimposed on the MNI152 standard space template image. The networks were paired automatically by using spatial cross-correlation, with mean $r = 0.53$ (0.25:0.79); the weakest of these correlations thus has a significance of $P < 10^{-5}$ (corrected). All ICA spatial maps were converted to z statistic images via a normalized mixture–model fit, and then thresholded at $Z = 3$.

"We conclude that the full repertoire of functional networks utilized by the brain in action is continuously and dynamically "active'' even when at "rest.'"

Smith et al. (2009) PNAS

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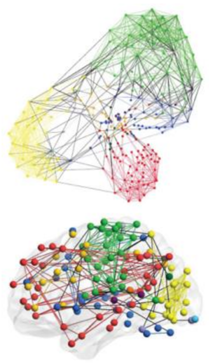
Biswal & Uddin (2025) Nature

"… discovery science has eluded the functional neuroimaging community. The core challenge remains the development of common paradigms for interrogating the myriad functional systems in the brain without the constraints of a priori hypotheses. Resting-state functional MRI (R-fMRI) constitutes a candidate approach capable of addressing this challenge. Imaging the brain during rest reveals large-amplitude spontaneous low-frequency (<0.1 Hz) fluctuations in the fMRI signal that are temporally correlated across functionally related areas. Referred to as functional connectivity, these correlations yield detailed maps of complex neural systems, collectively constituting an individual's **"functional connectome."** Reproducibility across datasets and individuals suggests the functional connectome has a common architecture, yet each individual's functional connectome exhibits unique features, with stable, meaningful interindividual differences in connectivity patterns and strengths…."

Biswal et al. (2010) PNAS



Smith et al. (2013) NeuroImage

Miller et al. (2016) Nature Neurosc.

Casey et al. (2018) Dev Cog Neurosc.

Taylor et al. (2017) NeuroImage

Smith et al. (2009) PNAS

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Biswal & Uddin (2025) Nature

Large, open datasets with MRI data.

Healthy, Young Adult Datasets

Dataset	Website	Number of Participants	Age Range	Multisite	Longitudinal	T1w	T2w	rs-fMRI	Task fMRI	Diffusion MRI	Field Strength	Data Use Agreement	Signing Official
HCP Young Adult	https://www.humanconnectome.org/study/hcp-young-adult	1,200	22-35	Yes	No	X	X	X	X	X	3T, 7T	Yes	No
Amsterdam Open MRI Collection	https://nilab-uva.github.io/AOMIC.github.io/	928	19-26	No	No	X	No	X	X	X	3T	No	No
Brain Genomics Superstruct Project	https://dataverse.harvard.edu/dataverse/GSP	1,570	18-36	No	No	X	No	X	No	No	3T	Yes	No
Southwest University Longitudinal Imaging Multimodal	http://fcon_1000.projects.nitrc.org/indi/retro/southwestuni_qiu_index.html	595	17-27	No	Yes	X	No	X	No	No	3T	No	No

Lifespan Datasets

Dataset	**Website**	**Number of Participants**	**Age Range**	**Multisite**	**Longitudinal**	**T1w**	**T2w**	**rs-fMRI**	**Task fMRI**	**Diffusion MRI**	**Field Strength**	**Data Use Agreement**	**Signing Official**
UK Biobank	https://www.ukbiobank.ac.uk	40,000+	40-69	Yes	Yes	X	X	X	X	X	3T	Yes	Yes
ABCD Study	https://abcdstudy.org	11,878	9-10	Yes	Yes	X	X	X	X	X	3T	Yes	Yes
HCP-Aging	https://www.humanconnectome.org/study/hcp-lifespan-aging	1,200	36-100	Yes	Yes	X	X	X	X	X	3T	Yes	Yes
HCP in Development	https://www.humanconnectome.org/study/hcp-lifespan-development	1,350	5-21	Yes	Yes	X	X	X	X	X	3T	Yes	Yes
Baby Connectome Project	https://www.humanconnectome.org/study/lifespan-baby-connectome-project	500	0-5	Yes	Yes	X	X	X	X	X	3T	Yes	Yes
Developing HCP	https://www.humanconnectome.org/study/lifespan-developing-human-connectome-project	1,500	20-44 weeks	Yes	Yes	X	X	X	No	X	3T	Yes	Yes
CamCAN	https://www.cam-can.org	~650	18-87	No	No	X	X	X	X	X	3T	Yes	No
OASIS-3	https://www.oasis-brains.org	1,098	42-95	No	Yes	X	X	X	No	X	1.5T, 3T	Yes	No

Dense Sampling and Datasets Featuring Many Tasks and Experimental Measures

Dataset	**Website**	**Number of Participants**	**Age Range**	**Multisite**	**Scan Sessions**	**T1w**	**T2w**	**rs-fMRI**	**Task fMRI**	**Diffusion MRI**	**Field Strength**	**Data Use Agreement**	**Signing Official**
MyConnectome	http://myconnectome.org	1	45	No	104 sessions	X	X	X	X	X	3T	No	No
Midnight Scan Club	https://openneuro.org/datasets/ds000224/versions/1.0.3	10	24-34	No	12 sessions/ppt	X	X	X	X	No	3T	No	No
StudyForrest	https://www.studyforrest.org	36	21-38	Yes	varies	X	X	X	X	X	3T, 7T	No	No
Natural Scenes Dataset	http://naturalscenesdataset.org	8	19-32	No	30-40 sessions/ppt	X	X	X	X	X	3T, 7T	Yes	No
BOLD5000	https://bold5000.github.io/	4	24-27	No	10-16 sessions/ppt	X	X	No	X	X	3T	No	No
"Narratives" Collection	https://openneuro.org/datasets/ds002345/versions/1.1.4	345	18-53	No	2-3/ppt	X	X	No	X	No	3T	No	No
Individual Brain Charting	https://project.inria.fr/IBC/	12	26-40	No	5 sessions/ppt	X	X	No	X	X	3T	No	No
Courtois NeuroMod	https://www.cneuromod.ca	6	*unknown*	No	weekly for 5 years	X	X	X	X	X	3T	Yes	Yes

Laird et al. (2021) NeuroImage

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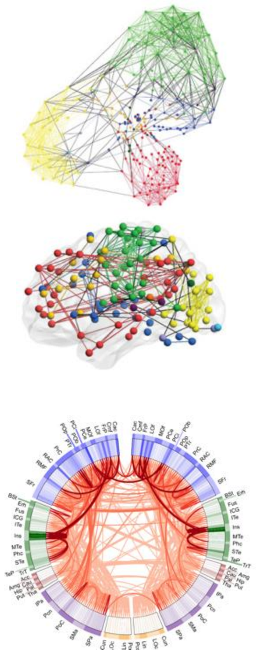
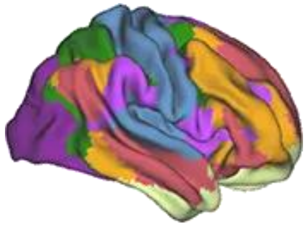
Biswal & Uddin (2025) Nature

PARCELLATIONS / FUNCTIONAL CONNECTOMES



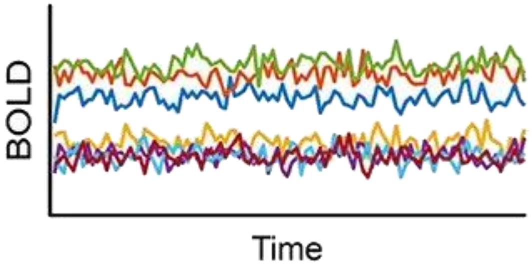
Functional Connectomes

rsfMRI Scans

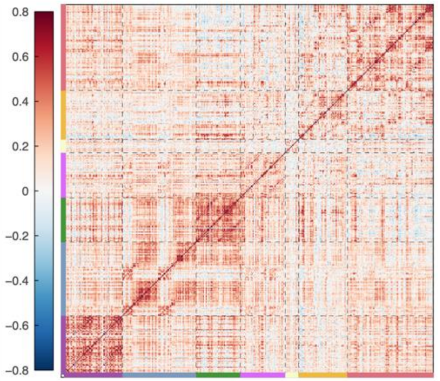


Parcellation

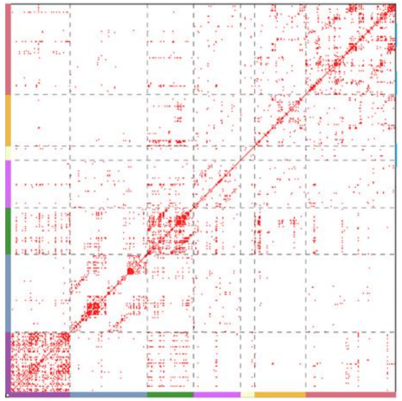
Extract Timeseries



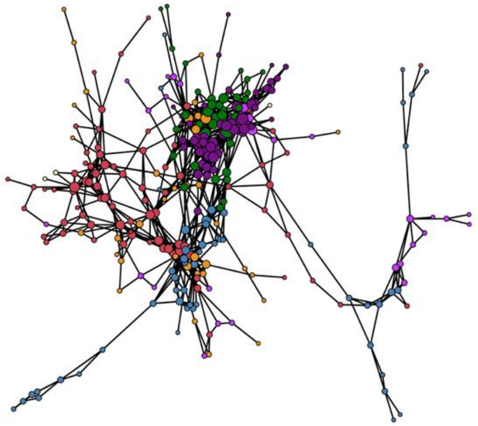
Compute Pair-wise Correlation

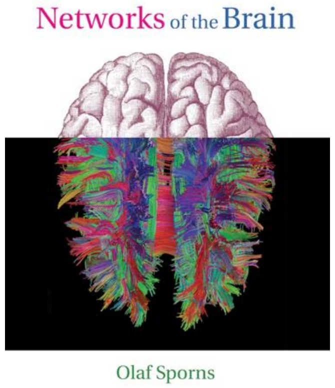


Threshold



Model as Graph





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Biswal & Uddin (2025) Nature

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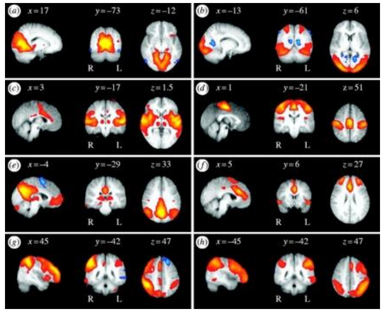
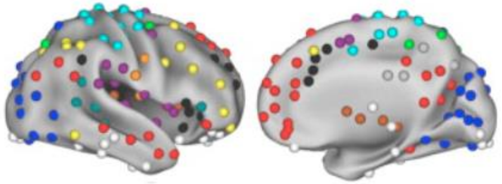
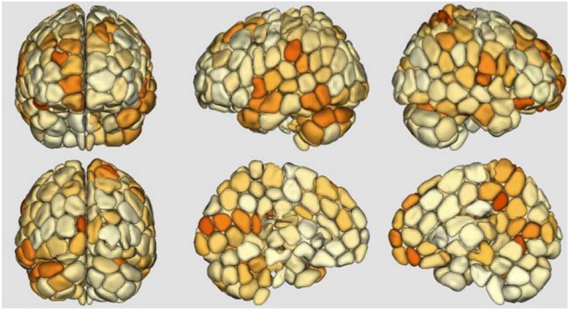


Beckmann et al. (2005) Phil. Trans. B

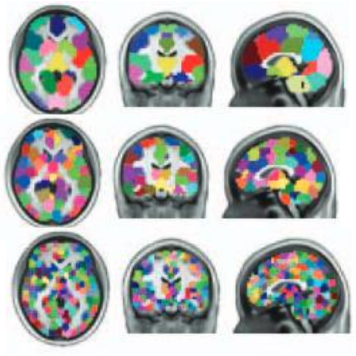
Klein et al. (2012) Front. Neurosc.



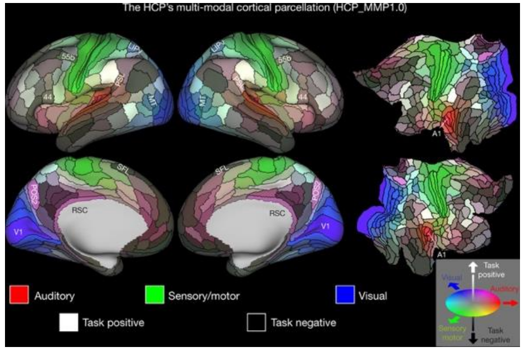
Power et al. (2012) Neuron



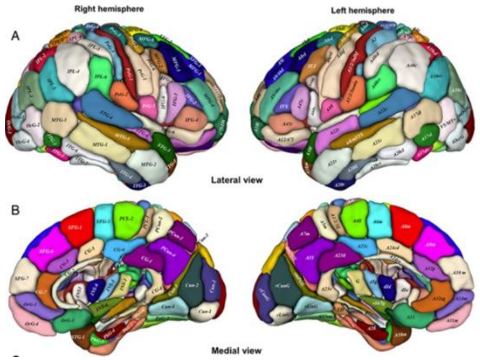
Shen et al. (2013) NeuroImage



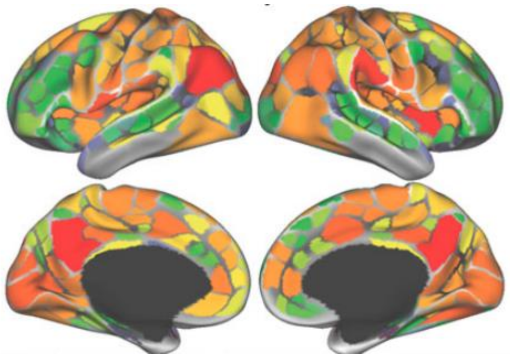
Craddock et al. (2012) HBM



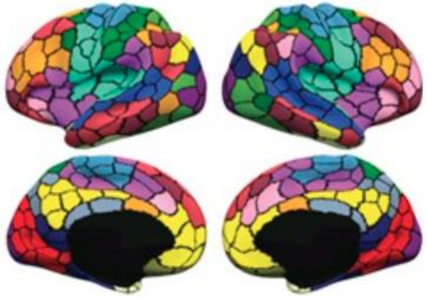
Glasser et al. (2016) Nature



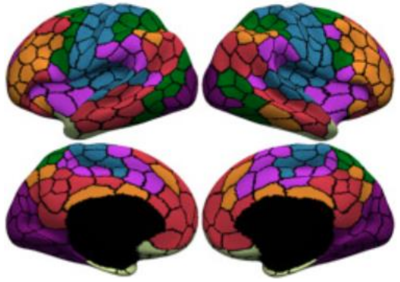
Fan et al. (2016) Cerebral Cortex



Gordon et al. (2016) Cerebral Cortex



Schaefer et al. (2018) Cerebral Cortex



Yan et al. (2023) NeuroImage

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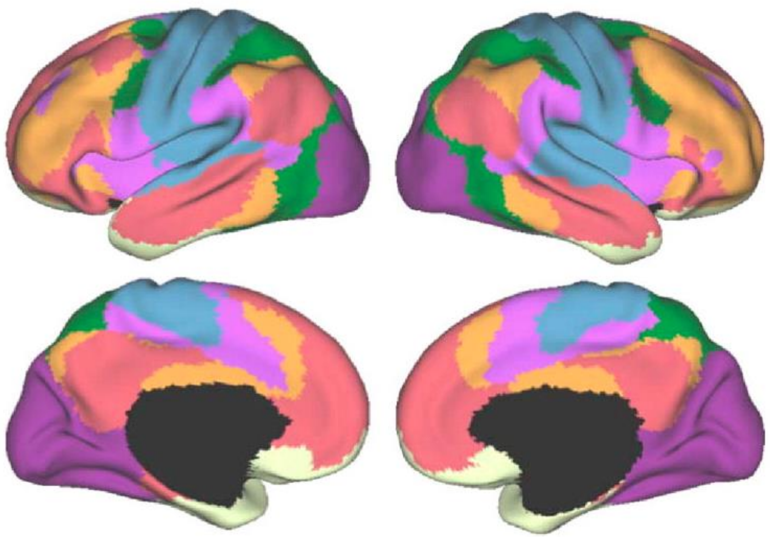
Biswal & Uddin (2025) Nature

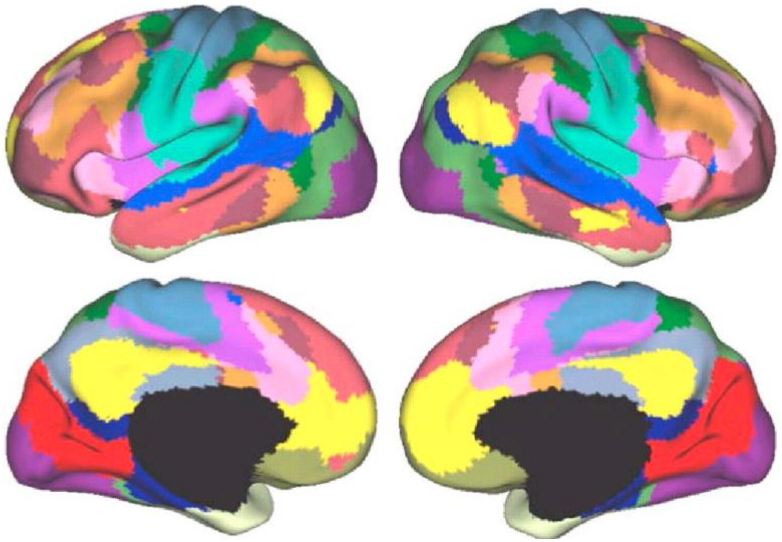
"Information processing in the cerebral cortex involves interactions among distributed areas… In this study the organization of networks in the human cerebrum was explored using resting-state functional connectivity MRI. Data from 1,000 subjects … A clustering approach was employed to identify and replicate networks of functionally coupled regions across the cerebral cortex. The results revealed local networks confined to sensory and motor cortices as well as distributed networks of association regions…"

7 Canonical Networks



- Purple (Visual)
- Blue (Somatomotor)
- Green (Dorsal Attention)
- Violet (Ventral Attention)
- Cream (Limbic)
- Orange (Frontoparietal)
- Red (Default)

17 Canonical Networks



- Visual A
- Visual B
- Somatomotor A
- Somatomotor B
- Temporal Parietal
- Dorsal Attention A
- Dorsal Attention B
- Salience/VenAttn A
- Salience/VenAttn B
- Control A
- Control B
- Control C
- Default A
- Default B
- Default C
- Visual C
- Auditory

