Brain Networks in Psychiatry

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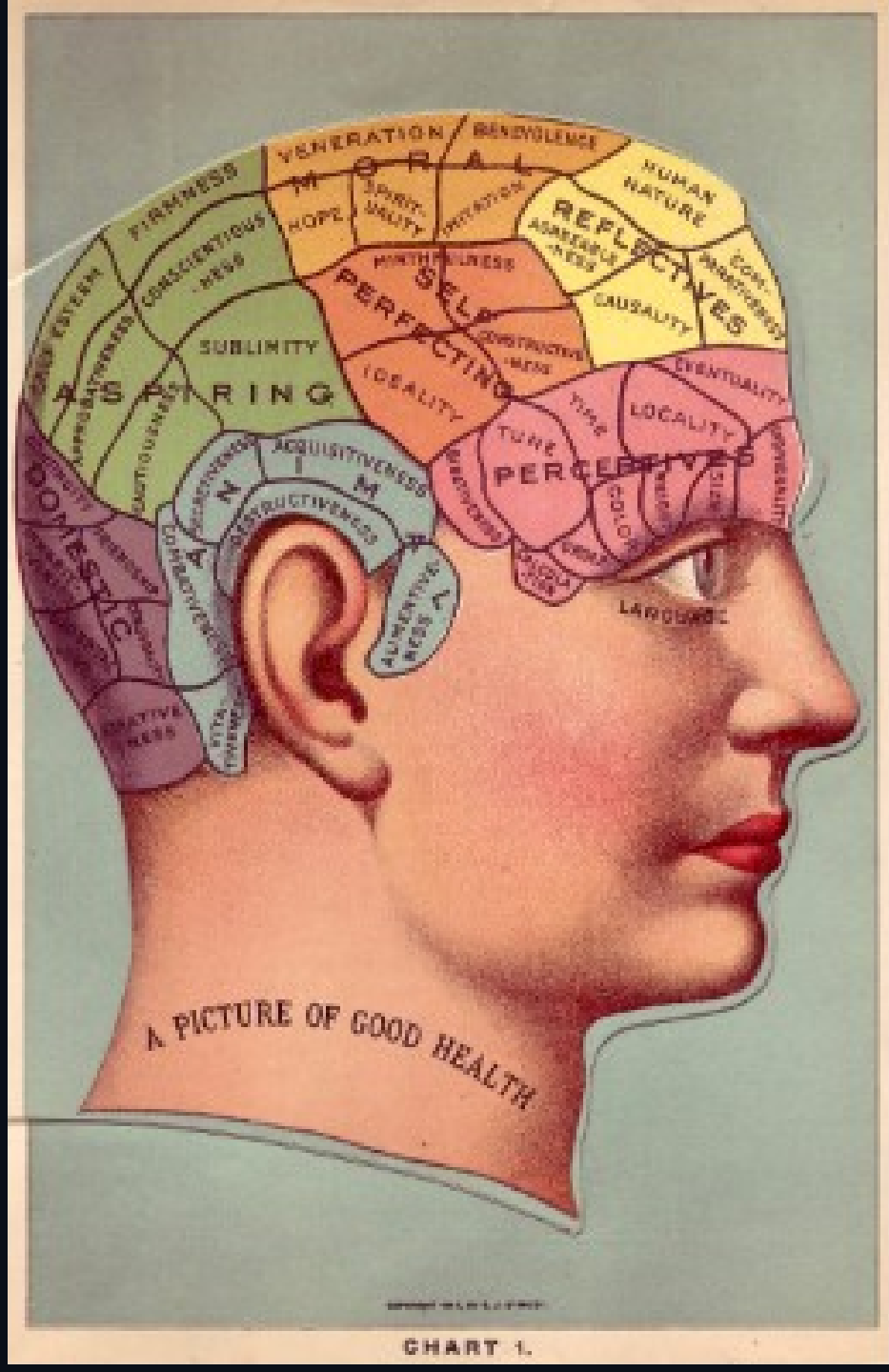
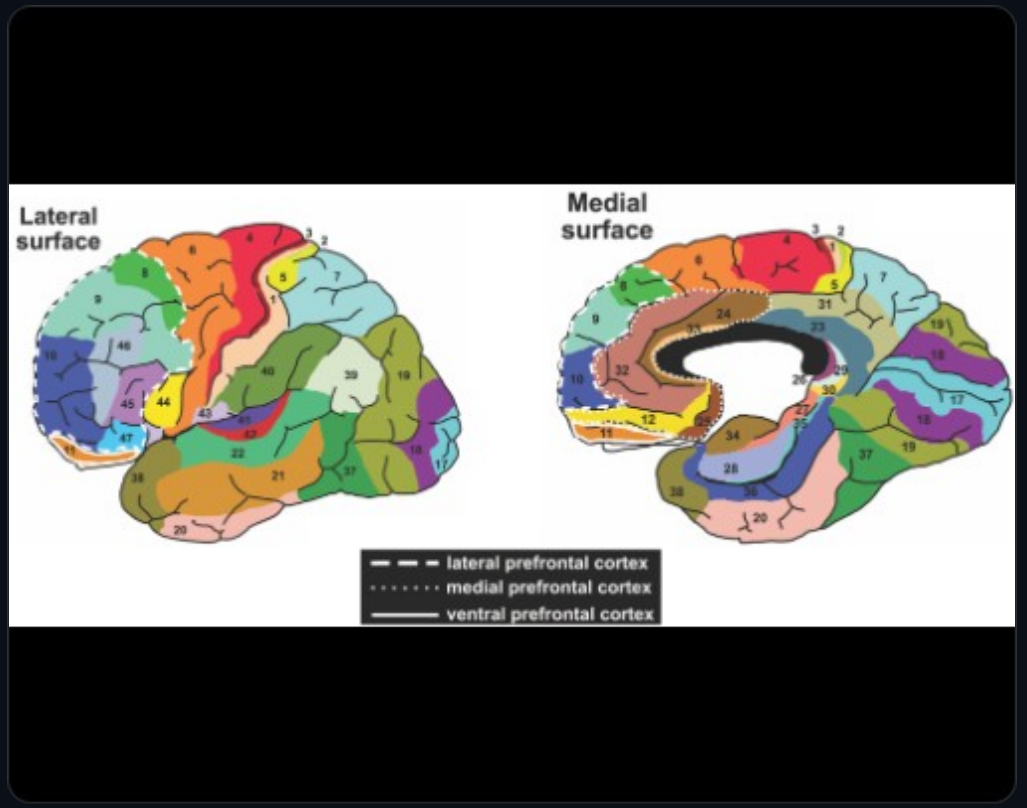
Historical Perspectives: Localization