Yeo et al. (2011) J. Neurophysiology

History |

1995 — First rsfMRI functional connectivity paper

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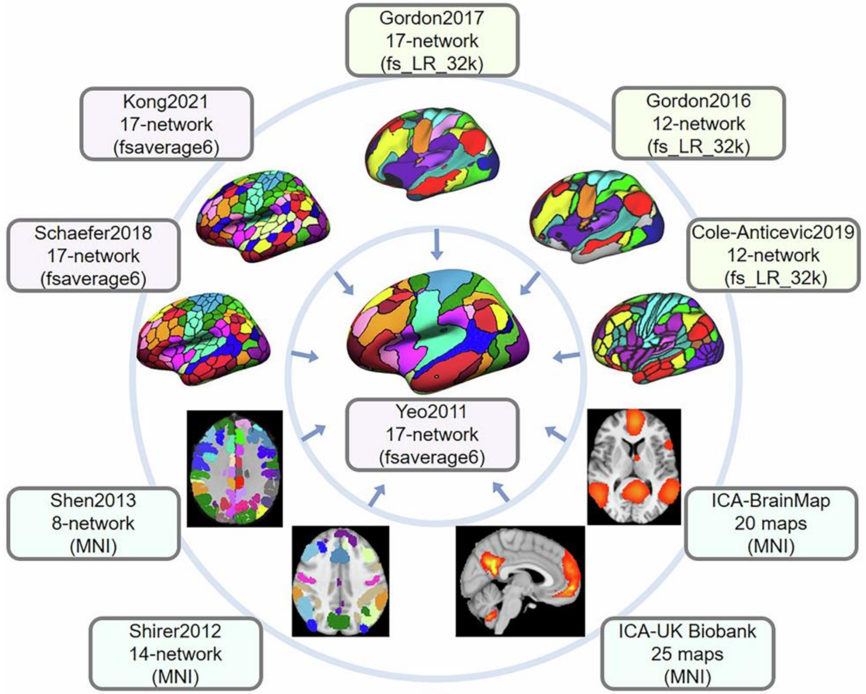
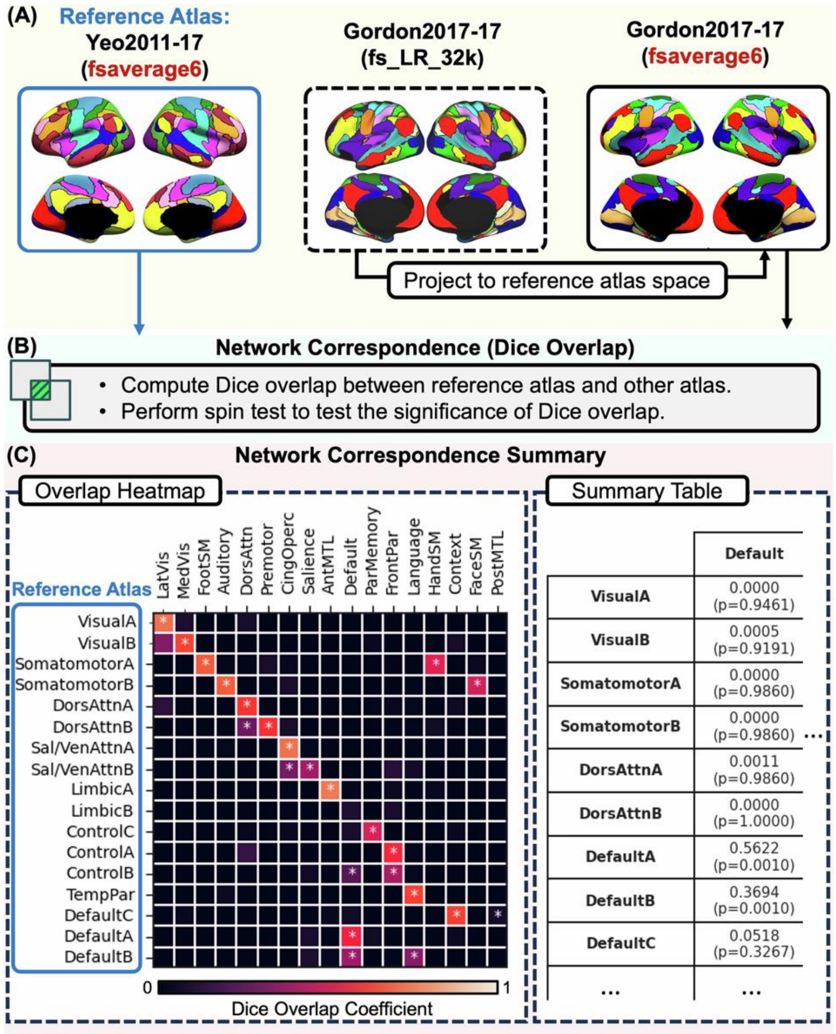
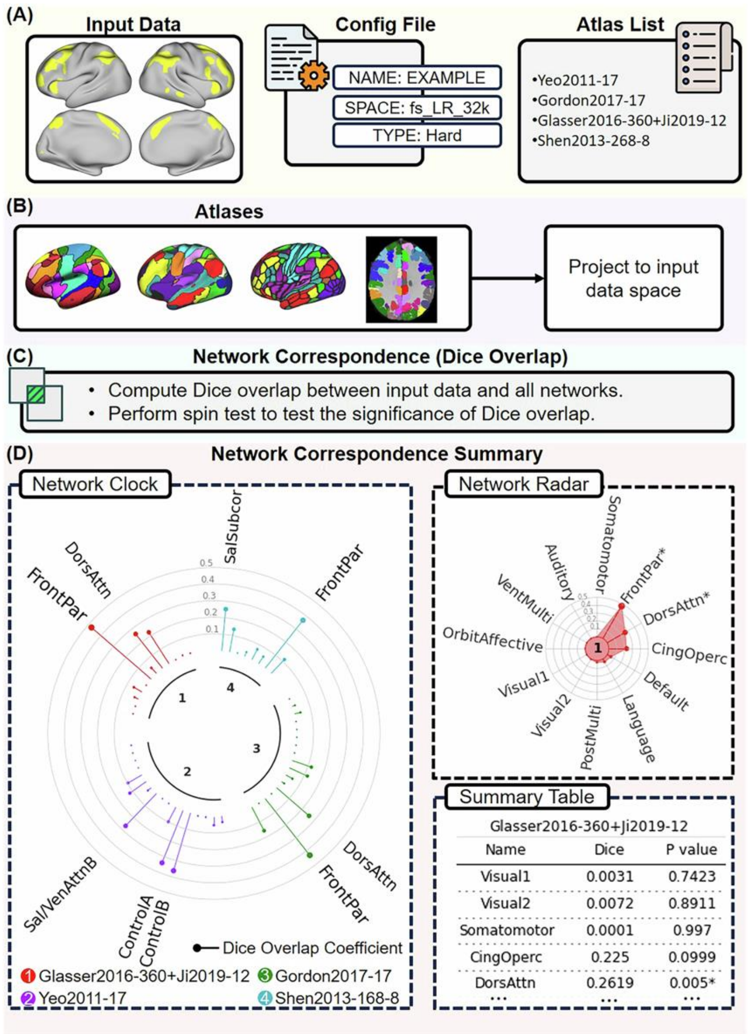
Biswal & Uddin (2025) Nature







Kong et al. (2025) Nature Communications

History |

- 1995 — First rsfMRI functional connectivity paper
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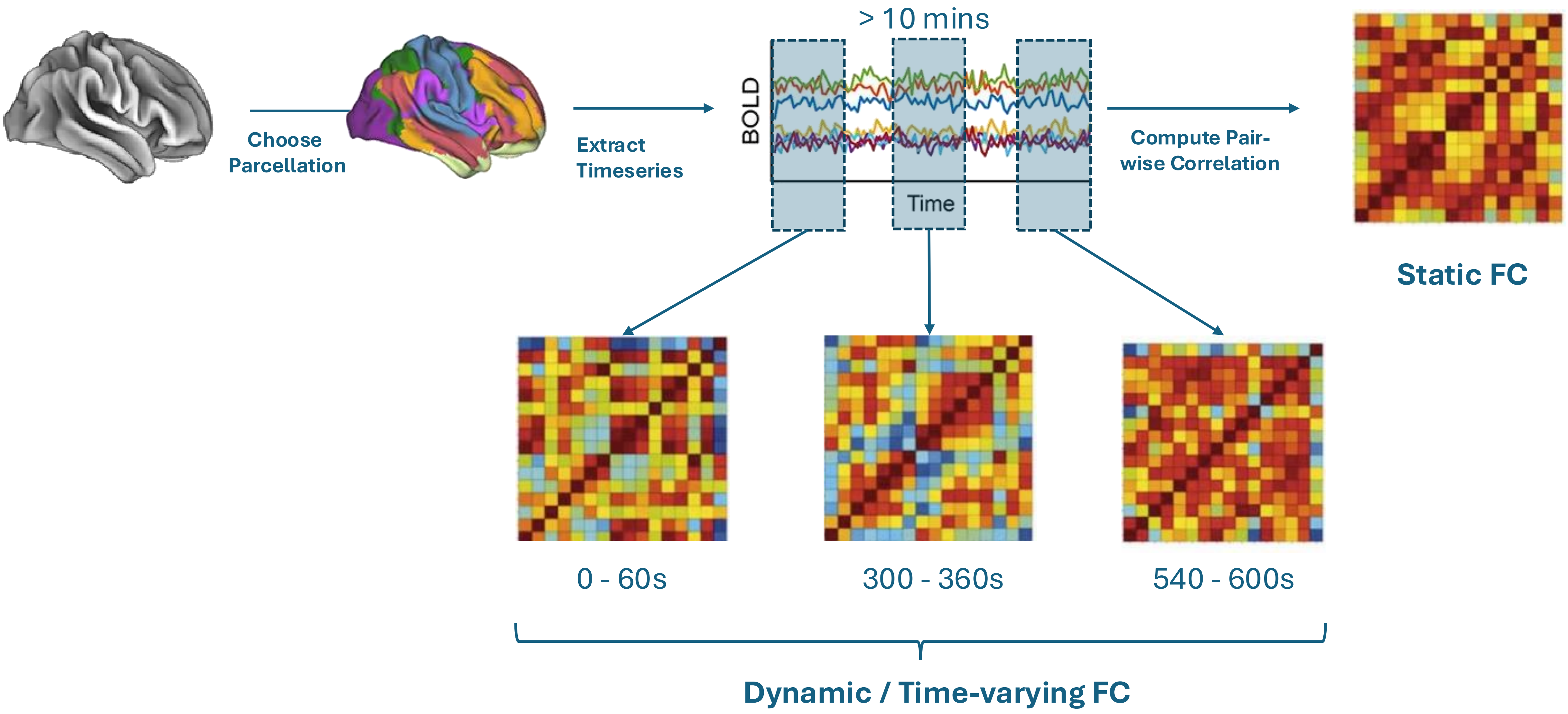
Biswal & Uddin (2025) Nature



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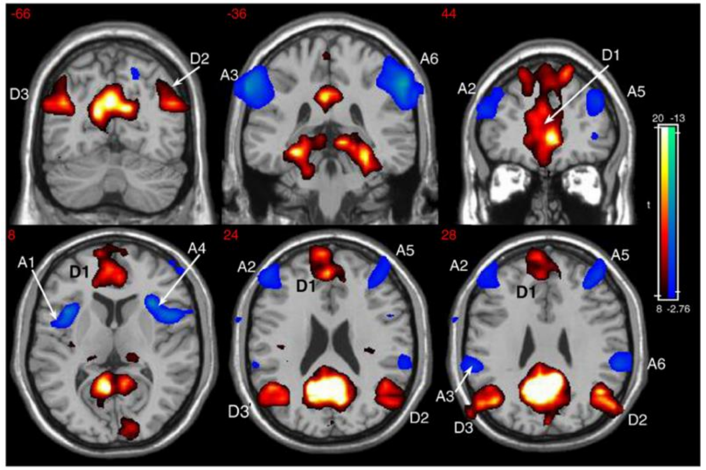
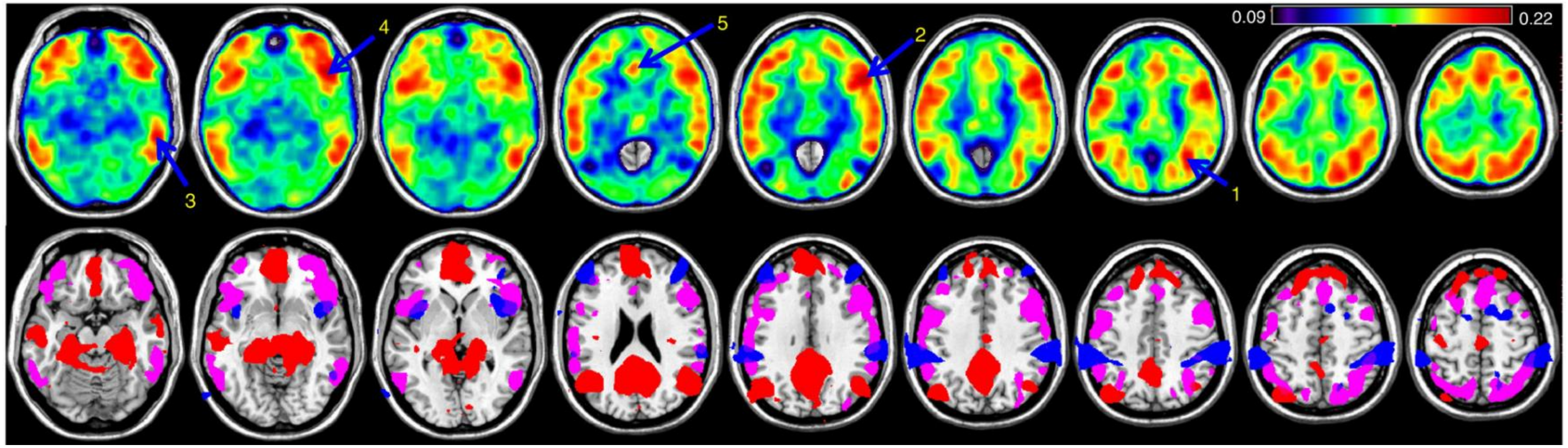
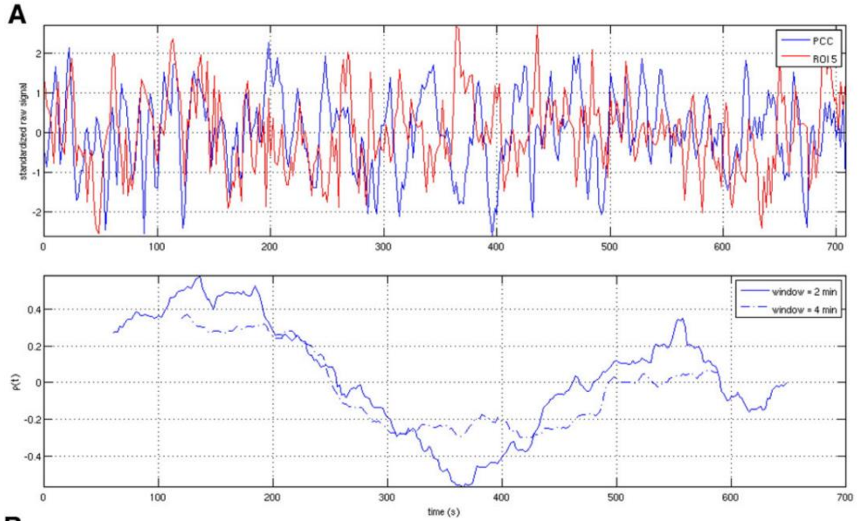
2025 Multiple ongoing population neuroscience data collection efforts continue to make researchers

Biswal & Uddin (2025) Nature

Variability in correlation to the PCC over a 2 mins window







Chang et al. (2010) NeuroImage

History |

ICA
Rest/Task
Yeo Netws.

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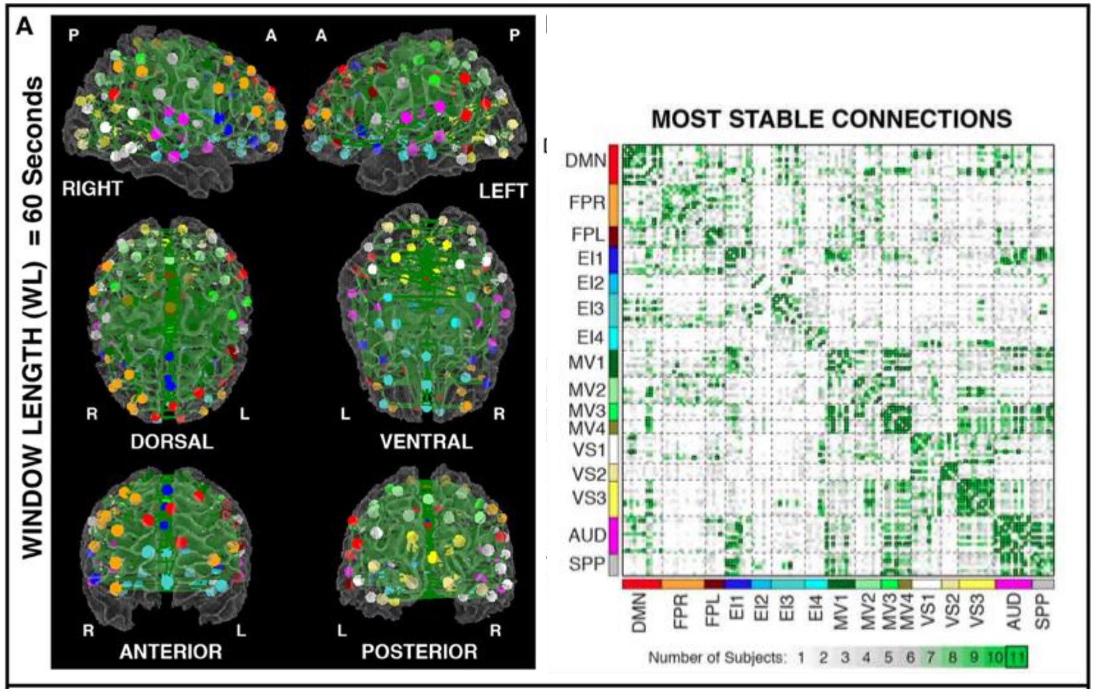
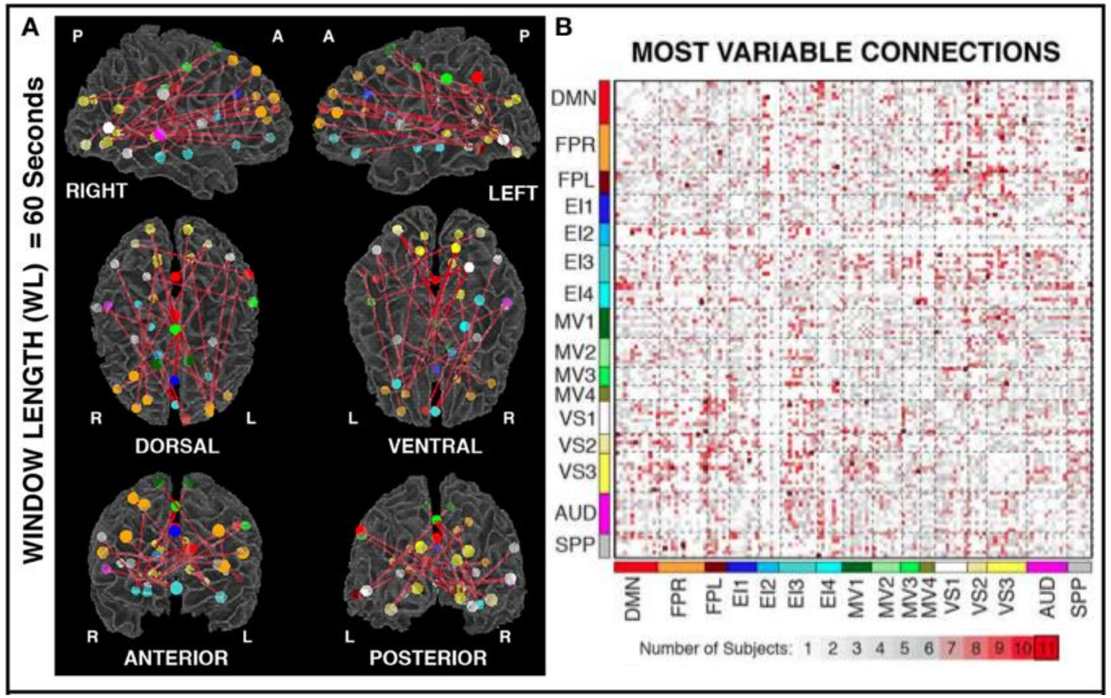
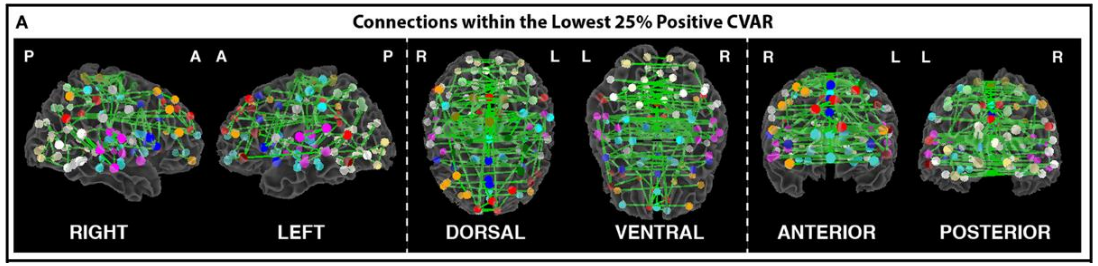
Biswal & Uddin (2025) Nature







Most Variable Connections correspond primarily inter-network, inter-hemispheric connections involving the fronto-parietal network and occipital regions. Also some DMN regions.

Mostly symmetric, inter-hemispheric connections between homologous L/R regions.
Only account for 32% of intra-network connections → Networks are flexible
Unimodal sensory-motor networks (VIS, AUD and MV) seem to be among the most stable.

Gonzalez-Castillo et al. (2014) Frontiers Neurosc.

History |

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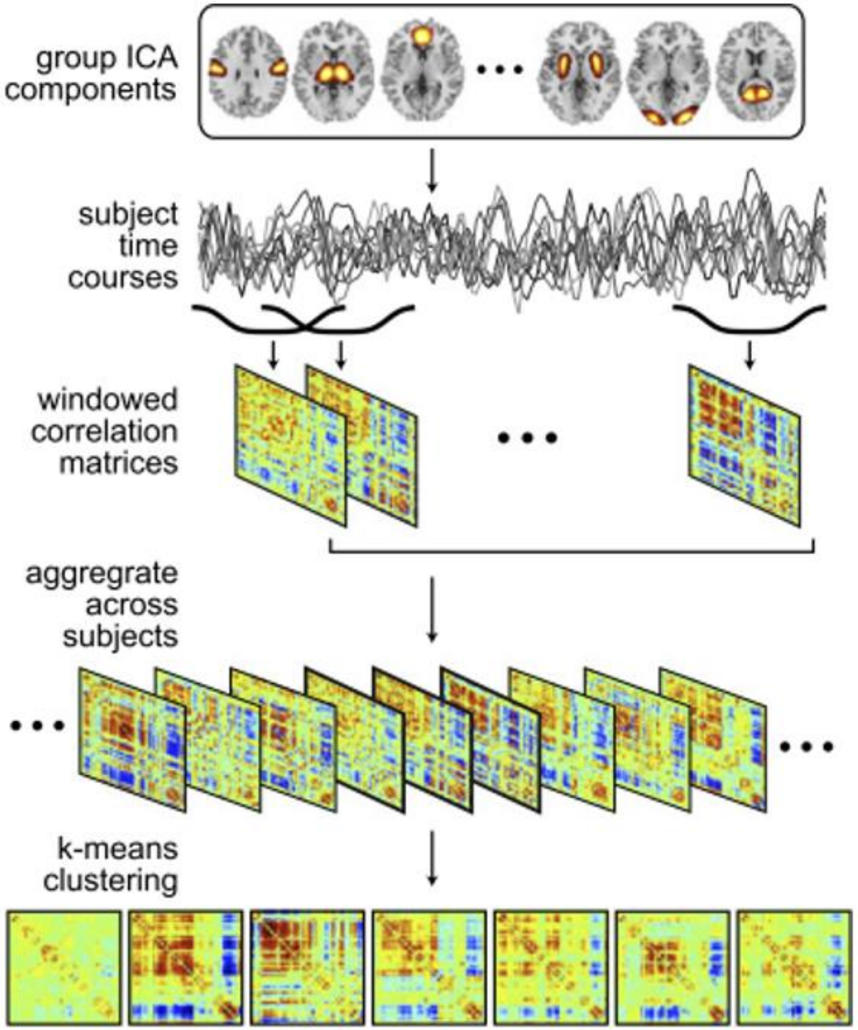

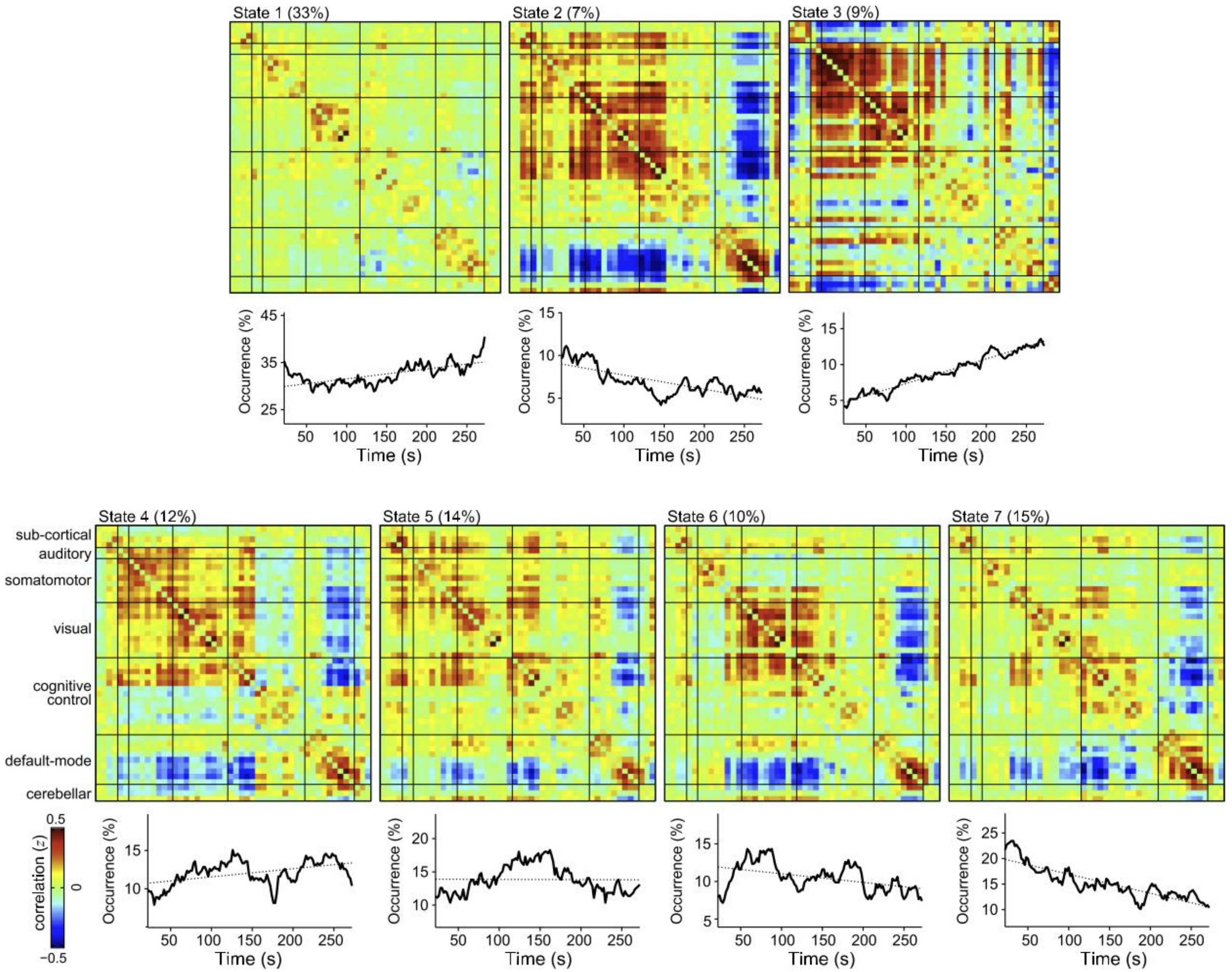

FC States

Allen et al. (2014) Cer. Cortex

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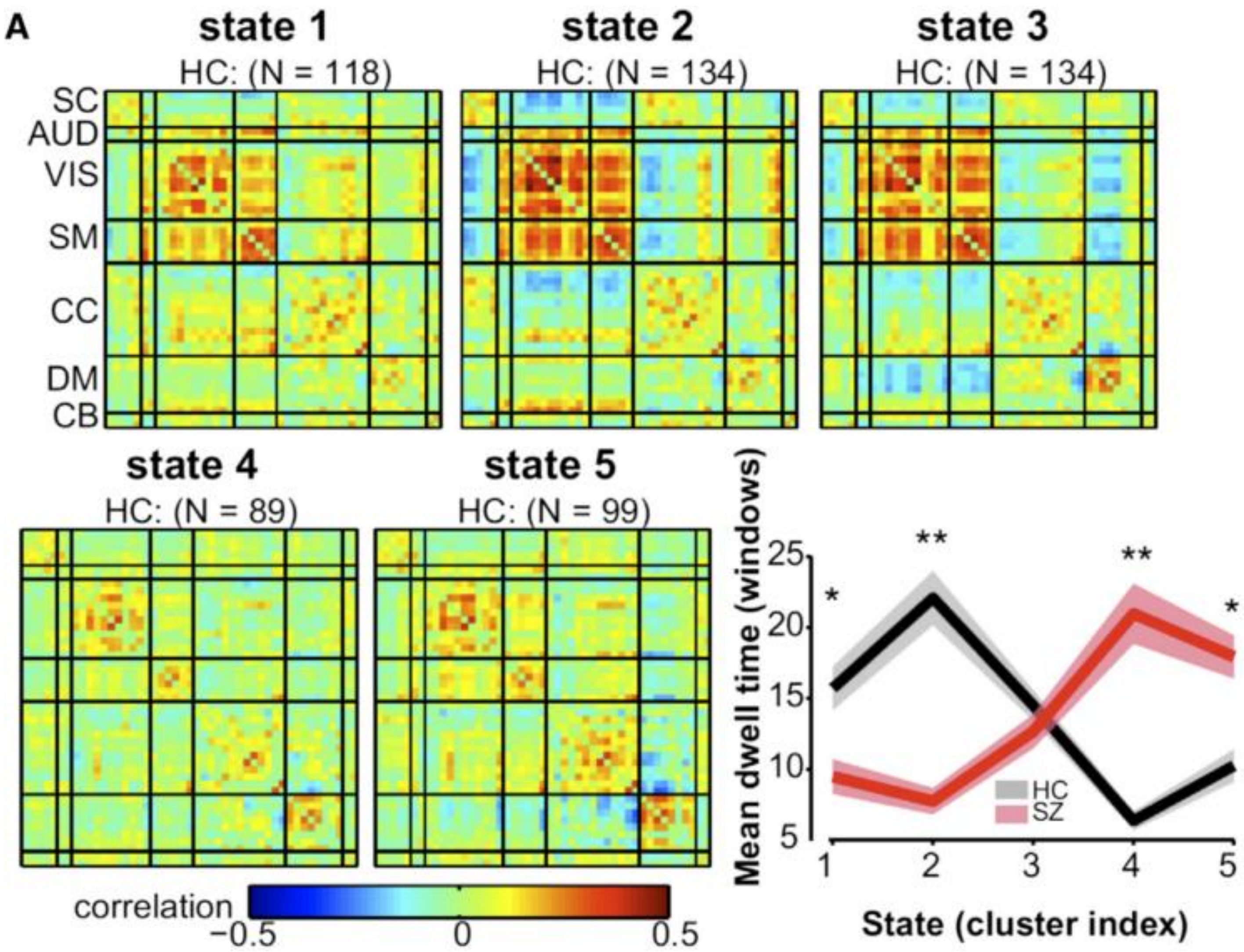
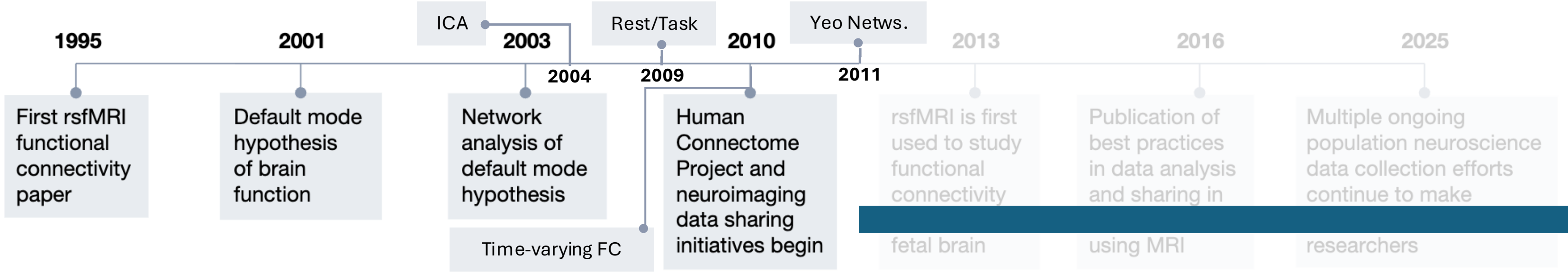
Biswal & Uddin (2025) Nature



Dynamic states in a large (n > 300) data set of schizophrenia patients and controls in which the patients are spending significantly more time in the relatively less connected state 4.

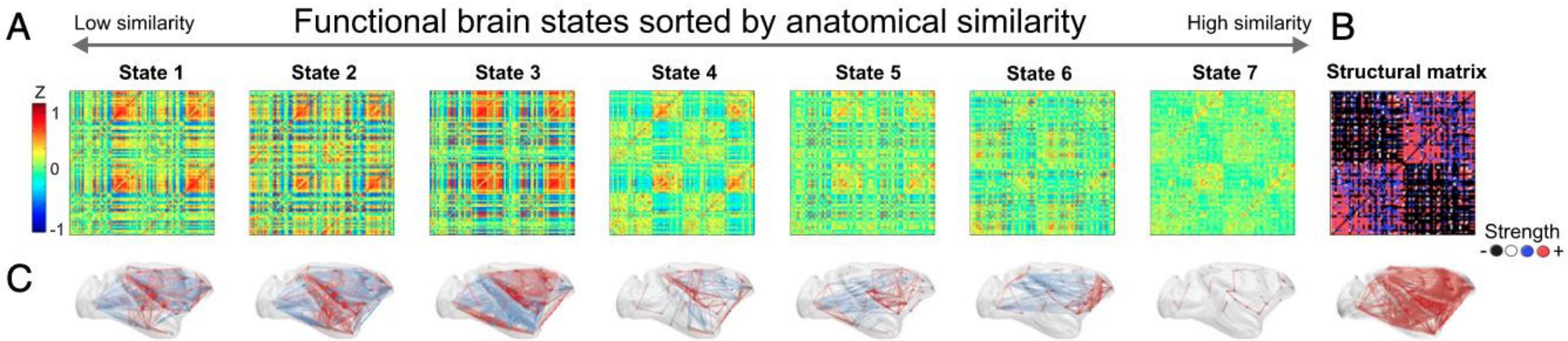
Damaraju et al. (2014) NeuroImage Clinical

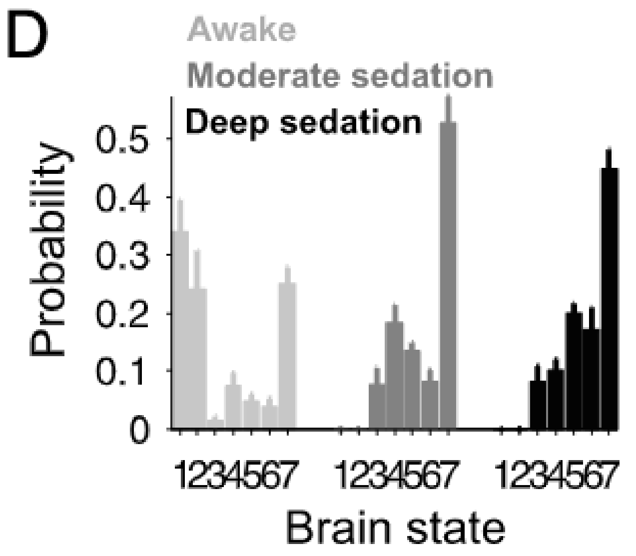
History |



Biswal & Uddin (2025) Nature

Dynamic FC is reduced as consciousness levels decrease





- "Under anesthesia, the more frequent functional connectivity patterns inherit the structure of anatomical connectivity, exhibit fewer small-world properties, and lack negative correlations"
- "Wakefulness is characterized by the sequential exploration of a richer repertoire of functional configurations, often dissimilar to anatomical structure, and comprising positive and negative correlations among brain regions"
- "Rich functional dynamics might constitute a signature of consciousness"

Barttfeld et al. (2015) PNAS

History |

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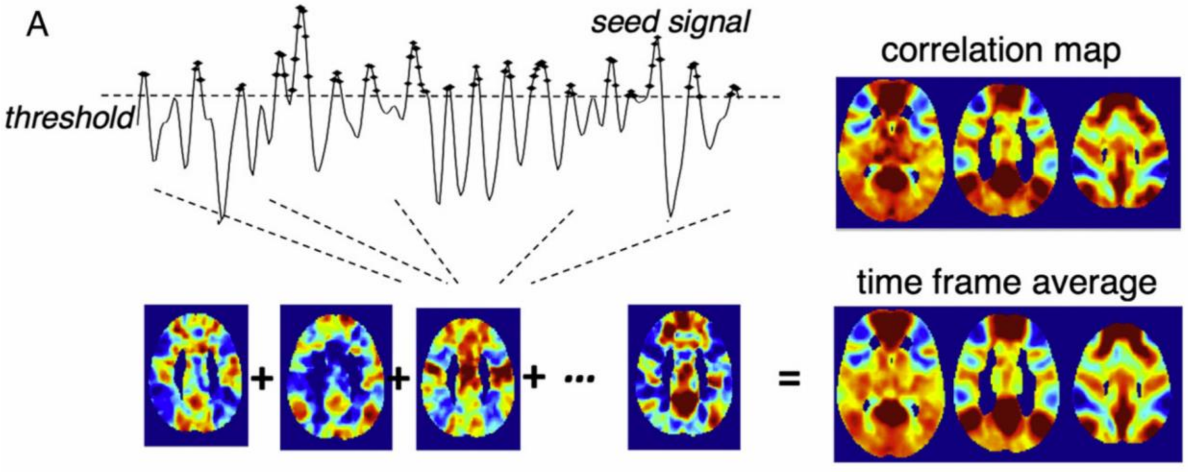
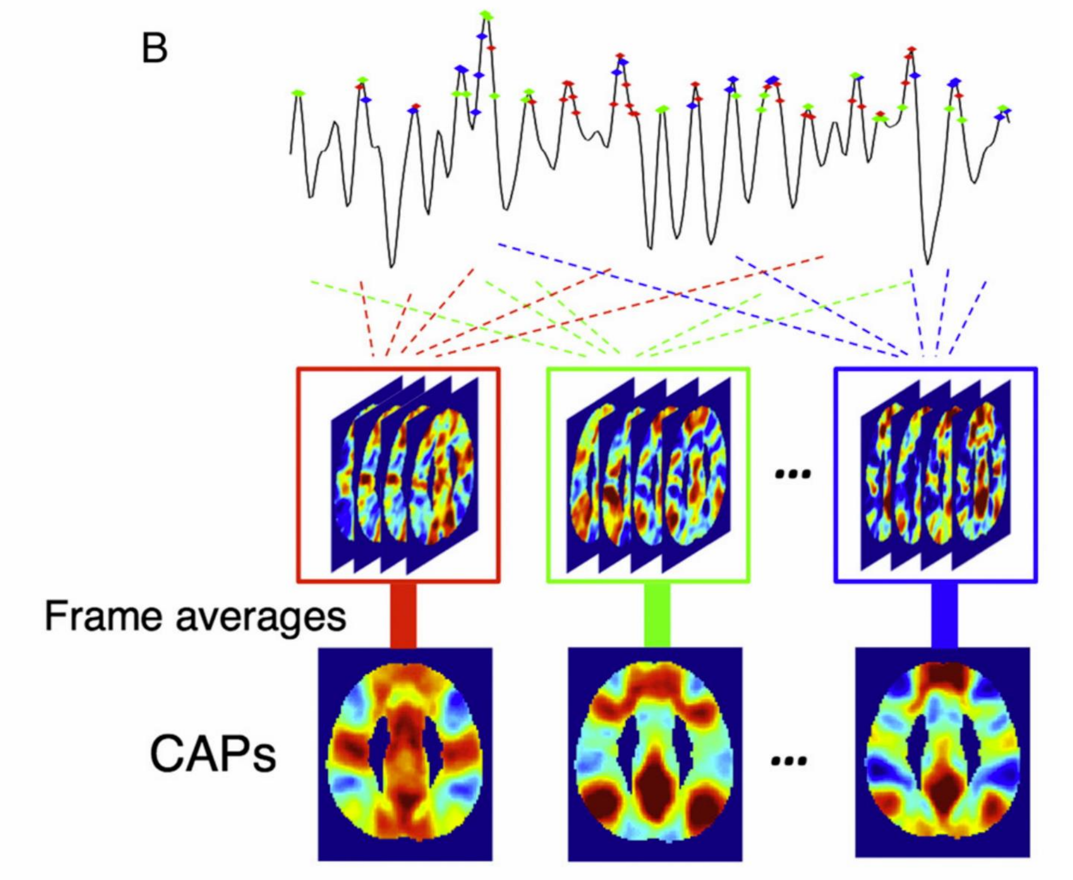
Biswal & Uddin (2025) Nature

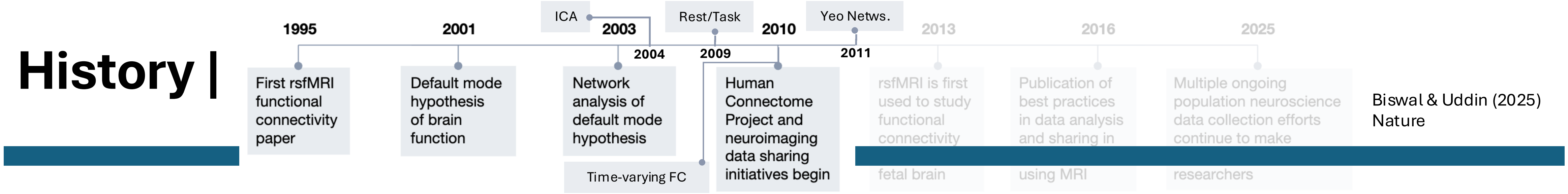
Co-Activation Patterns





Liu et al. (2013) PNAS, Chen et al. (2015) NeuroImage

History |



Biswal & Uddin (2025) Nature

2013

NeuroImage 80 (2013) 360–378

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Dynamic functional connectivity: Promise, issues, and interpretations

R. Matthew Hutchison [a,*,1], Thilo Womelsdorf [b], Elena A. Allen [c,d], Peter A. Bandettini [e], Vince D. Calhoun [d,f], Maurizio Corbetta [g,h], Stefania Della Penna [g], Jeff H. Duyn [i], Gary H. Glover [j], Javier Gonzalez-Castillo [e], Daniel A. Handwerker [e], Shella Keilholz [k], Vesa Kiviniemi [l], David A. Leopold [m], Francesco de Pasquale [g], Olaf Sporns [n], Martin Walter [o,p], Catie Chang [i,**,1]

2017

NeuroImage 160 (2017) 41–54

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

The dynamic functional connectome: State-of-the-art and perspectives

Maria Giulia Preti [a,b,*,1], Thomas AW Bolton [a,b,1], Dimitri Van De Ville [a,b]

[a] Institute of Bioengineering, Center for Neuroprosthetics, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
[b] Department of Radiology and Medical Informatics, University of Geneva (UNIGE), Geneva, Switzerland

2020

February 01 2020

Questions and controversies in the study of time-varying functional connectivity in resting fMRI

In Special Collection: CogNet

Daniel J. Lurie, Daniel Kessler, Danielle S. Bassett, Richard F. Betzel, Michael Breakspear, Shella Kheilholz, Aaron Kucyi, Raphaël Liégeois, Martin A. Lindquist, Anthony Randal McIntosh, Russell A. Poldrack, James M. Shine, William Hedley Thompson, Natalia Z. Bielczyk, Linda Douw, Dominik Kraft, Robyn L. Miller, Muthuraman Muthuraman, Lorenzo Pasquini, Adeel Razi, Diego Vidaurre, Hua Xie, Vince D. Calhoun