- **Phrenology (19th C.):** The earliest hypothesis. distinct mental faculties localized to specific cortical organs.
- **Strict Modularity:** The idea that complex behavioral phenotypes could be mapped exclusively to isolated regions.
- **Clinical Limitation:** Utterly failed to account for the integrated nature of higher-order cognition and transdiagnostic psychiatric symptoms.



The Cytoarchitectural Map

- **Korbinian Brodmann (1909):** Mapped the cortex into 52 distinct regions based entirely on cellular architecture and histological structure.
- **Clinical Paradigm:** Fueled classical behavioral neurology, linking focal lesions directly to specific deficits (e.g., Broca's Area, Wernicke's Area).
- **The Gap:** While structurally accurate, it could not explain network-level psychiatric disorders like schizophrenia or bipolar illness.



Evolution of Brain Mapping in Psychiatry

19th Century

Phrenology & strict modular localization of mental traits.

Early 20th C.

Brodmann Areas define rigid cytoarchitectural boundaries.

Late 20th C.

Lobar function models (e.g., frontal lobe syndrome).

21st Century

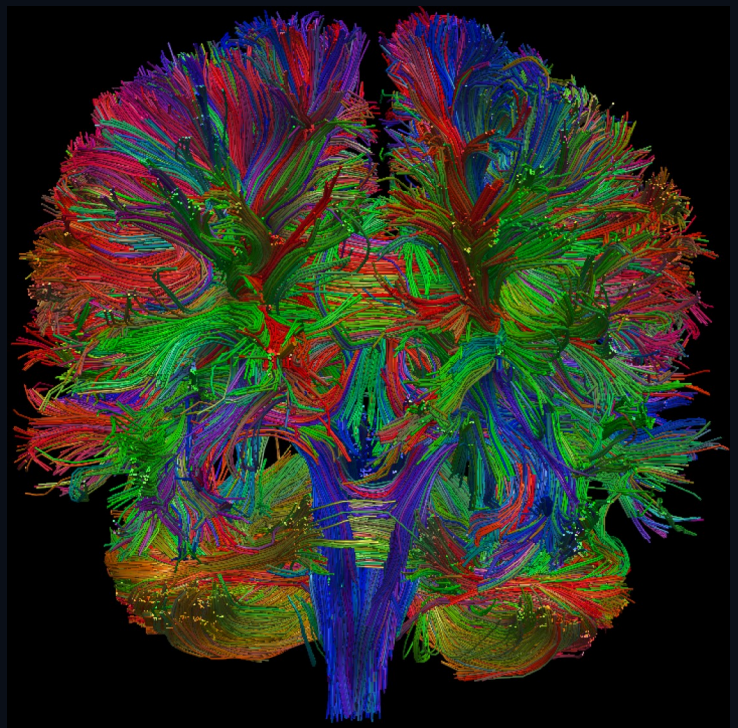
Connectomics: The brain as an integrated dynamic network.

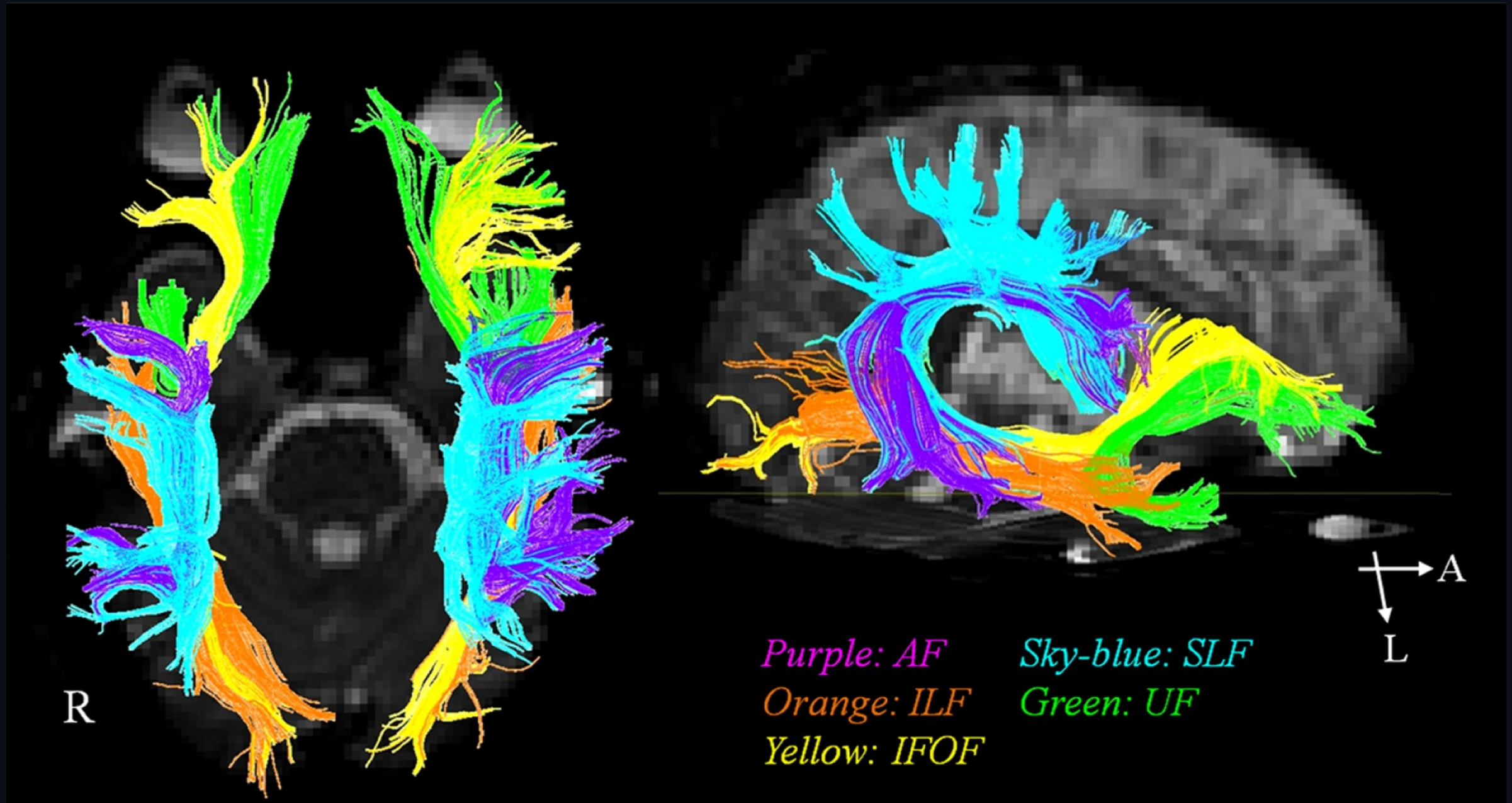
Structural Connectivity (SC)