History |

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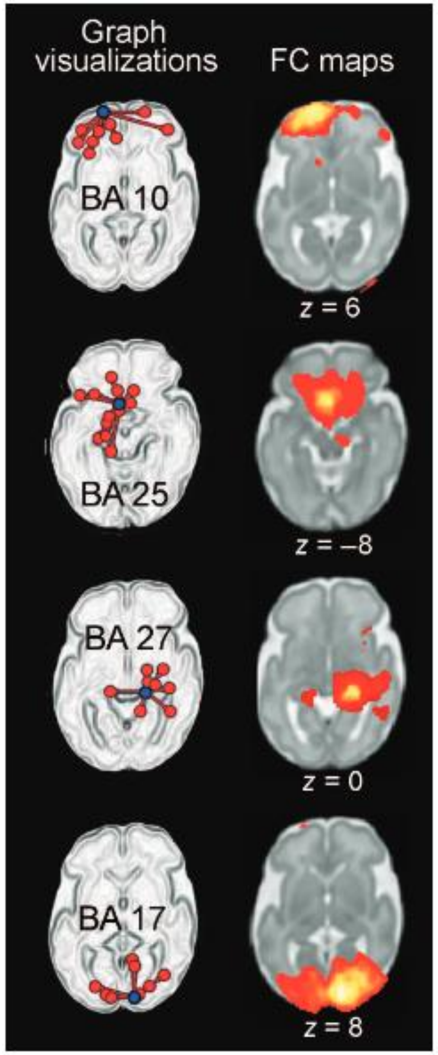
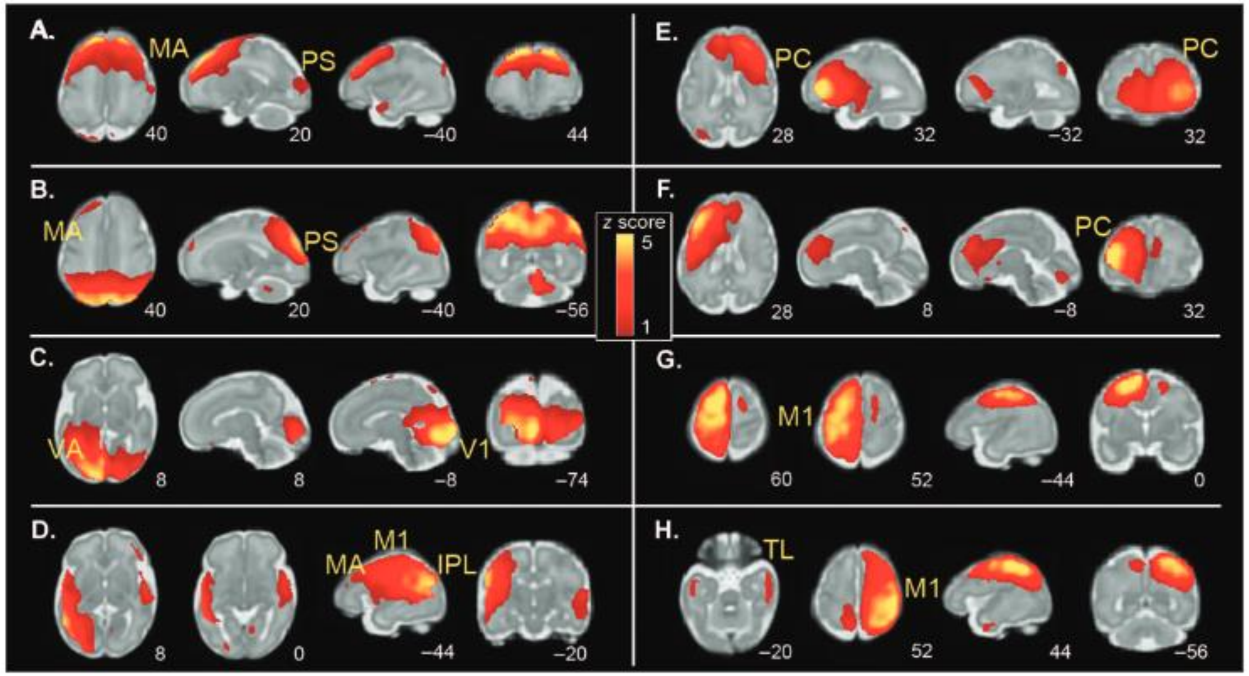
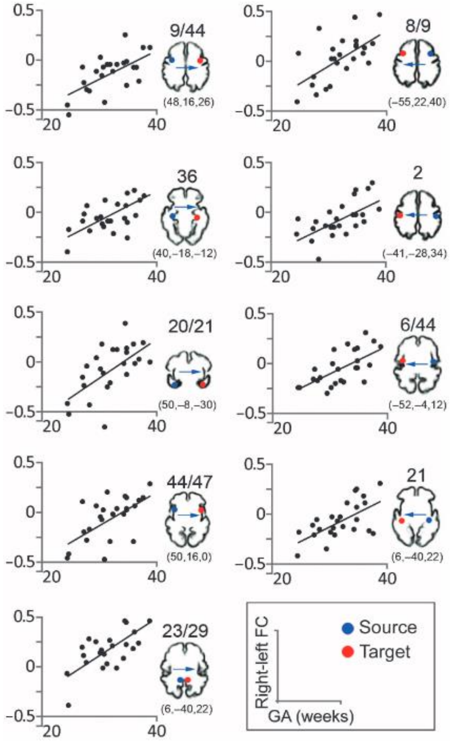
- 2025: Multiple ongoing population neuroscience data collection efforts continue to make ... researchers

Biswal & Uddin (2025) Nature



"…rsfMRI performed in <u>25 healthy human fetuses</u> in the second and third trimesters of pregnancy <u>(24 to 38 weeks of gestation).</u> We report the presence of bilateral fetal brain FC and regional and age-related variation in FC. Significant bilateral connectivity was evident in half of the 42 areas tested, and the strength of FC between homologous cortical brain regions increased with advancing gestational age…"





Thomason et al. (2013) PNAS

History |

ICA
Rest/Task
Yeo Netws.

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Time-varying FC

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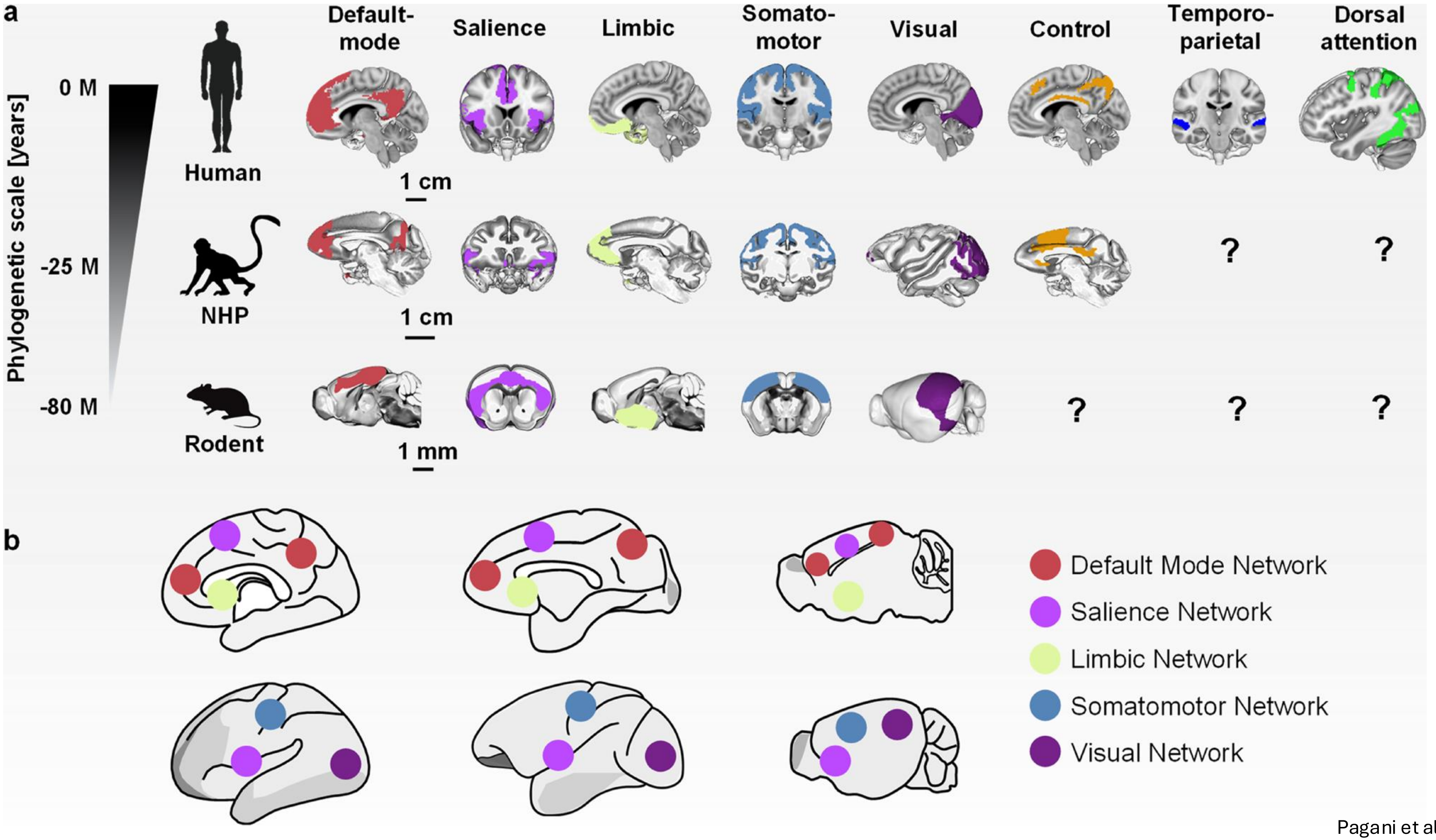
Biswal & Uddin (2025) Nature



Pagani et al. (2023) Communications Biology

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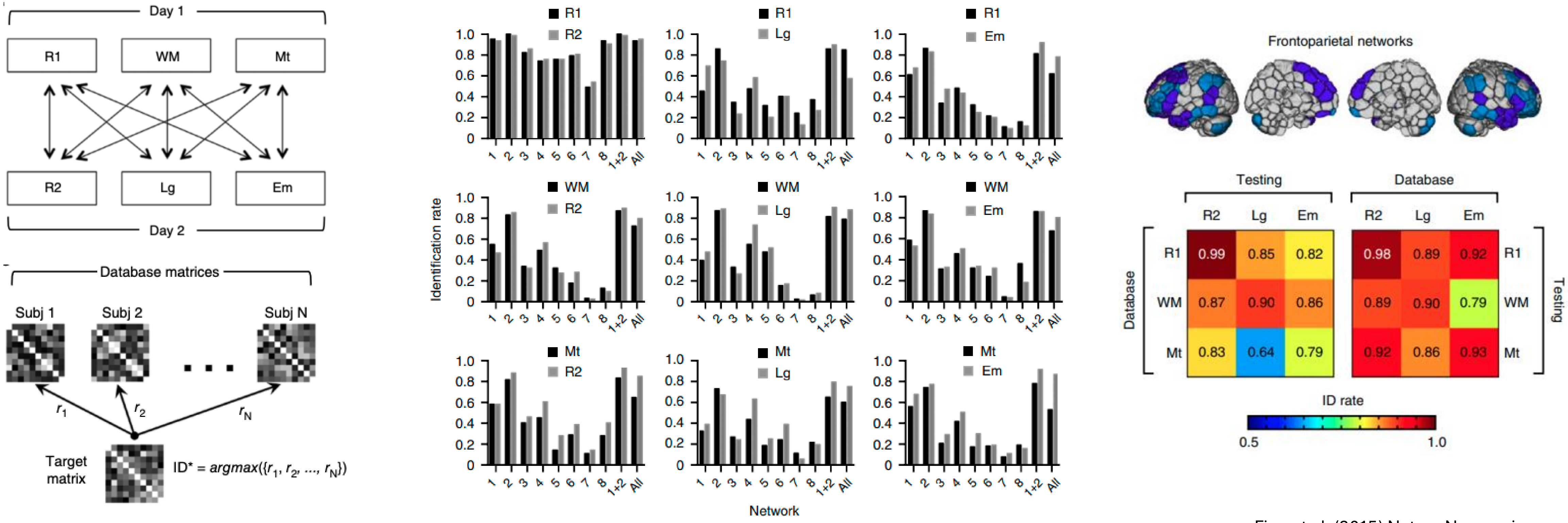
Biswal & Uddin (2025) Nature

"…brain functional organization varies between individuals. Here we establish that this individual variability is both robust and reliable, using data from the Human Connectome Project to demonstrate that functional connectivity profiles act as a 'fingerprint' that can accurately identify subjects from a large group… Characteristic connectivity patterns were distributed throughout the brain, but the frontoparietal network emerged as most distinctive…"



Finn et al. (2015) Nature Neuroscience

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Biswal & Uddin (2025) Nature

Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/neuroimage

Methods for cleaning the BOLD fMRI signal

César Caballero-Gaudes[a,*], Richard C. Reynolds[b]

[a] Basque Center of Cognition, Brain and Language, San Sebastian, Spain
[b] Scientific and Statistical Computing Core, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, USA

Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/neuroimage

Towards a consensus regarding global signal regression for resting state functional connectivity MRI

Kevin Murphy[a,b,*], Michael D. Fox[c,d,e]

In summary, including global signal regression in the processing of resting state functional connectivity data is not inherently right or wrong. Whether GSR is a useful processing step likely depends on the scientific question one seeks to address. Results must be interpreted properly within the context of the pre-processing method applied and different methods may provide complementary insights into the brain's functional organization.

Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

BOLD fractional contribution to resting-state functional connectivity above 0.1 Hz

Jingyuan E. Chen[a,b,*], Gary H. Glover[a]

Evaluation of different cerebrospinal fluid and white matter fMRI filtering strategies—Quantifying noise removal and neural signal preservation

Marek Bartoň[1,2] | Radek Mareček[1] | Lenka Krajčovičová[1] | Tomáš Slavíček[1] | Tomáš Kašpárek[3] | Petra Zemánková[1,2,3] | Pavel Říha[1] | Michal Mikl[1]

Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

Methods to detect, characterize, and remove motion artifact in resting state fMRI

Jonathan D. Power[a,*], Anish Mitra[a], Timothy O. Laumann[a], Abraham Z. Snyder[a,b], Bradley L. Schlaggar[a,b,c,d], Steven E. Petersen[a,b,d,e,f,g]

Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

The nuisance of nuisance regression: Spectral misspecification in a common approach to resting-state fMRI preprocessing reintroduces noise and obscures functional connectivity☆

Michael N. Hallquist[a,b,d,*], Kai Hwang[a,d], Beatriz Luna[a,b,c,d]

History |

Year	Event
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2004	ICA
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2009	Time-varying FC
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2016	Hierarchical gradient structure of FC
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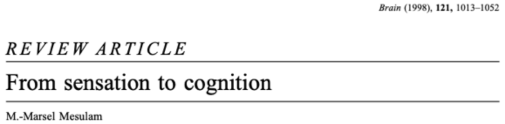
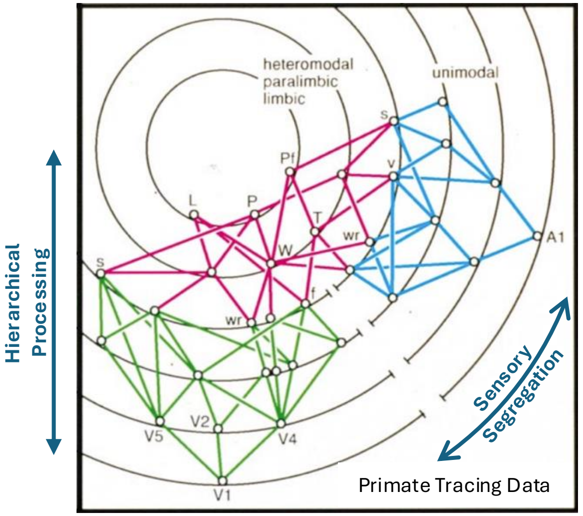
Biswal & Uddin (2025) Nature



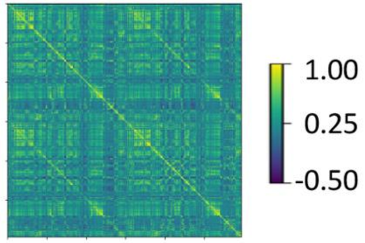


"Sensory information undergoes extensive associative elaboration and attentional modulation as it becomes incorporated into the texture of cognition. This process occurs along a core synaptic hierarchy which includes the primary sensory, upstream unimodal, downstream unimodal, heteromodal, paralimbic and limbic zones of the cerebral cortex."

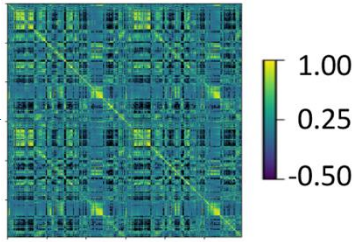
Mesulam et al. (1998) Brain

HUMAN CONNECTOME PROJECT

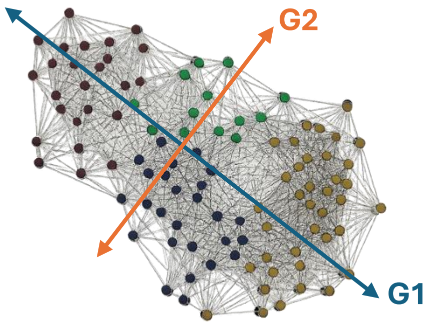
820 Participants
1 h rest / each

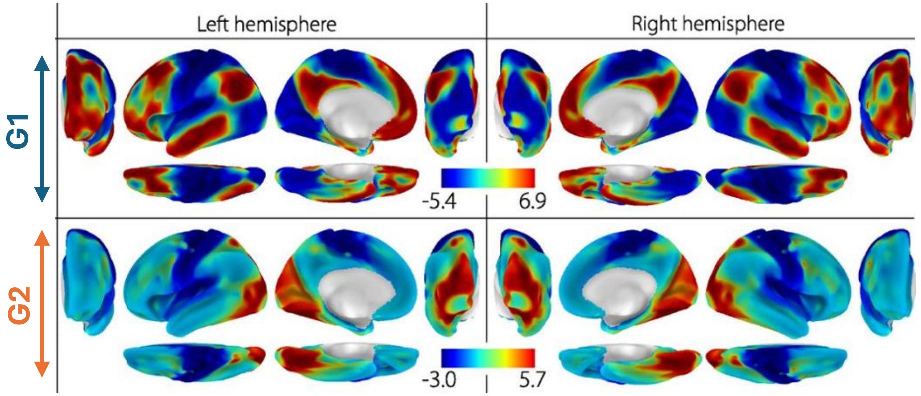


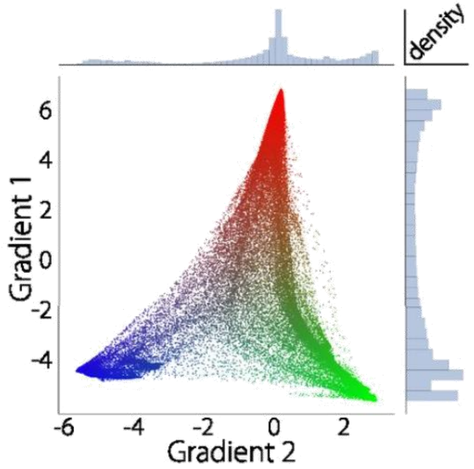
Vertex-wise FC (59,412 x 59,412)

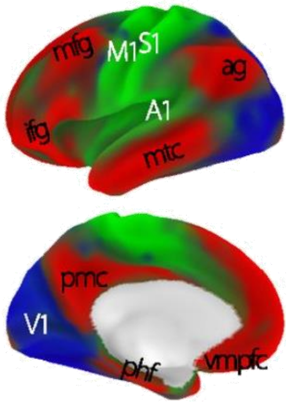


Vertex-wise Adjacency Matrix









Margulies et al. (2016) PNAS

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2016 — Hierarchical gradient structure of FC

2025 — Multiple ongoing population neuroscience data collection efforts continue to make ... researchers

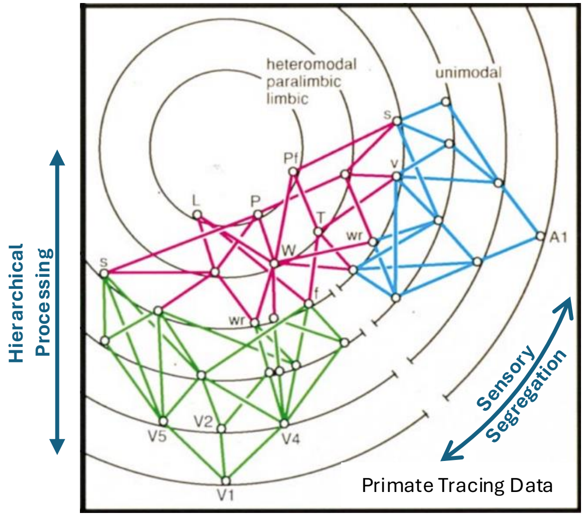
Biswal & Uddin (2025) Nature

Brain (1998), **121**, 1013–1052

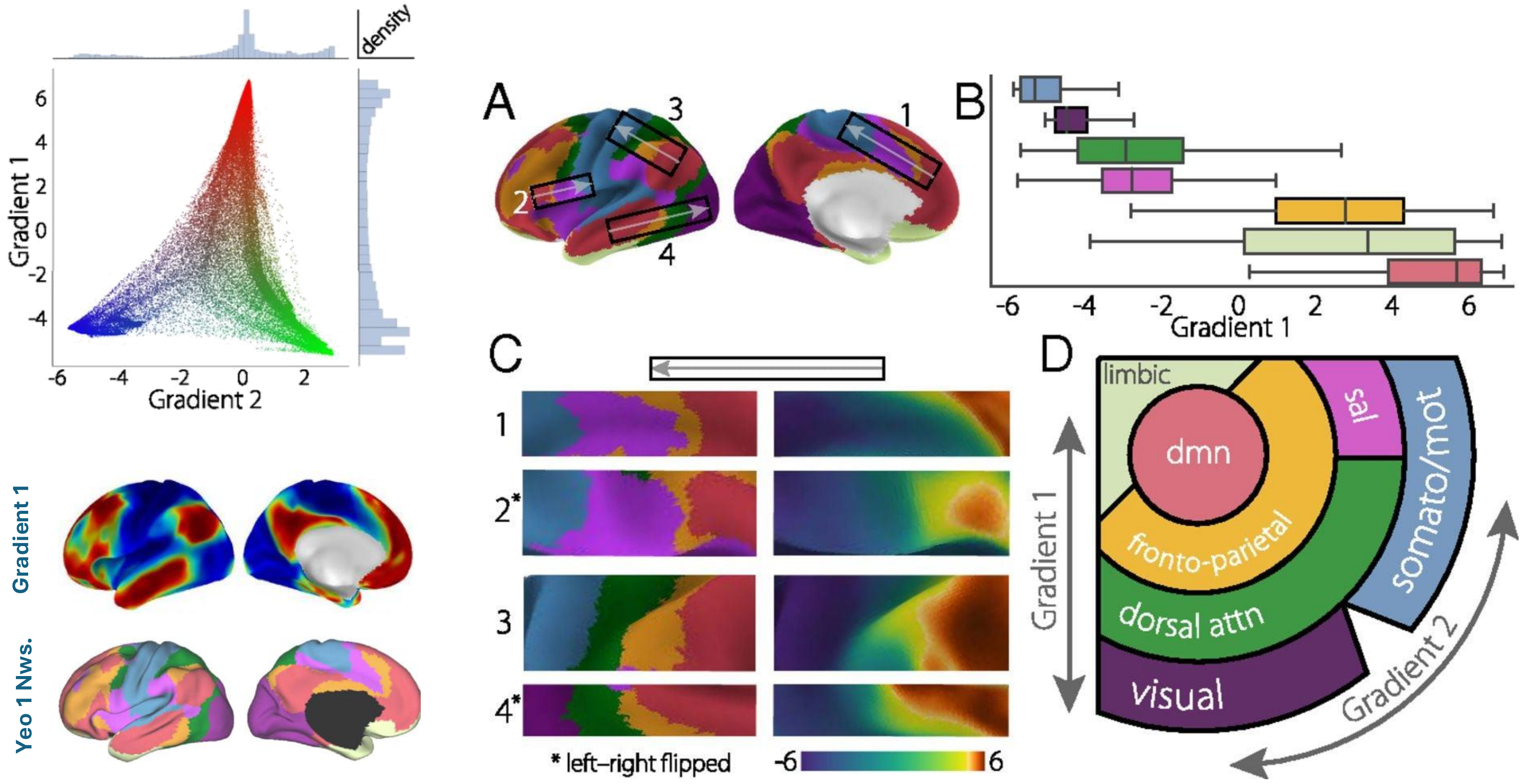
REVIEW ARTICLE

From sensation to cognition

M.-Marsel Mesulam



"Sensory information undergoes extensive associative elaboration and attentional modulation as it becomes incorporated into the texture of cognition. This process occurs along a core synaptic hierarchy which includes the primary sensory, upstream unimodal, downstream unimodal, heteromodal, paralimbic and limbic zones of the cerebral cortex."