The anatomical highways of the central nervous system.

Defining Structural Connectivity

- **The Infrastructure:** Maps the physical white matter tracts (Axonal bundles) connecting distinct spatial nodes of the brain.
- **Imaging Modality:** Assessed via Diffusion Tensor Imaging (DTI), tracking the diffusion of water molecules along myelin sheaths.
- **Key Metric:** *Fractional Anisotropy (FA)* quantifies directional diffusion, serving as a proxy for tract integrity and demyelination.





the arcuate fasciculus (AF), the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF), the uncinate fasciculus (UF), and inferior fronto-occipital fasciculus (IFOF).

SC Core Concepts

White Matter

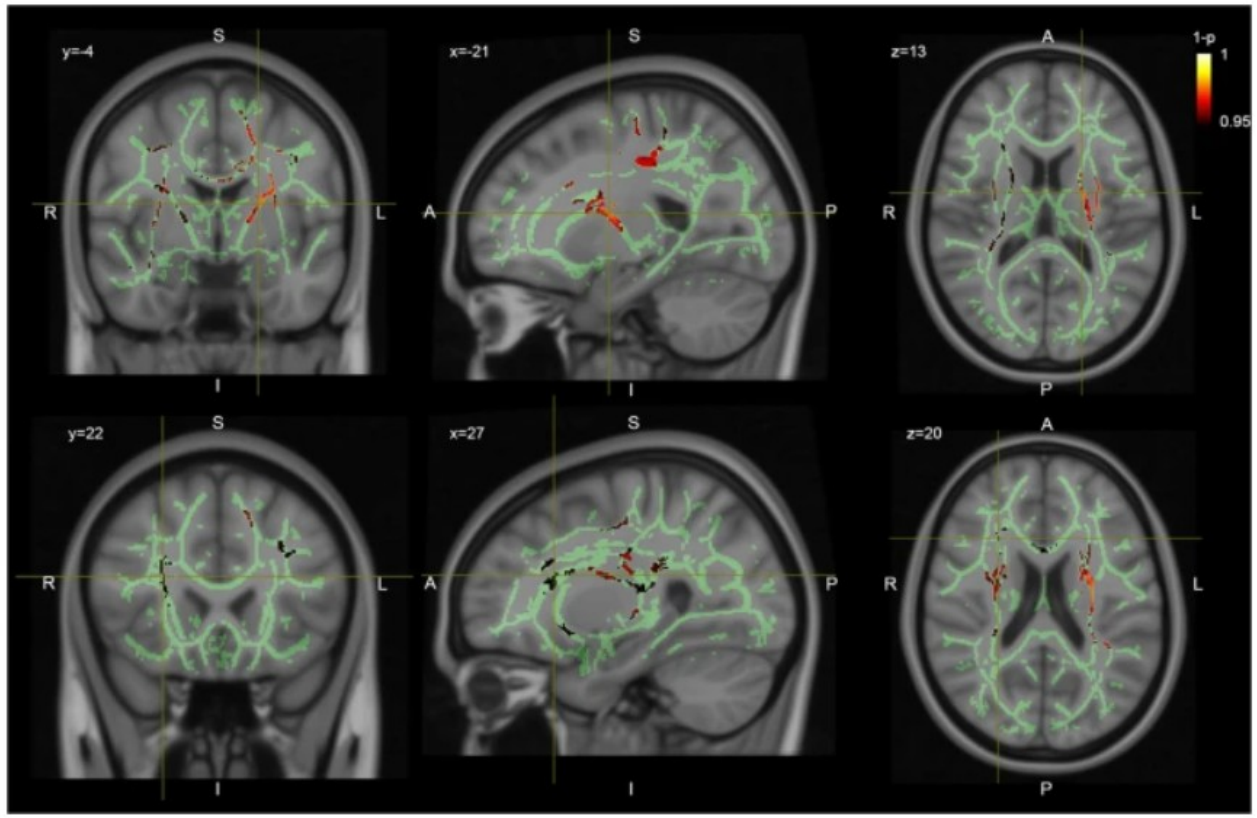
Lipid-rich myelin sheaths forming macroscopic cables that enable rapid signal transmission across distant cortical lobes.

Tractography

Computational reconstruction of DTI data into 3D visual models of the brain's internal wiring and axonal pathways.

The Connectome

A comprehensive map of all structural neuronal connections, essential for identifying pathogenic vulnerability hubs.



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Whole brain differences in FD HC > SZ. TBSS results of the comparison of the FD values between SZ patients and healthy controls. Clusters exhibiting statistically significant decreases in the patient population ($p < 0.05$) are shown in red on the green TBSS FA skeleton.

SC Symptom Focus: Psychomotor Retardation

Motor Circuit Integrity

Psychomotor slowing in severe depression is not purely subjective; it correlates directly with physical degradation of motor execution pathways.

Replicated Findings

Reduced FA values in the anterior limb of the internal capsule, dlPFC, (pre-)motor cortex, parietal cortex and cingulum in treated and untreated MDD patients.

Neurobiology of Disease, Volume 47, Issue 1, 2012, Pages 13–19.

SC Symptom Focus: Executive Dysfunction

The SLF Tract

The Superior Longitudinal Fasciculus (SLF) acts as the primary physical bridge linking frontal executive centers with parietal and temporal regions.

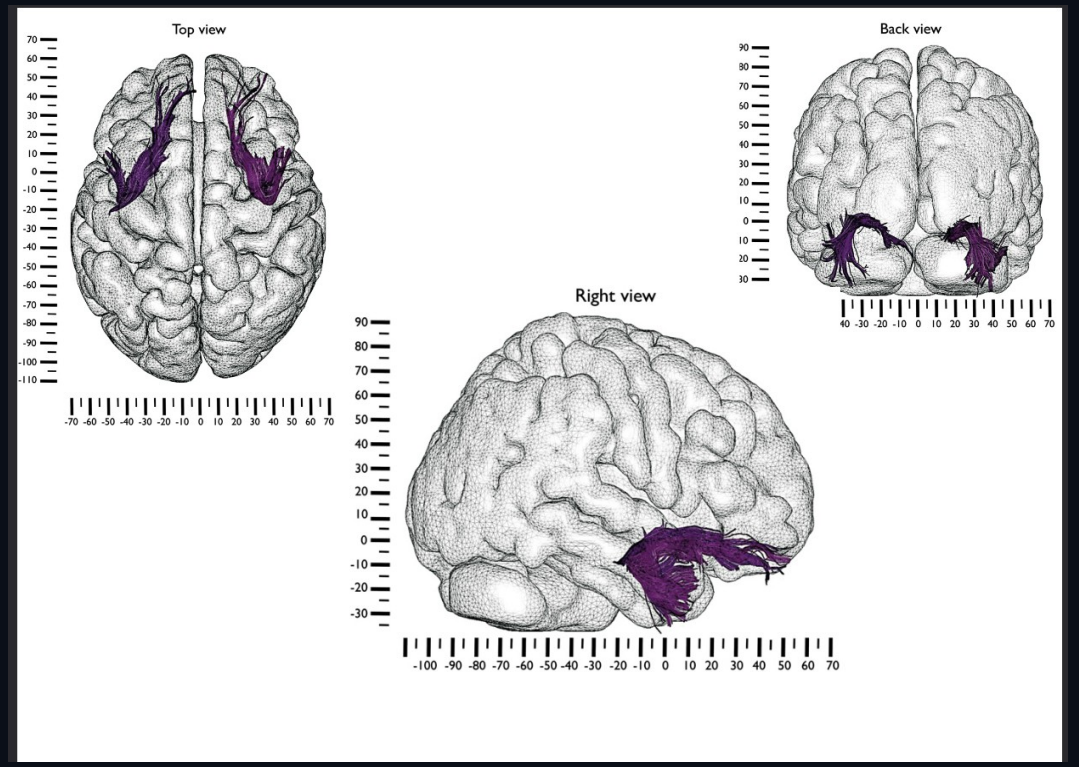
FA reduction in the second half of the SLF in Sz group compared to HC or BMD group. Higher FA in posterior right SLF → Higher Manic-Hostility score on BPRS.