Margulies et al. (2016) PNAS

History |

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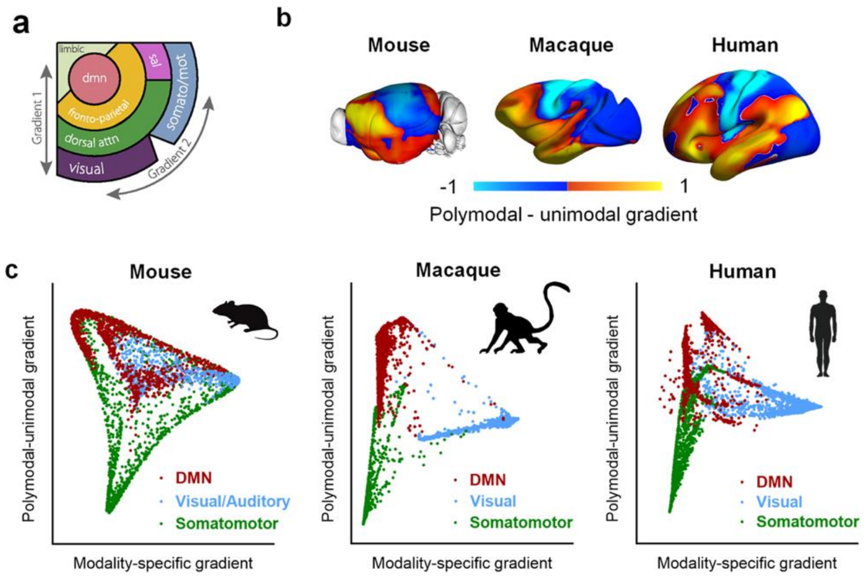
researchers

Biswal & Uddin (2025) Nature

Gradient organization across species



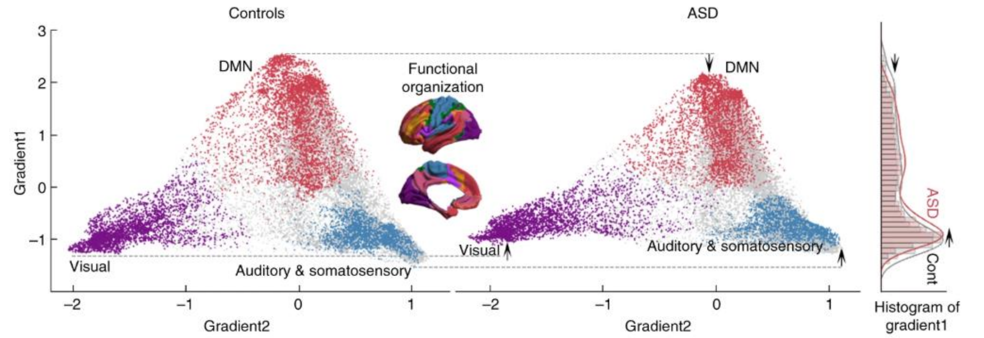
Pagani et al. (2023) Communications Biology

Gradient organization across the lifespan

Taylor IV et al. (2026) Nature

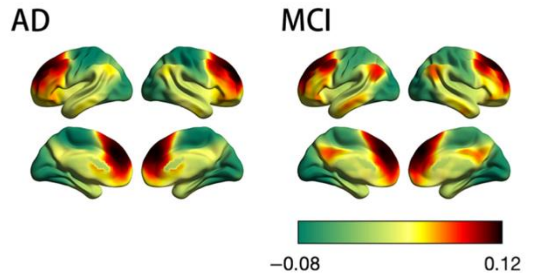
Gradient re-organization in clinical populations

Autism Spectrum Disorder



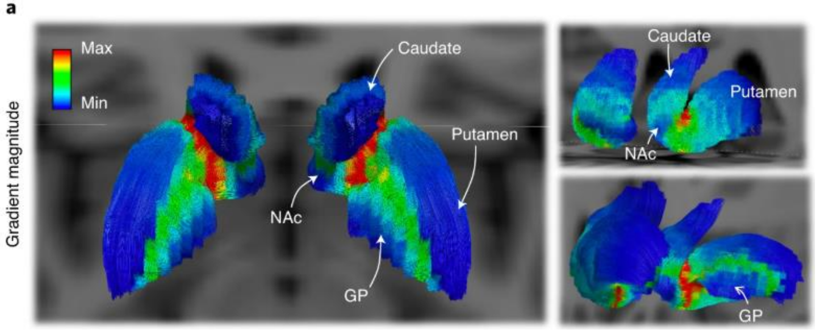
Hong et al. (2019) Nature Communications

Dementia



Hu et al. (2022) HBM

Gradient organization in subcortical regions



Tian et al. (2020) Nature Communications

History |

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Biswal & Uddin (2025) Nature

COMMUNICATIONS BIOLOGY

https://doi.org/10.1038/s42003-020-0794-7 OPEN

BrainSpace: a toolbox for the analysis of macroscale gradients in neuroimaging and connectomics datasets

Reinder Vos de Wael[1,7], Oualid Benkarim[1,7], Casey Paquola[1], Sara Lariviere[1], Jessica Royer[1], Shahin Tavakol[1], Ting Xu[1,2], Seok-Jun Hong[1,2], Georg Langs[3], Sofie Valk[4], Bratislav Misic[1], Michael Milham[2], Daniel Margulies[5], Jonathan Smallwood[6,7] & Boris C. Bernhardt[1,7]✉

BrainSpace

latest

Search docs

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Docs » Welcome to BrainSpace's documentation! Edit on GitHub

Welcome to BrainSpace's documentation!

https://github.com/MICA-MNI/brainspace/workflows/Python%20package/badge.svg

codecov 75% | build passing | pypi v0.2.1 | License BSD | python 3.9 | 3.10 | 3.11 | 3.12 | 3.13

BrainSpace is a lightweight cross-platform toolbox primarily intended for macroscale gradient mapping and analysis of neuroimaging and connectome level data. The current version of BrainSpace is available in Python and MATLAB, programming languages widely used by the neuroimaging and network neuroscience communities. The toolbox also contains several maps that allow for exploratory analysis of gradient correspondence with other brain-derived features, together with tools to generate spatial null models.

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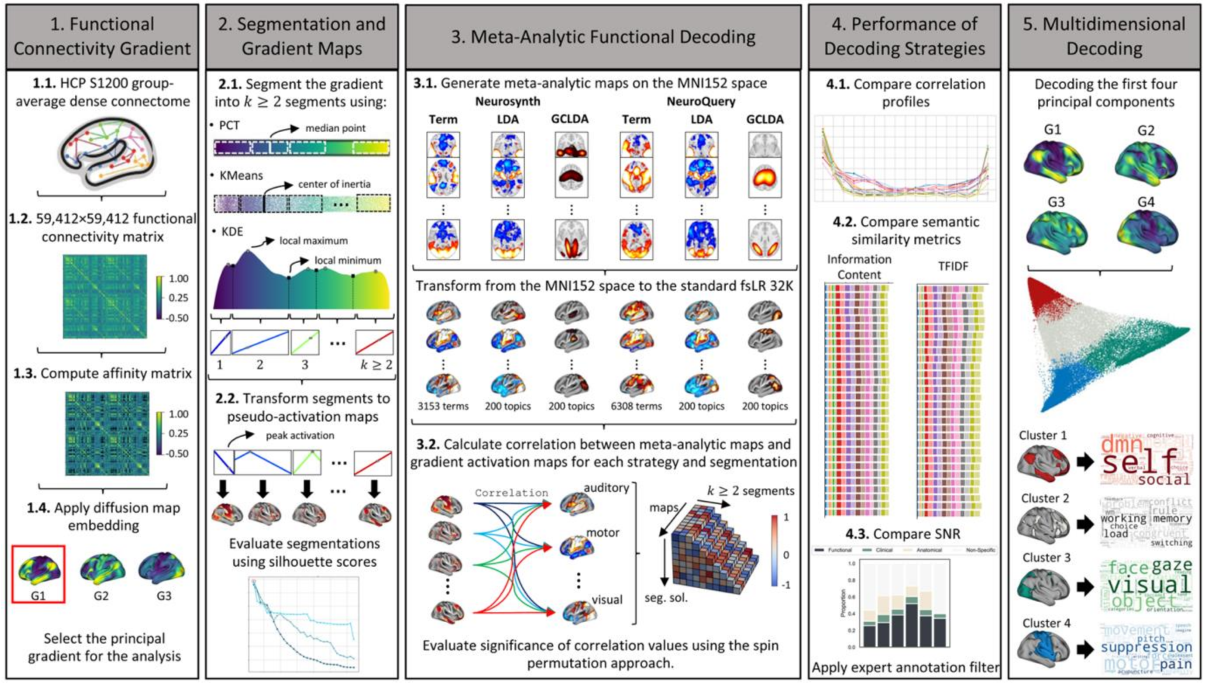
Imaging Neuroscience

an open access journal

Research Article

Methods for decoding cortical gradients of functional connectivity

Julio A. Peraza[a], Taylor Salo[b], Michael C. Riedel[c], Katherine L. Bottenhorn[d], Jean-Baptiste Poline[e], Jérôme Dockès[e], James D. Kent[f], Jessica E. Bartley[a], Jessica S. Flannery[g], Lauren D. Hill-Bowen[h], Rosario Pintos Lobo[h], Ranjita Poudel[i], Kimberly L. Ray[f], Jennifer L. Robinson[j], Robert W. Laird[a], Matthew T. Sutherland[h], Alejandro de la Vega[f], Angela R. Laird[a]



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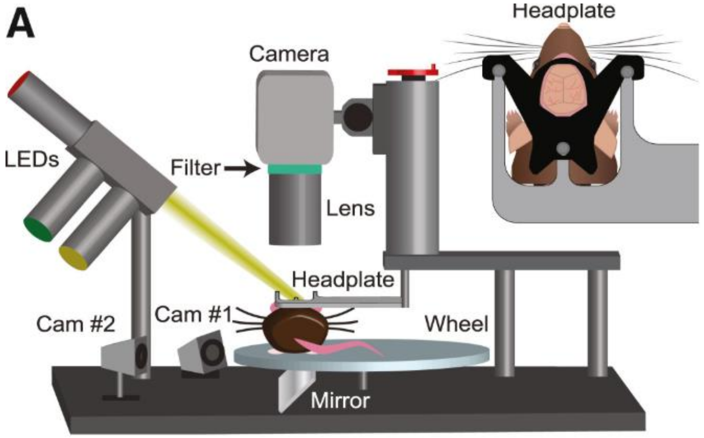
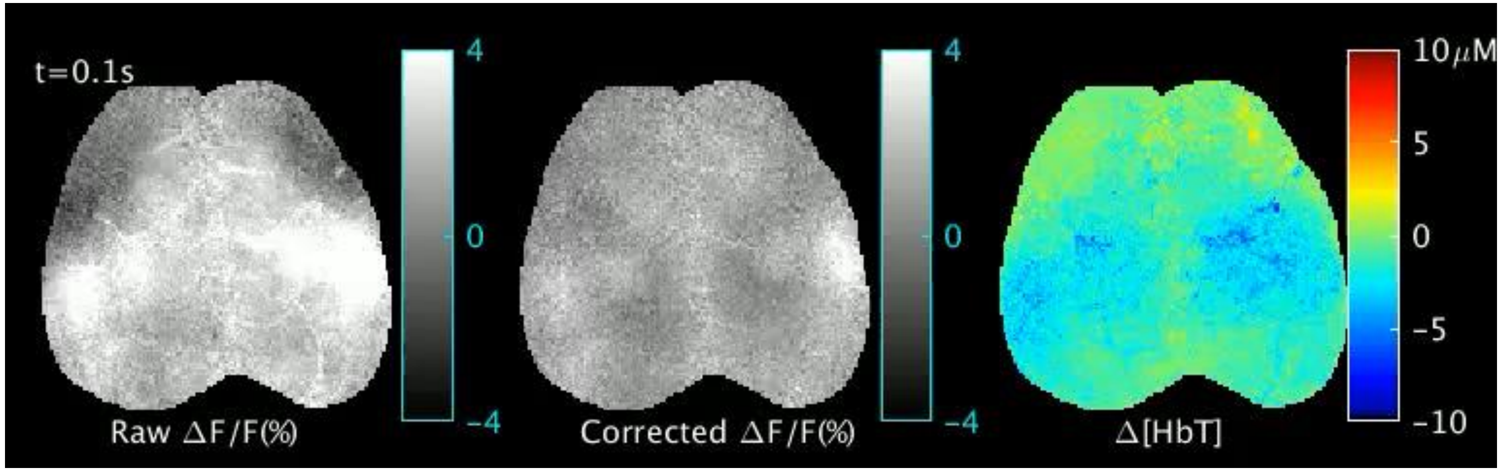
Biswal & Uddin (2025) Nature

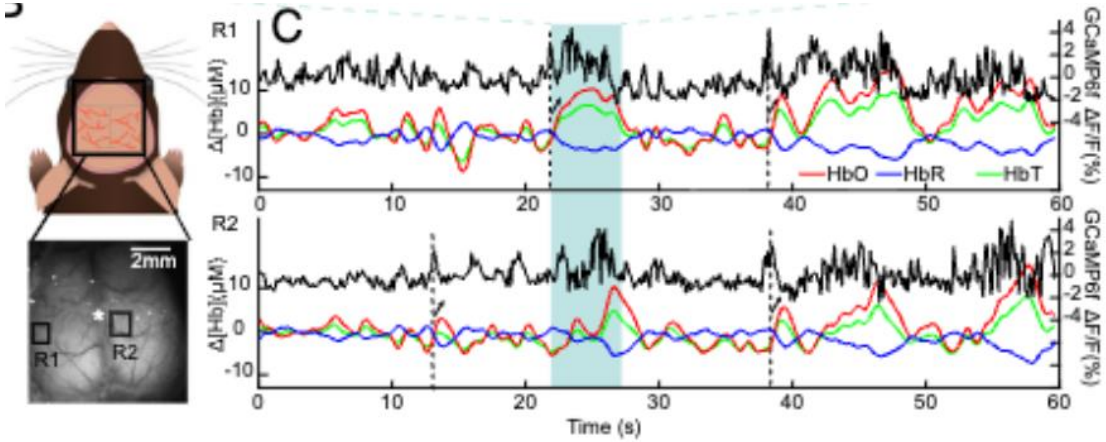
"In rs-fMRI, hemodynamic fluctuations have been found to exhibit patterns of bilateral synchrony... **<u>However, the relationship between resting-state hemodynamics and underlying neural activity has not been well established</u>**, making the neural underpinnings of FC networks unclear"



Neural Activity

Hemodynamic Activity





"Characteristic patterns of resting-state hemodynamics were accompanied by more rapidly changing bilateral patterns of resting-state neural activity."

Ma et al. (2016) PNAS

History |

- **1995** — First rsfMRI functional connectivity paper
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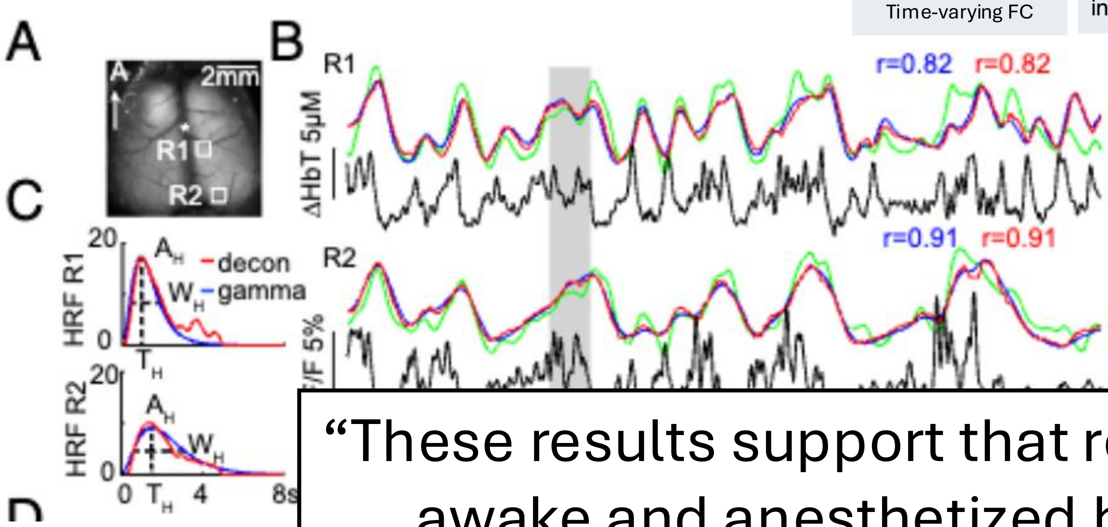
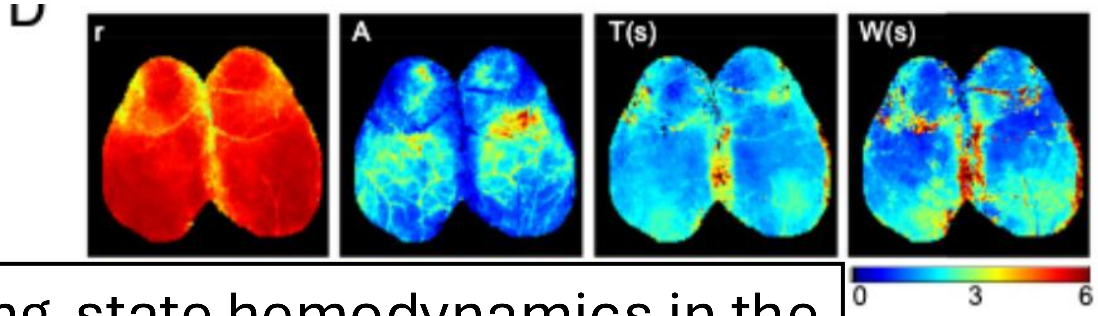
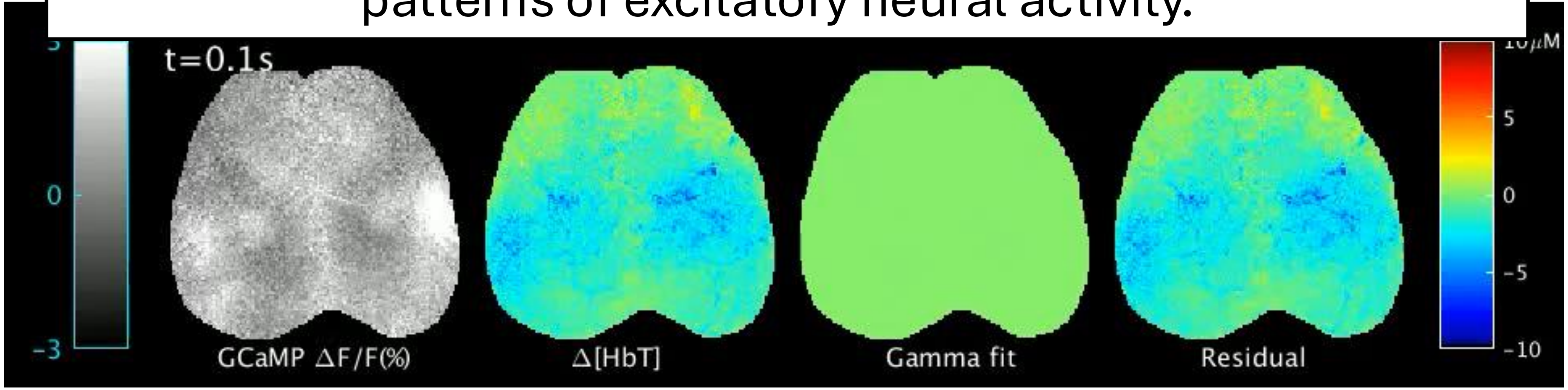
Biswal & Uddin (2025) Nature





“These results support that resting-state hemodynamics in the awake and anesthetized brain are coupled to underlying patterns of excitatory neural activity.”



“Spatiotemporal hemodynamics could be modeled by convolving this neural activity with hemodynamic response functions derived through both deconvolution and gamma-variate fitting.”

Ma et al. (2016) PNAS

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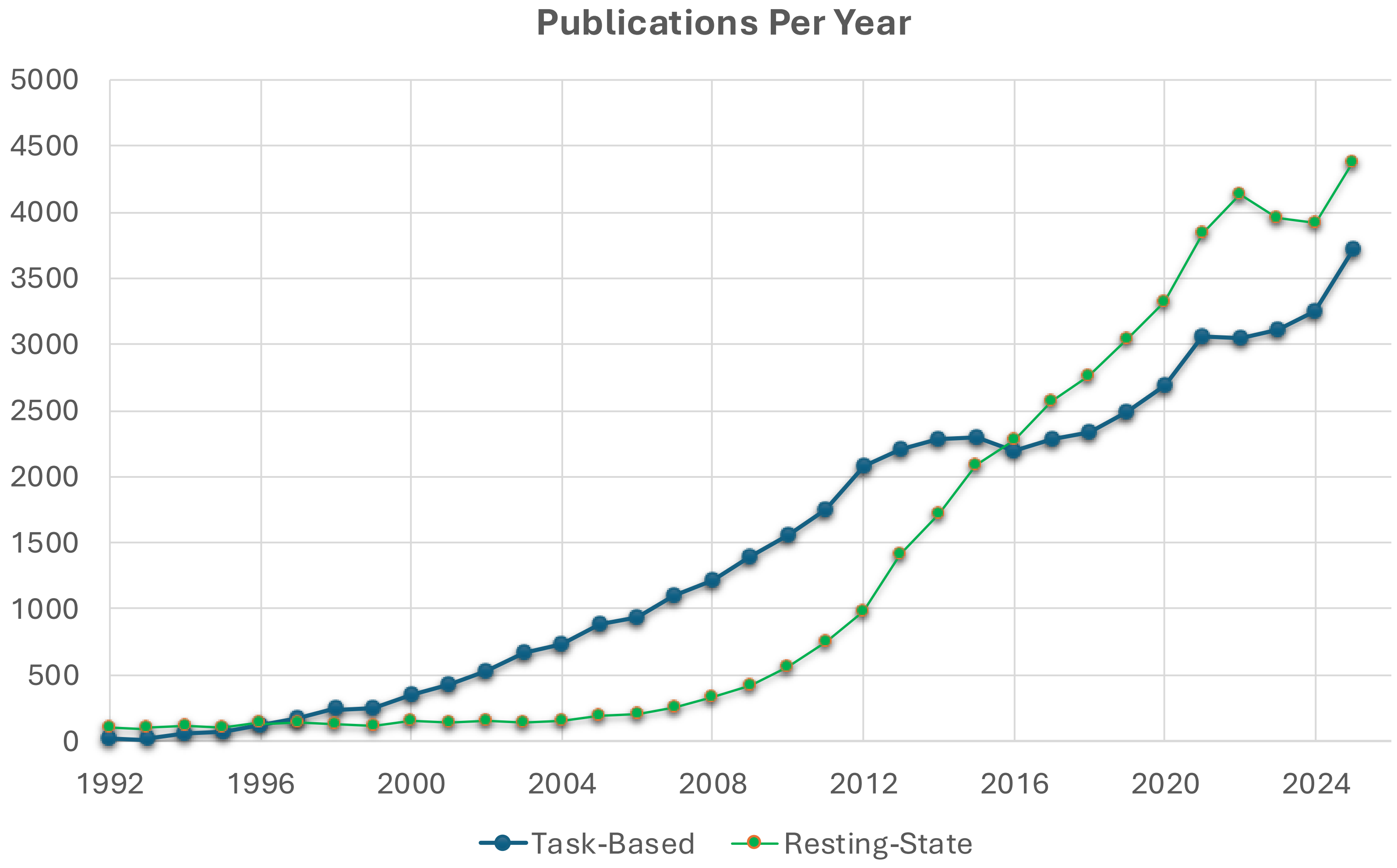
Biswal & Uddin (2025) Nature



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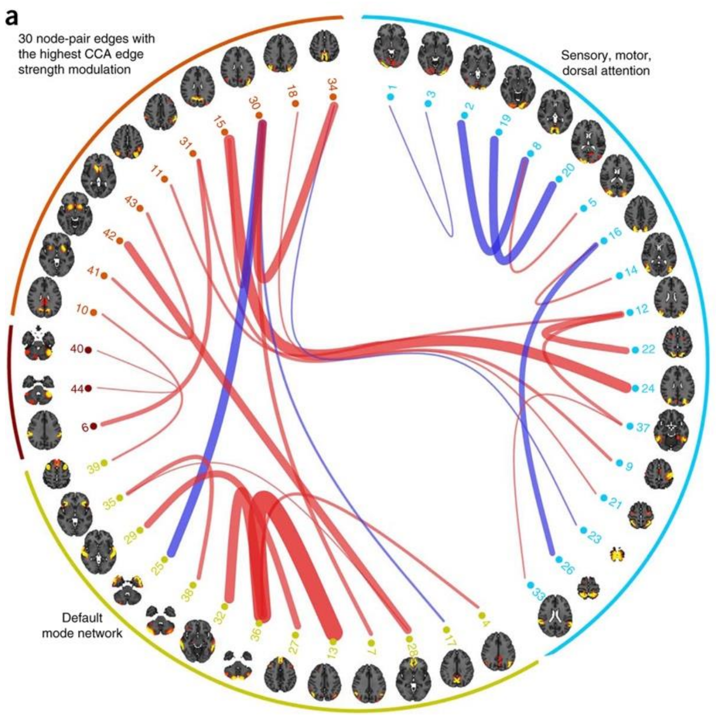
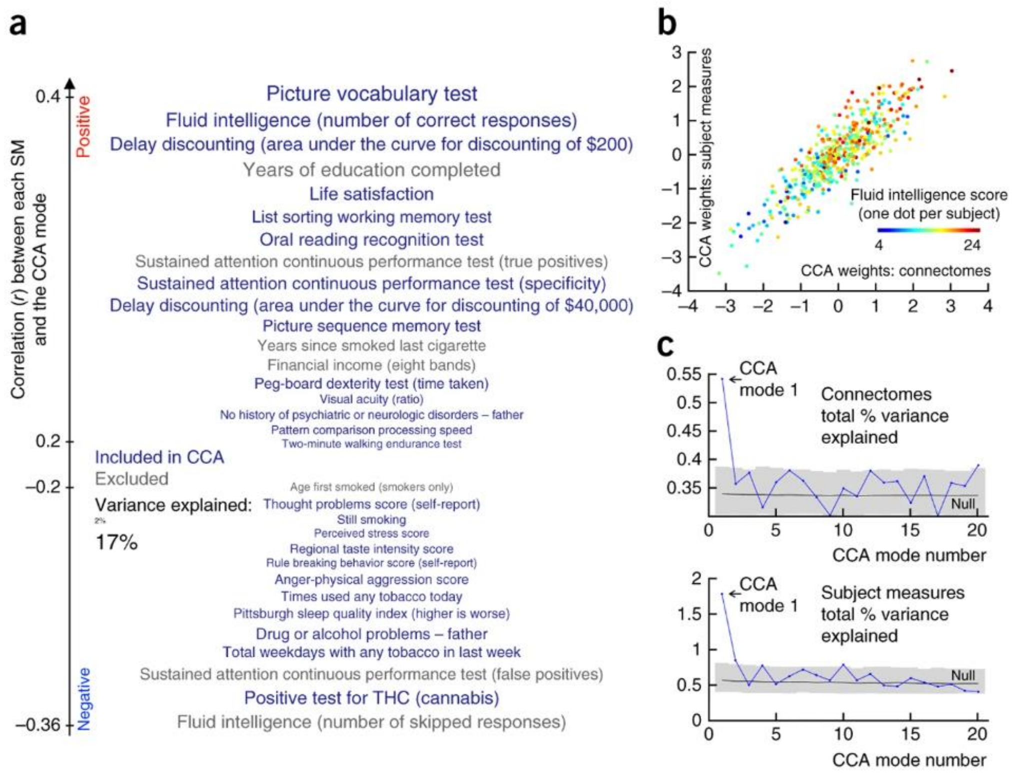
- Demonstrated coupling to neural activity
- 2025 — Multiple ongoing population neuroscience data collection efforts continue to make rsfMRI data available to researchers
- Brain-wide associations

Biswal & Uddin (2025) Nature

Functional Neuroimaging Data ⟷ Behavioral / Clinical / Phenotype Data



461 Subjects from the Human Connectome Project



280 Behavioral and Demographic Measures

Smith et al. (2015) Nature Neuroscience

History |

- **1995** — First rsfMRI functional connectivity paper
- **2001** — Default mode hypothesis of brain function
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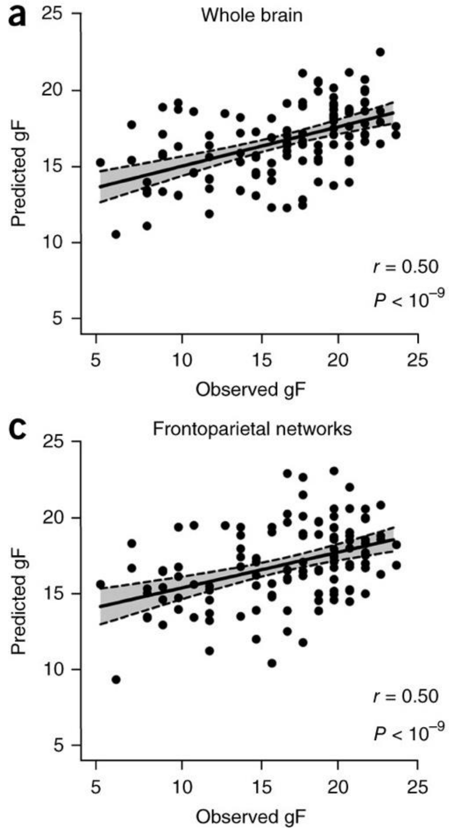
Brain-wide associations

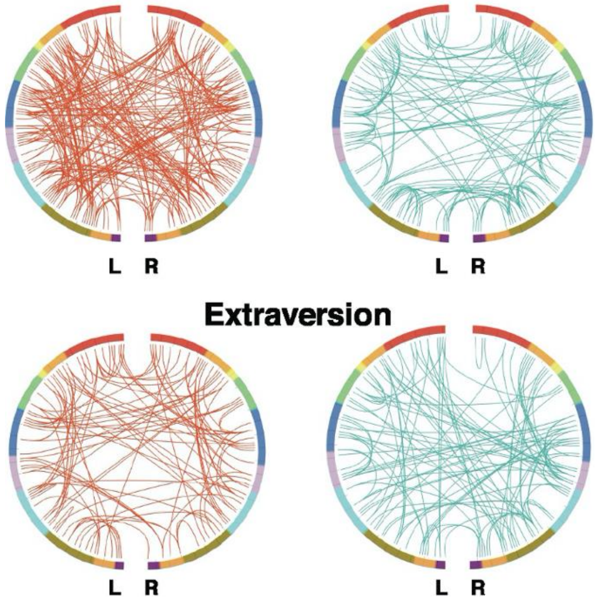
Biswal & Uddin (2025) Nature

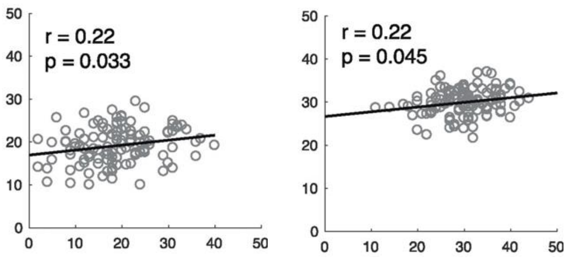
Fluid Intelligence



Finn et al. (2015) Nat. Neurosc.

Personality Traits

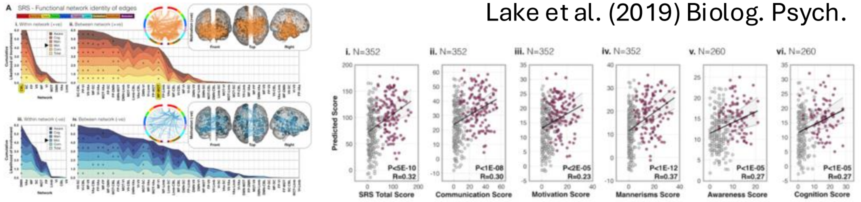




Hsu et al. Soc Gogn & Affect Neuro (2018)

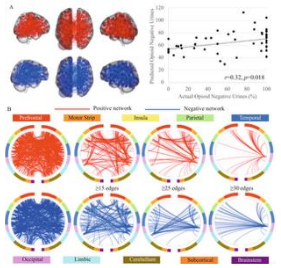
Clinical Markers

ASD



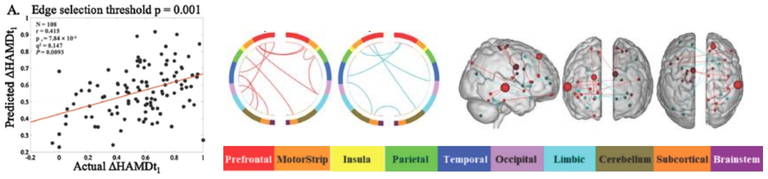
Lake et al. (2019) Biolog. Psych.

Addiction



Lichenstein et al. (2019) Molecular Psych.

Depression



Ju et al. (2020) J Affect. Disorders

OCD, PTSD, Schizophrenia,...

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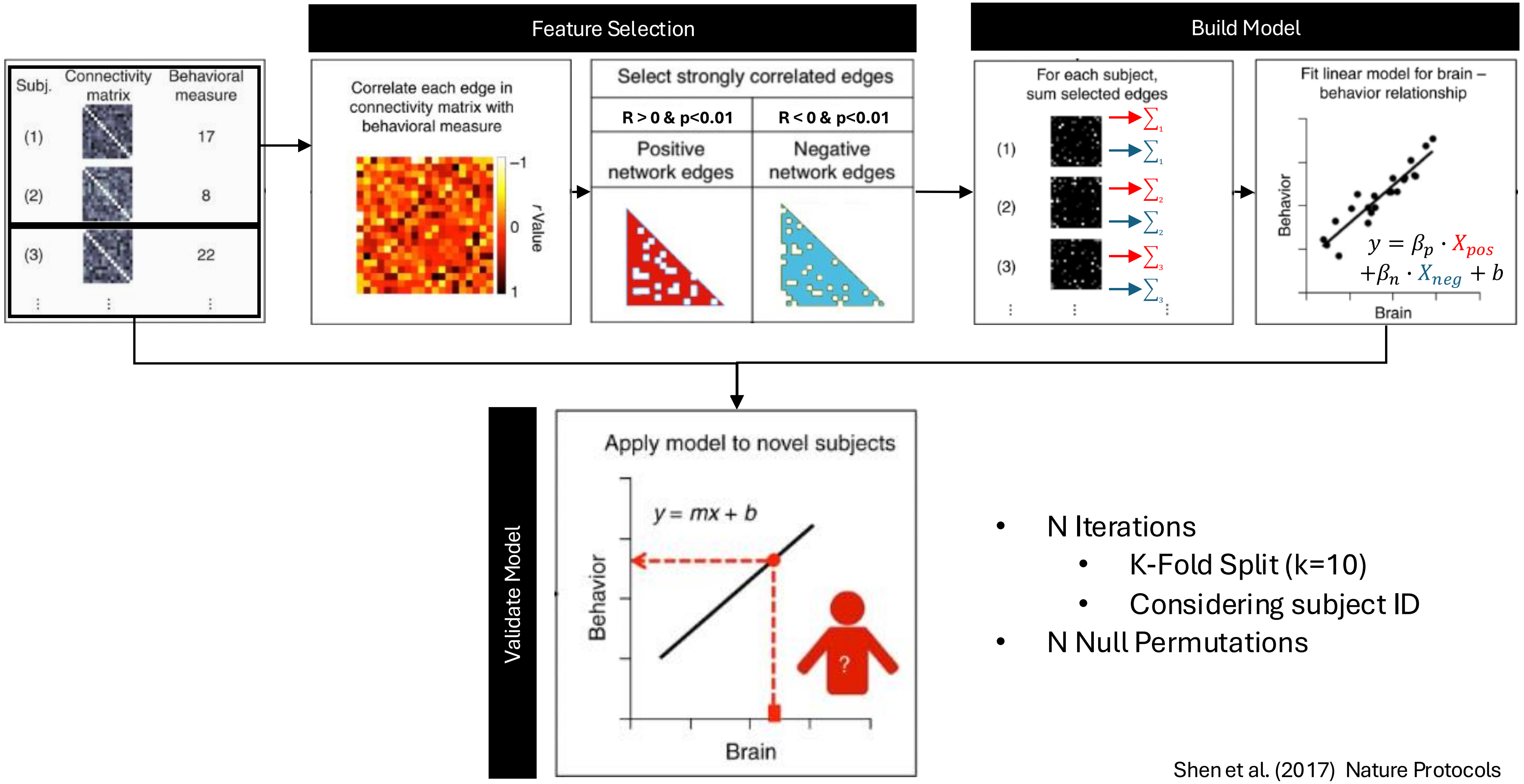
- Brain-wide associations

Biswal & Uddin (2025) Nature

Connectome Predictive Modeling (CPM)



- N Iterations
  - K-Fold Split (k=10)
  - Considering subject ID
- N Null Permutations

Shen et al. (2017) Nature Protocols

10 Rules for CPM studies

Rule #1: Use out-of-sample prediction for better models

Rule #2: Keep training and test data independent

Rule #3: Use cross-validation if no external dataset available

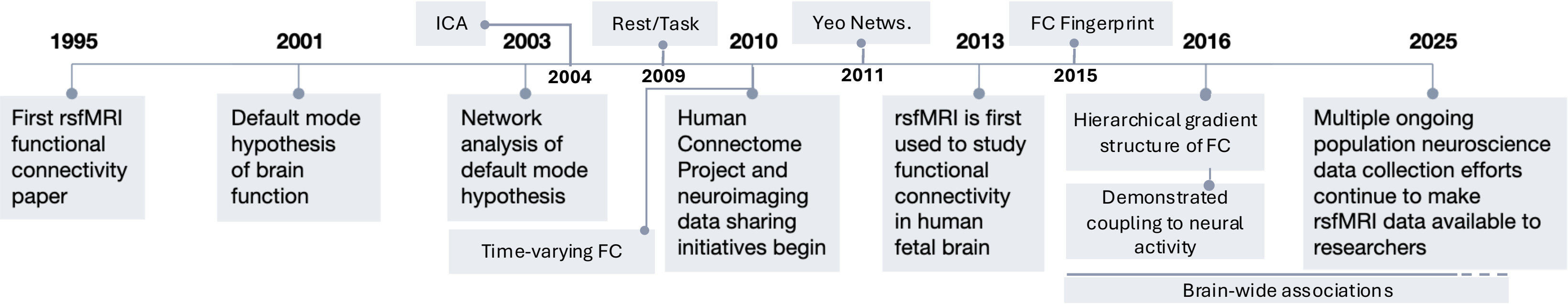
Rule #4: Share data, code and models to facilitate external validation

Rule #5: Properly assess statistical significance

…

Scheinost et al. (2019) NeuroImage

History |



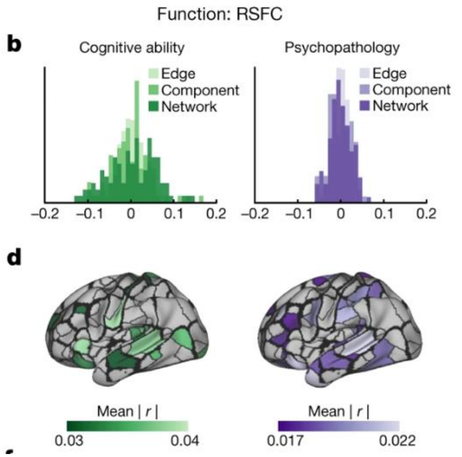
Biswal & Uddin (2025) Nature

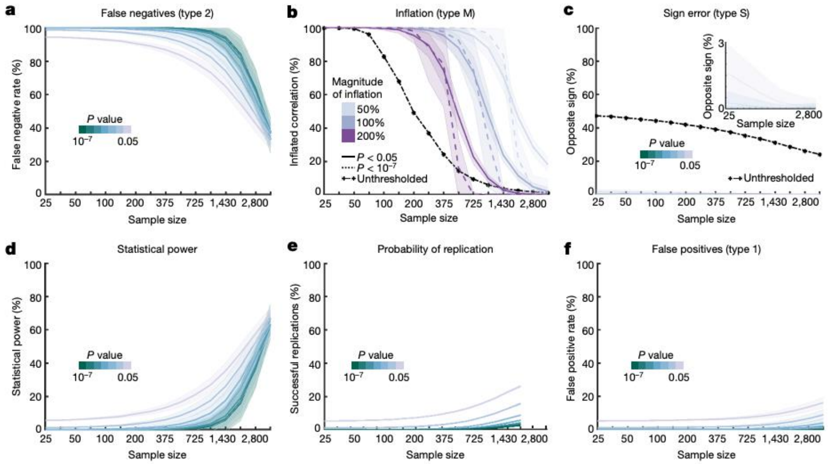
Article

Reproducible brain-wide association studies require thousands of individuals

"…A primary challenge [for MRI] has been replicating associations between inter-individual differences in brain structure or function and complex cognitive or mental health phenotypes (brain-wide association studies (BWAS)). Such BWAS have typically relied on [samples ~ 25 subjects]… potentially too small [samples] for capturing reproducible brain– behavioural phenotype associations. Here we used three of the largest neuroimaging datasets currently available—with a total sample size of around 50,000 individuals—to quantify BWAS effect sizes and reproducibility as a function of sample size."

"BWAS associations were smaller than previously thought, resulting in statistically underpowered studies, inflated effect sizes and replication failures at typical sample sizes. As sample sizes grew into the thousands, replication rates began to improve and effect size inflation decreased. More robust BWAS effects were detected for functional MRI (versus structural), cognitive tests (versus mental health questionnaires) and multivariate methods (versus univariate)."