positive relationship between FA and executive function in the bilateral SLF and SLF-temporal fiber tracts, and also clinical outcomes

Front Psychiatry. 2022 Dec 6;13:999384
Am J Geriatr Psychiatry. 2021 Jan 23;29(12):1188-1198

SC Symptom Focus: Emotion Dysregulation

- **The Limbic Link:** The Uncinate Fasciculus Connects the Amygdala, Entorhinal cortex and Perirhinal cortex to the Orbitofrontal Cortex (OFC).
- **Role:** It provides the structural highway essential for prefrontal inhibition of limbic hyperreactivity and fear response.
- **Clinical Correlate:** Impaired integrity here is a robust finding in impulsive and emotionally dysregulated states (e.g., Anxiety, Depression, Early life stress and maltreatment).



Neurobiol Learn Mem. 2020 Dec 4;177:107359

Structural vs. Functional Connectivity

Structural (SC)

Calculated via Diffusion Tensor Imaging (DTI). Represents the actual, physical white-matter axonal cables of the brain.

Functional (FC)

Derived using resting-state fMRI. Tracks the statistical correlation of blood-oxygen level-dependent (BOLD) signals over time.

The Divergence

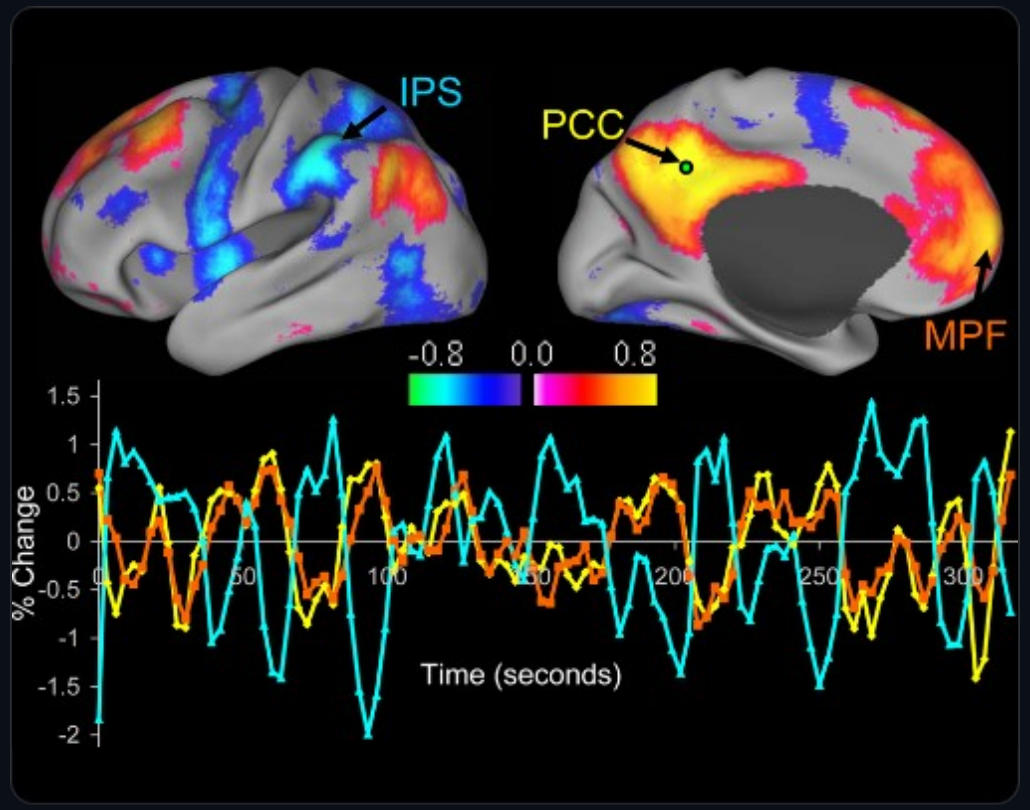
Functional connections often exist without direct structural connections, mediated via indirect multisynaptic pathways.