Marek et al. (2022) Nature

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Demonstrated coupling to neural activity

Brain-wide associations

2025 — Multiple ongoing population neuroscience data collection efforts continue to make rsfMRI data available to researchers

Biswal & Uddin (2025) Nature

How to establish robust brain–behavior relationships without thousands of individuals

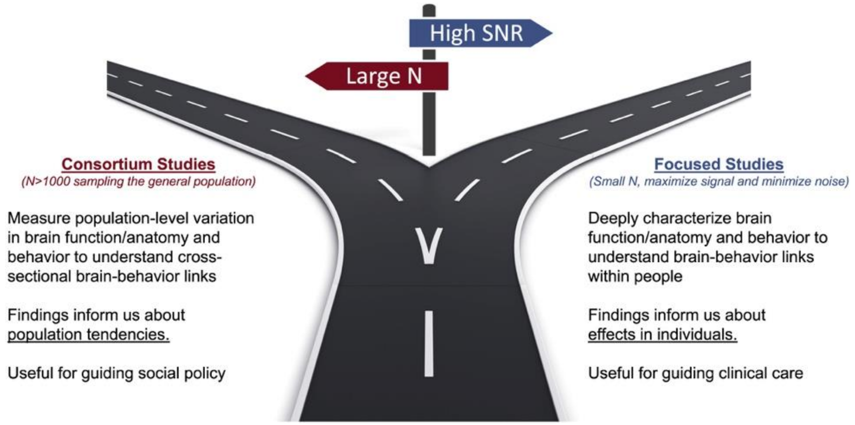
Can studying individual differences in brain structure and function reveal individual differences in behavior? Analyses of MRI data from nearly 50,000 individuals may suggest that the possibility is fleeting. Although sample size is important for brain-based prediction, researchers can take other steps to build better biomarkers. These include testing model generalizability across people, datasets, and time points and maximizing model robustness by optimizing brain data acquisition, behavioral measures, and prediction approaches.

Monica D. Rosenberg and Emily S. Finn (2022) Nature Neuroscience

Brain-behavior correlations: Two paths toward reliability

Caterina Gratton,[1,2,*] Steven M. Nelson,[3,4] and Evan M. Gordon[5]
[1]Department of Psychology, Northwestern University, Evanston, IL, USA
[2]Department of Neurology, Northwestern University, Evanston, IL, USA
[3]Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA
[4]Masonic Institute for the Developing Brain, University of Minnesota, Minneapolis, MN, USA
[5]Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA
*Correspondence: caterina.gratton@gmail.com
https://doi.org/10.1016/j.neuron.2022.04.018

In a recent issue of *Nature*, Marek et al. (2022) demonstrate that cross-sectional brain-behavior correlations are often small and unreliable without large samples. This observation pushes human neuroscience toward study designs that either maximize sample sizes to detect small effects or maximize effect sizes using focused investigations.



Gratton et al. (2022) Neuron

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Brain-wide associations

Interpretational Challenge: what is the functional role of the spontaneous activity that we measure during resting-state fMRI?

Biswal & Uddin (2025) Nature

Unconscious Processes

Memory Consolidation

Lewis et al. (2009) PNAS, Laumann & Snyder (2021) Cur Op Bio Sci

Homeostatic Processes

Marder & Goaillard (2006) Nat Rev. Neuroscience

Interoceptive Monitoring

Choe et al. (2021) PLoS One

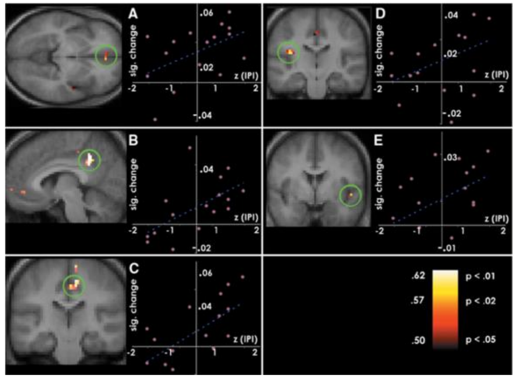
Internal Model Optimization

Pezzulo et al. (2021) Trends Cog Science

Fluctuations in Vigilance

Liu X et al. (2018) Nat. Comms., Laumann & Snyder (2021), Gonzalez-Castillo et al. (2021) NeuroImage

Conscious Experience / Processes

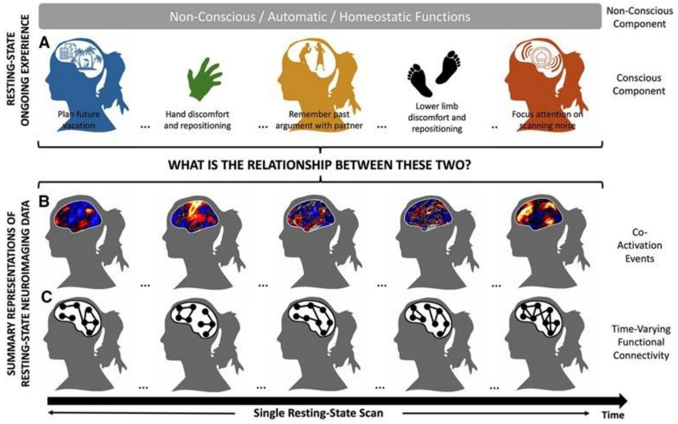


Wandering Minds: The Default Network and Stimulus-Independent Thought

Malia F. Mason,[1*§] Michael I. Norton,[2] John D. Van Horn,[1†] Daniel M. Wegner,[3] Scott T. Grafton,[1‡] C. Neil Macrae[4]

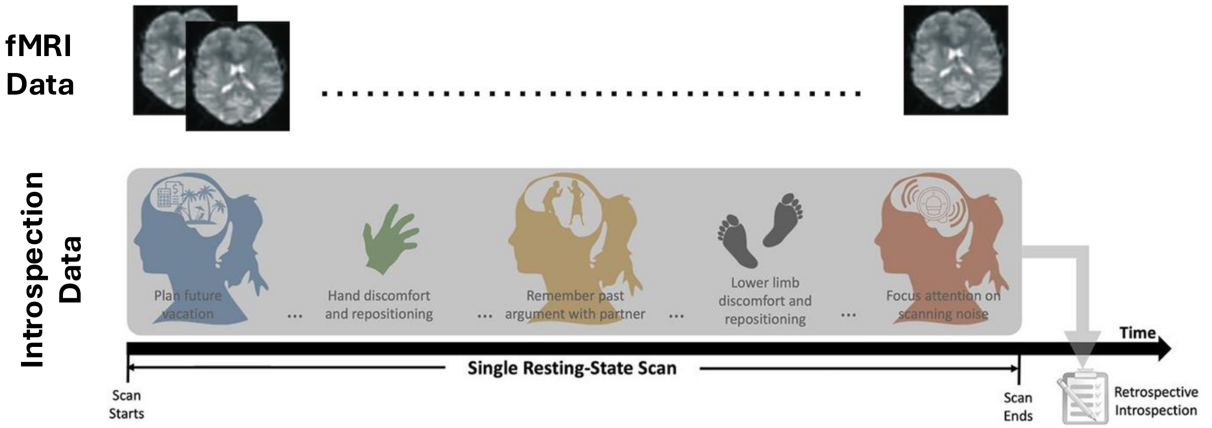
Despite evidence pointing to a ubiquitous tendency of human minds to wander, little is known about the neural operations that support this core component of human cognition. Using both thought sampling and brain imaging, the current investigation demonstrated that mind-wandering is associated with activity in a default network of cortical regions that are active when the brain is "at rest." In addition, individuals' reports of the tendency of their minds to wander were correlated with activity in this network.

Mason et al. (2007) Science

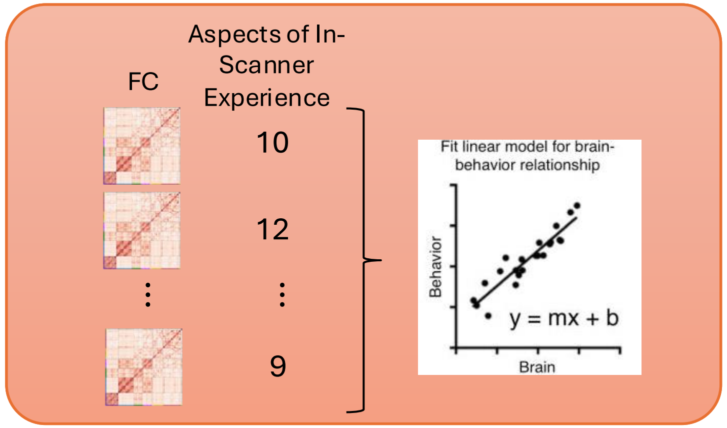


Gonzalez-Castillo et al (2021) J of Neuroscience

Should we consider experience when interpreting resting-state fMRI?



Predictive Framework



Q1 | Do subjects tend to be in the same mental state when asked to rest?

Q2 | Can we detect differences in FC if we group scans according to thought pattern?

Q3 | Can we predict characteristics of ongoing thought based on FC measures?

Q4 | Are these observations driven by other underlying phenotypes?

Gonzalez-Castillo et al. Nature Comms (In Press)

Max Planck Institute – Mind-Brain-Body Dataset

Neuroimaging Data

175 Subjects
1 – 4 rs-fMRI scans (Eyes Open)
15 min rs-fMRI
TR = 1.4s | 2.3mm^3 | 3T

↓

471 Scans from 133 subjects passed QA

Basic Demographics Data

Age Range (5 year intervals) & Gender

Phenotype Data

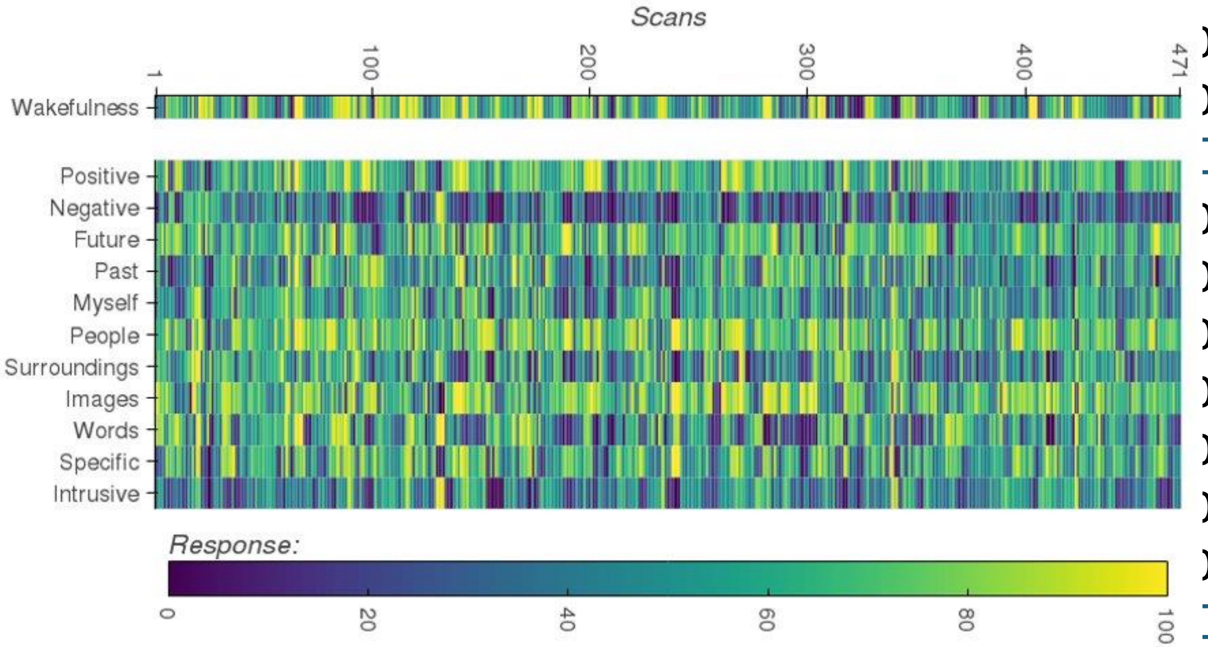
- Personality / Habitual Behaviors (21)
- Mind Wandering / Mindfulness (4)
- Synesthesia (1)
- Cognitive Controls / Sustained Att. (1)
- Creativity (4)

Multidimensional Experience Sampling Reports

FORM

My thoughts were intrusive 0 ... 100
My thoughts were more specific than vague 0 ... 100

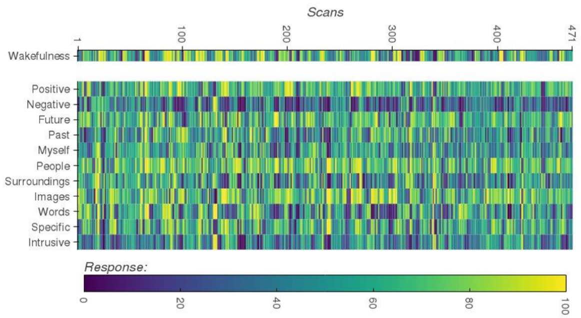
CONTENT

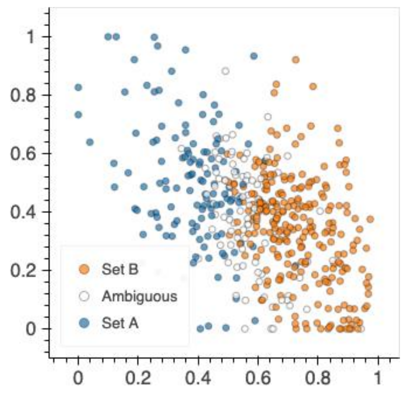


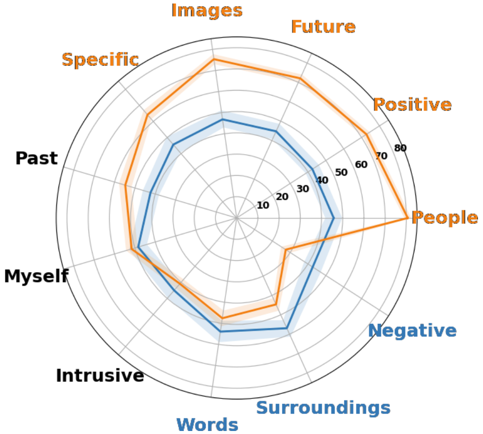
VIGILANCE I was completely awake 0 ... 100

Mendes et al. Scientific Reports (2019)

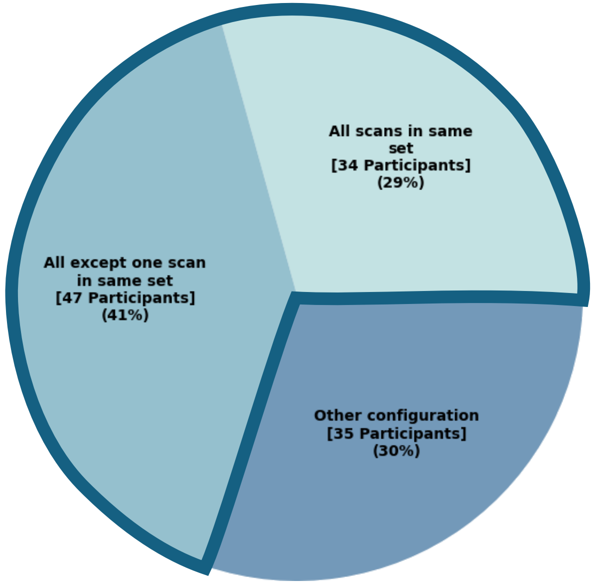
Q1 | Do subjects tend to be in the same mental state when asked to rest?



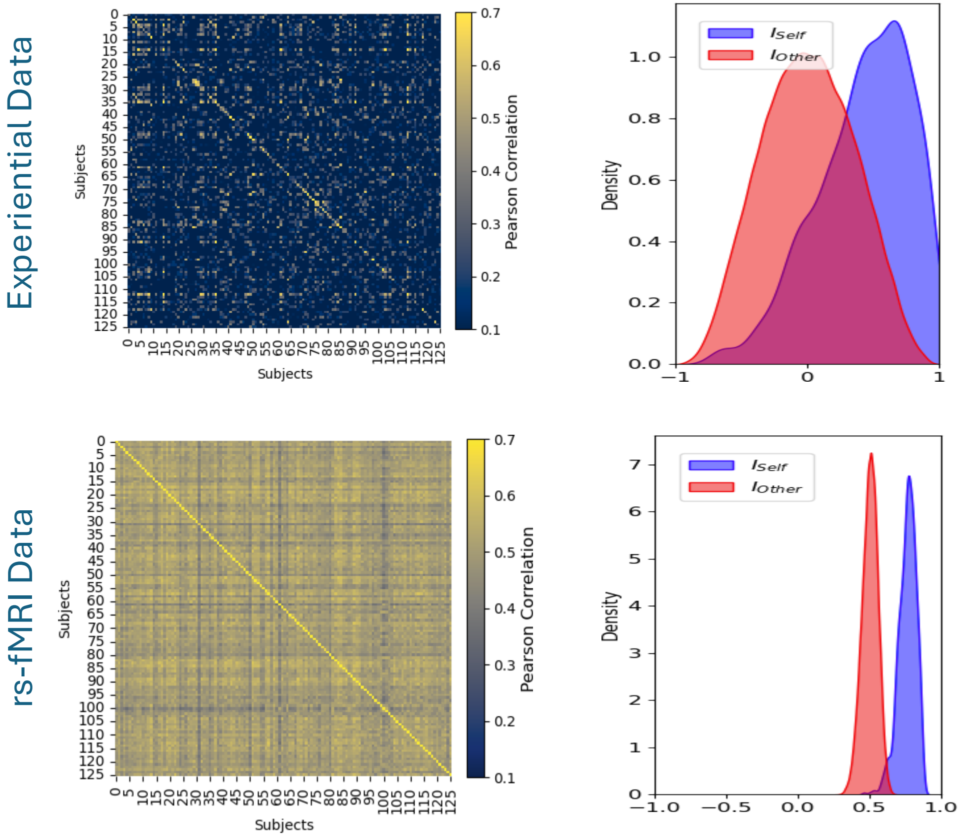




Repeated Set Membership



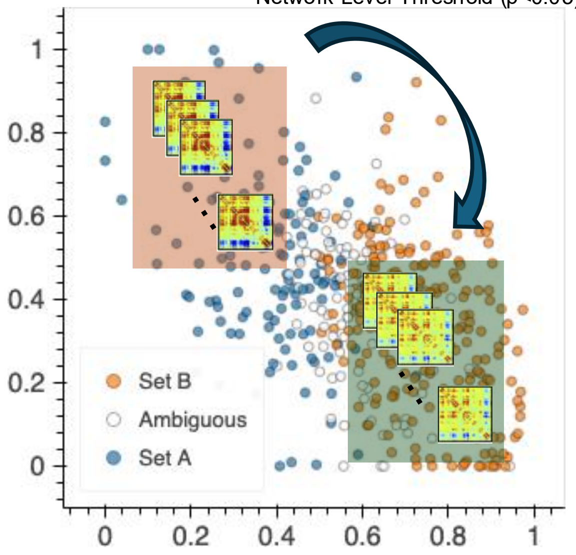
Identifiability Matrix

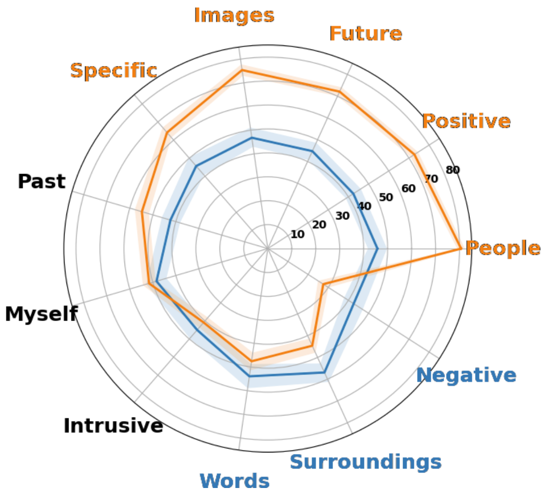


Gonzalez-Castillo et al. Nature Comms (In Press)

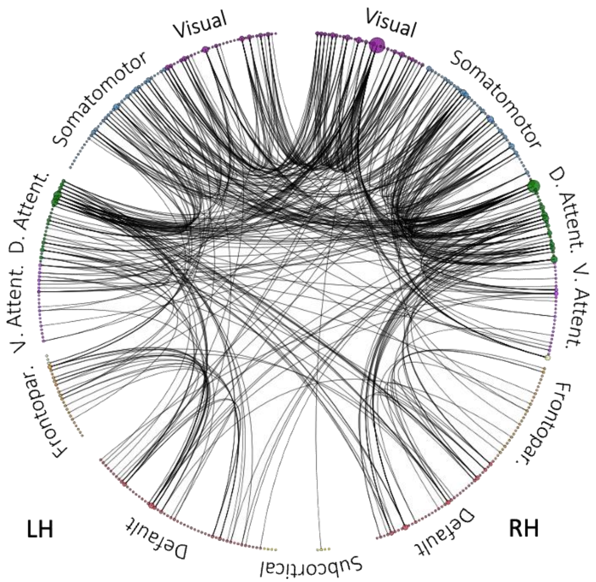
Q2 | Can we detect differences in FC if we group scans according to thought pattern?

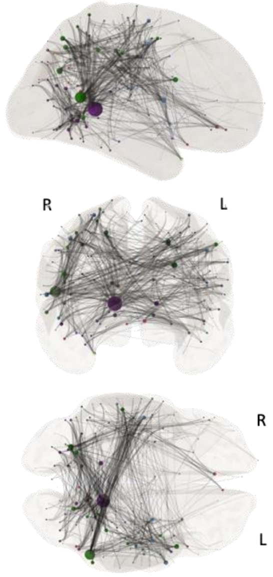
NBS | 5000 Permutations
Edge-Level Threshold (T=3.1; p < 0.001)
Network-Level Threshold (p<0.05)

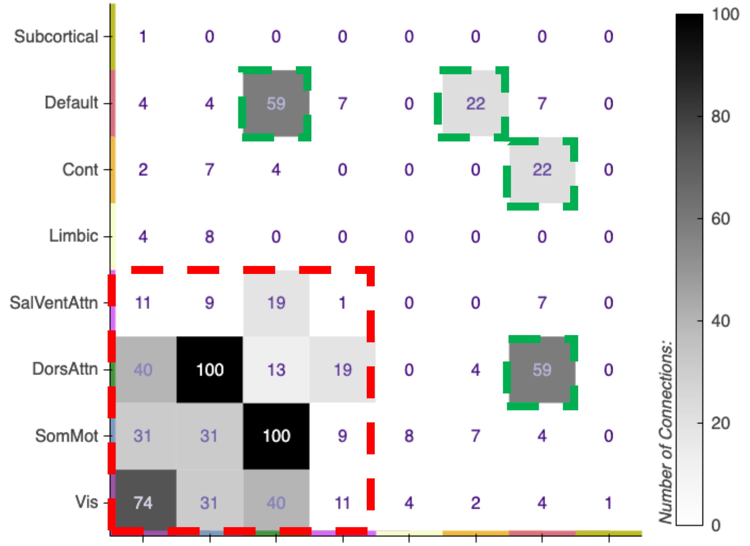




Set A > Set B

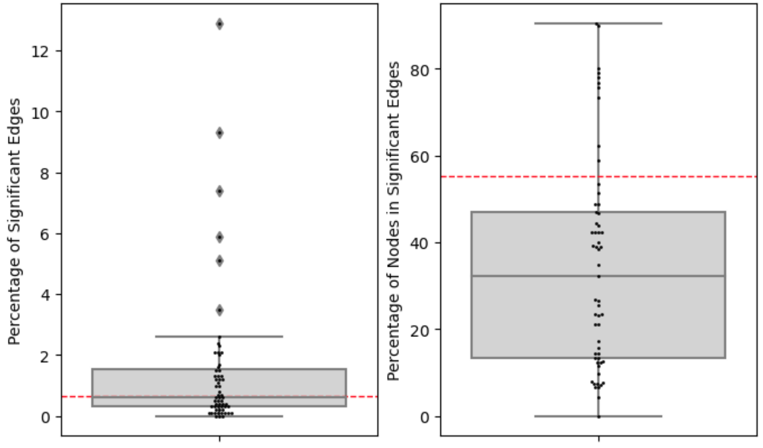






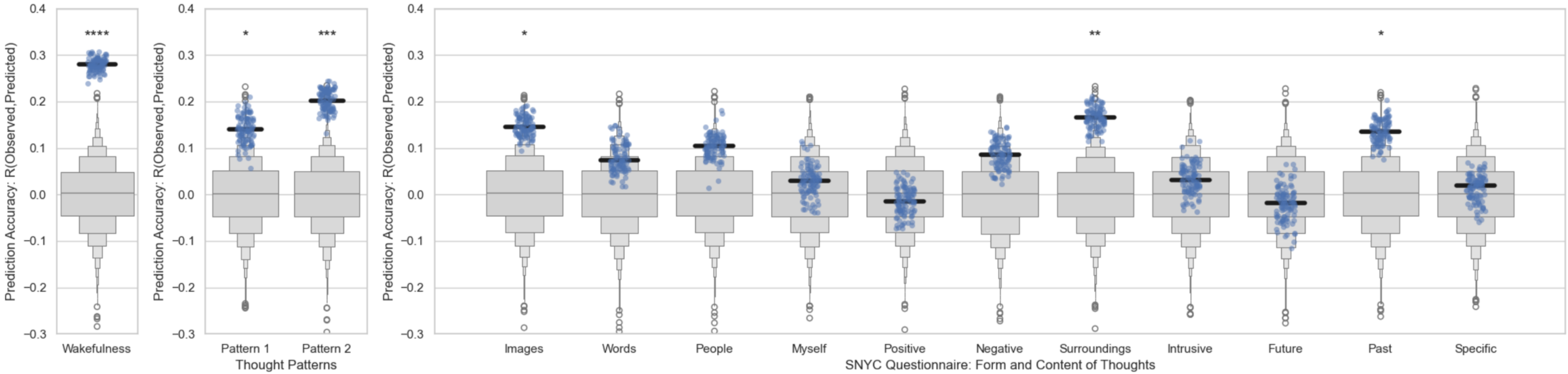
Laterality Index = -0.32 (right)
Number of Nodes = 210 (out of 380) → 55%
Number of Connections = 458 → 0.7%

Comparison to Prior Literature



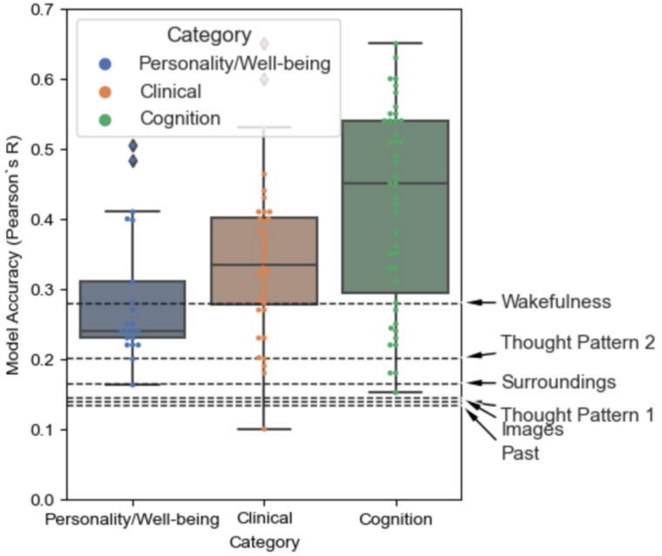
Gonzalez-Castillo et al. Nature Comms (In Press)

Q3 | Can we predict characteristics of ongoing thought based on FC measures?



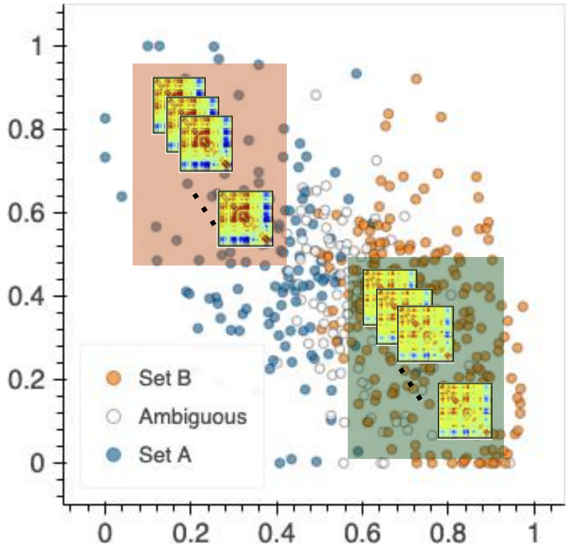
* p<0.05 | ** p<0.01 | *** p< 1e-3 | **** p < 1e-4

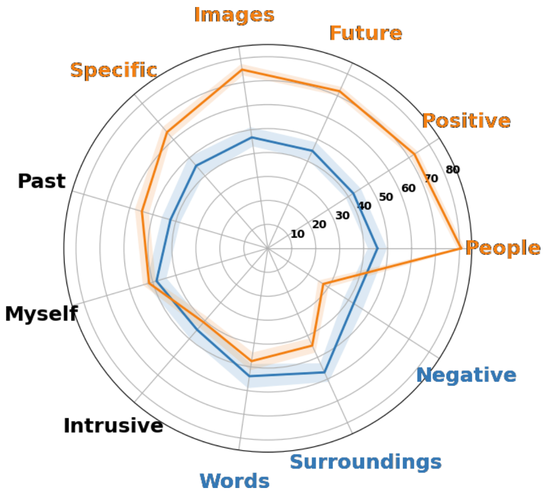
Comparison to Prior Literature



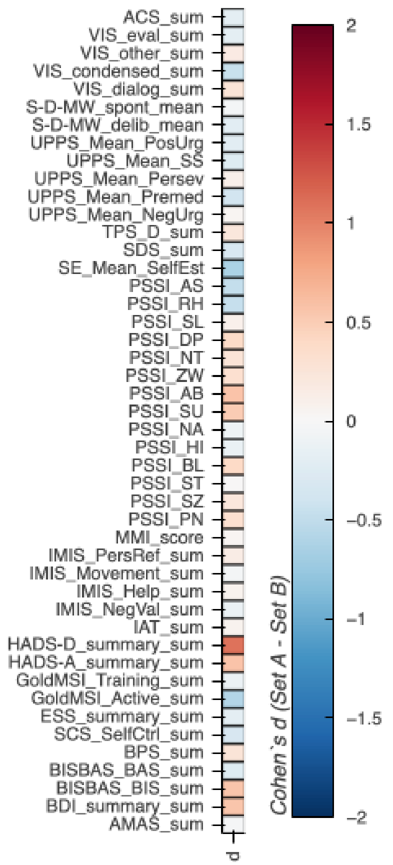
Gonzalez-Castillo et al. Nature Comms (In Press)

Influence of trait-level phenotypes on group differences

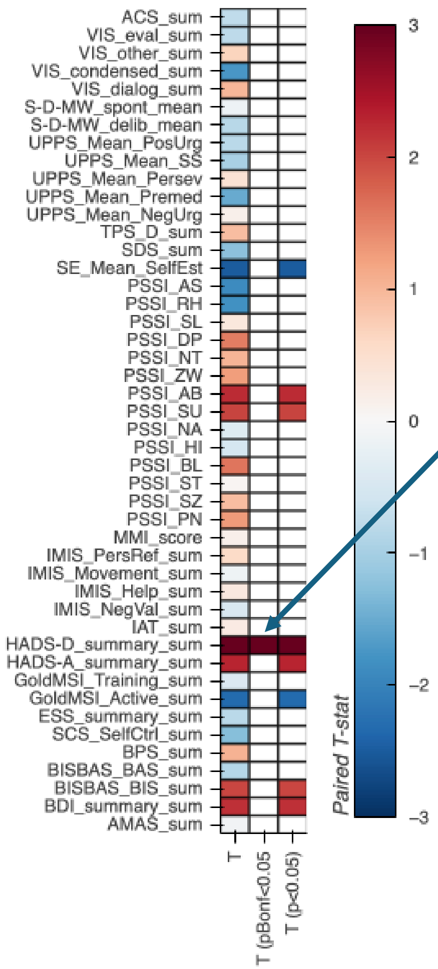




Cohen's d (A – B)



T-test

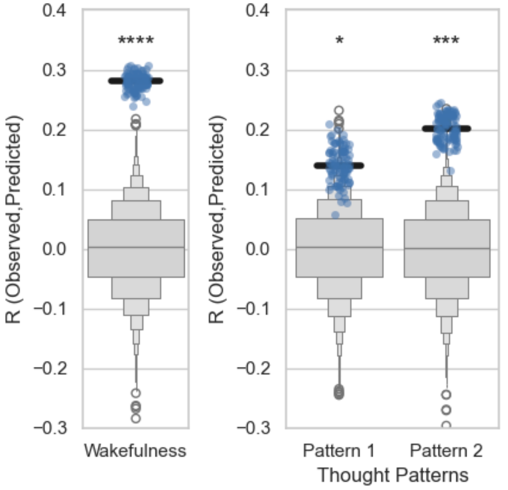


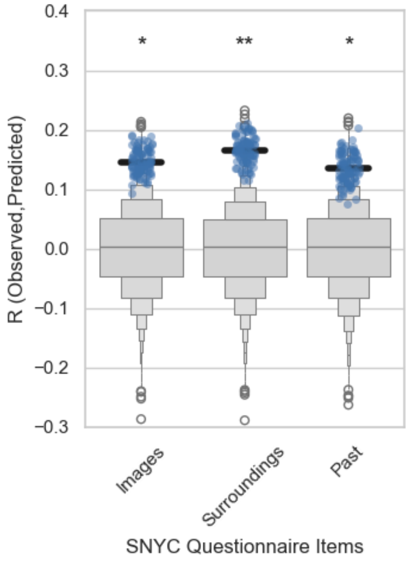
Hospital Anxiety and Depression Scale (HADS)

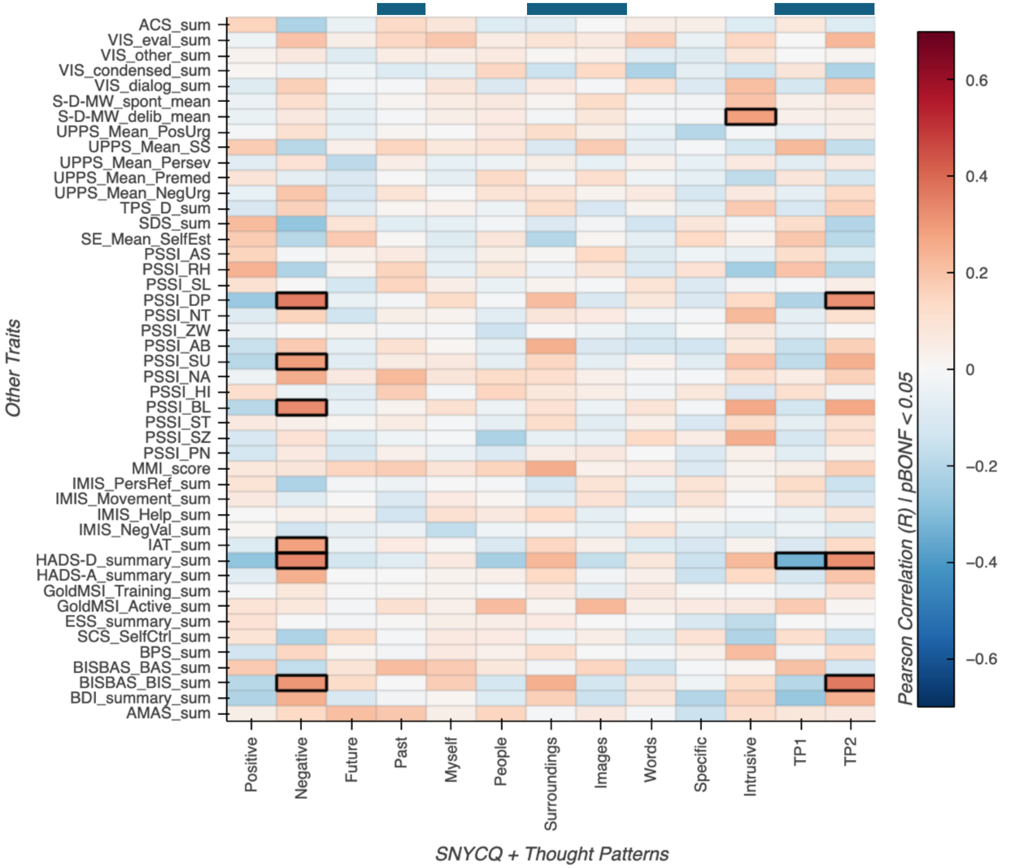
"measures the severity of depression (D) and anxiety (A) related symptoms for the week prior to completion and can be used to assess subclinical tendencies of depression and anxiety."

Gonzalez-Castillo et al. Nature Comms (In Press)

Influence of trait-level phenotypes in predictive modeling







PSSI: Personality Style and Disorder Inventory

IAT: Internet Addiction Test

BIS: Behavioral Inhibition System

SD-MW Delib: Deliberate Spontaneous Mind Wandering

Gonzalez-Castillo et al. Nature Comms (In Press)

Conclusions

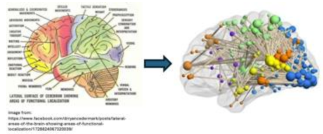
1995	2001	2003	2004	2009	2010	2011	2013	2015	2016	2025
First rsfMRI functional connectivity paper	Default mode hypothesis of brain function	Network analysis of default mode hypothesis	ICA	Rest/Task	Human Connectome Project and neuroimaging data sharing initiatives begin	Yeo Netws.	rsfMRI is first used to study functional connectivity in human fetal brain	FC Fingerprint	Hierarchical gradient structure of FC; Demonstrated coupling to neural activity	Multiple ongoing population neuroscience data collection efforts continue to make rsfMRI data available to researchers

Time-varying FC

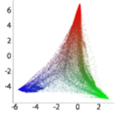
Brain-wide associations

Interpretational Challenge: what is the functional role of the spontaneous activity that we measure during resting-state fMRI?

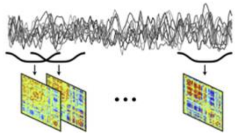
- Resting-state fMRI is a powerful research tool in cognitive and clinical neuroscience, continuing to advance our understanding of the brain



LOCALIZATION → CONNECTOME

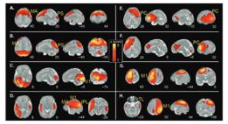


FC AS FINGERPRINT

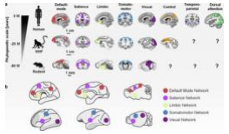


STATIC & DYNAMIC

- Its relative simplicity allows rs-fMRI to address questions other paradigms cannot: fetal & across-species fMRI, unable populations.



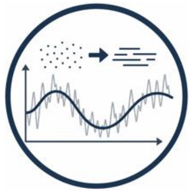
ACROSS-SPECIES & LIFETIME STUDIES



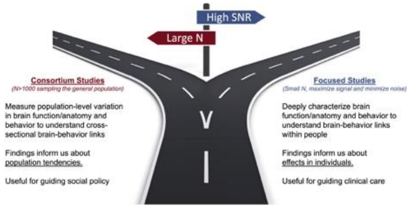
ACROSS-SPECIES & LIFESPAN STUDIES

- Current challenges for the field of rs-fMRI include:

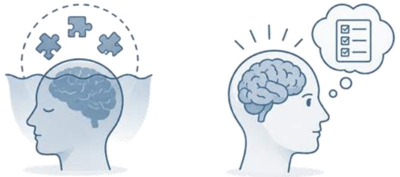
LACK OF STANDARDS



NOISE MITIGATION



DEEP SAMPLING vs. LARGE-N



UNCERTAIN INTERPRETATIONS

- Although rs-fMRI is well positioned to support a new era of precision psychiatry, the field must still bridge the gap between group-level findings and individualized, reliable biomarkers.

Where to go next...

HISTORY

Review

nature

The history and future of resting-state functional magnetic resonance imaging

https://doi.org/10.1038/s41586-025-08953-9

Bharat B. Biswal[1,2] & Lucina Q. Uddin[3,4]

Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI

Bharat Biswal, F. Zerrin Yetkin, Victor M. Haughton, James S. Hyde

METHODOLOGY / DENOISING

nature communications

Article

https://doi.org/10.1038/s41467-024-48781-5

Systematic evaluation of fMRI data-processing pipelines for consistent functional connectomics

Received: 4 October 2022

Accepted: 10 May 2024

Published online: 04 June 2024

Andrea I. Luppi[1,2,3,4], Helena M. Gellersen[5,6], Zhen-Qi Liu[4], Alexander R. D. Peattie[1,2], Anne E. Manktelow[1,2], Ram Adapa[1,2], Adrian M. Owen[7,8], Lorina N... Stavros I. Dimitriadis[10,11]...

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Methods for cleaning the BOLD fMRI signal

César Caballero-Gaudes[a,*], Richard C. Reynolds[b]

[a] Basque Center of Cognition, Brain and Language, San Sebastian, Spain

[b] Scientific and Statistical Computing Core, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, USA

INTERPRETATION DEBATE

Viewpoints

1130 • The Journal of Neuroscience, February 10, 2021 • 41(6):1130–1141

How to Interpret Resting-State fMRI: Ask Your Participants

Javier Gonzalez-Castillo,[1] Julia W.Y. Kam,[2,3] Colin W. Hoy,[4] and Peter A. Bandettini[1,5]

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Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

Brain activity is not only for thinking

Timothy O Laumann[1] and Abraham Z Snyder[2,3]

APPLICATIONS

Article

Frontostriatal salience network expansion in individuals in depression

https://doi.org/10.1038/s41586-024-07805-2

Received: 2 August 2023

Accepted: 9 July 2024

Published online: 4 September 2024

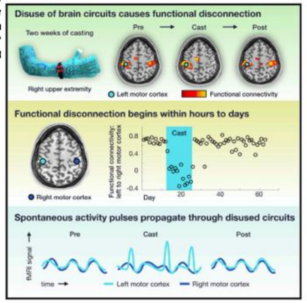
Open access

Charles J. Lynch[1], Immanuel G. Elbau[1], Tommy Ng[1], Aliza Ayaz[1], ... Nicola Manfredi[1], Megan Johnson[1], Megan Chang[1], Jolin Chou[1], ... Claire Ho[1], Maximilian Lueckel[2,3], Hussain Bukhari[1], Derrick Buchan... Nili Solomonov[1], Eric Goldwaser[1], Stefano Moia[5,6,7], Cesar Caballer... Jonathan Downar[8], Fidel Vila-Rodriguez[9], Zafiris J. Daskalakis[10], ... Kendrick Kay[13], Amy Aloysi[14], Evan M. Gordon[15], Mahendra T. Bhati... Jonathan D. Power[1], Benjamin Zebley[1], Logan Grosenick[1], Faith M. ...

Neuron

Plasticity and Spontaneous Activity Pulses in Disused Human Brain Circuits

Graphical Abstract



Authors

Dillan J. Newbold, Timothy O. Laumann, Catherine R. Hoyt, ..., Steven E. Petersen, Abraham Z. Snyder, Nico U.F. Dosenbach

Correspondence

newbold@wustl.edu (D.J.N.), dosenbachn@wustl.edu (N.U.F.D.)

In Brief

Newbold et al. induced human brain plasticity by casting the dominant arm for 2 weeks. Disused brain regions rapidly (<48 h) disconnected from the motor system and manifested large, spontaneous activity pulses. Maintaining the brain's functional architecture may require regular use, and spontaneous activity pulses could serve as a substitute.