Functional Connectivity (FC)

"Neurons that fire together, wire together."

The Concept of Functional Connectivity

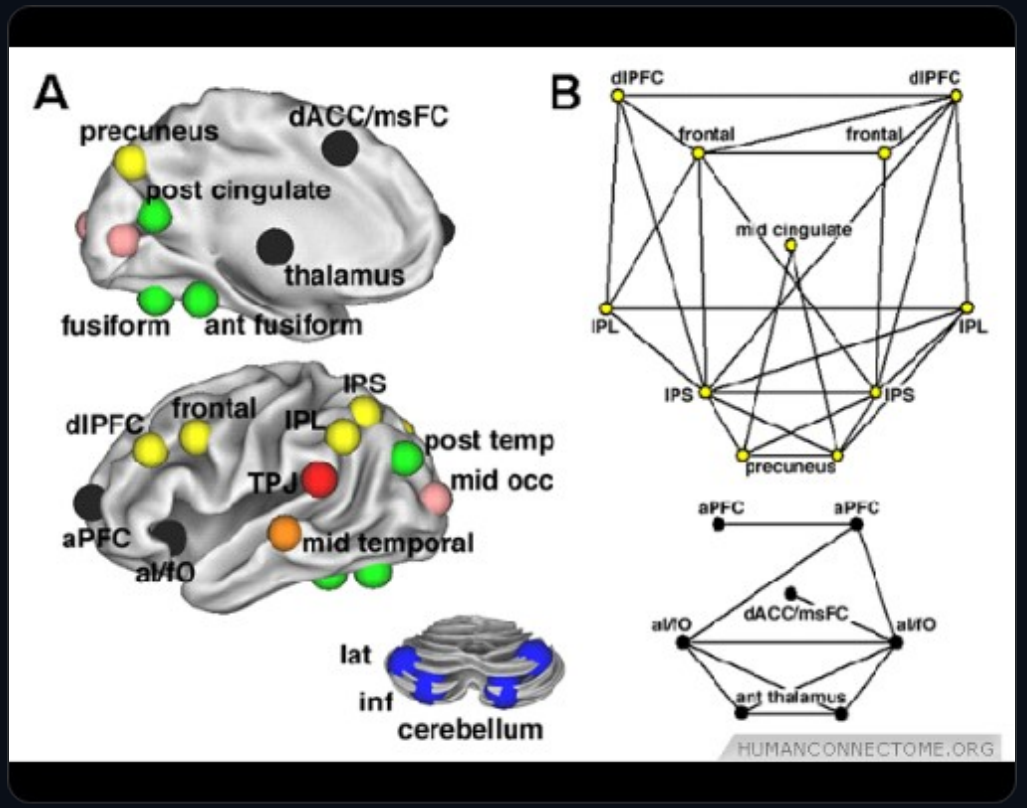
- **Definition:** FC quantifies the statistical temporal dependency (synchronization) of neuronal activation between spatially separated regions.
- **The Signal:** Typically measured using resting-state BOLD (Blood-Oxygen-Level-Dependent) functional MRI (rs-fMRI).
- **Implication:** Regions with synchronous low-frequency BOLD fluctuations are functionally coupled into networks, independent of direct structural links.



Fox, Michael. (2010). Frontiers in Systems Neuroscience. 19. 10.3389/fnsys.2010.00019.

Graph Theory in Psychiatry

- **Nodes & Edges:** Brain regions act as 'nodes' and functional correlations as 'edges', allowing mathematical quantification of global brain topology.
- **Small-Worldness**: Healthy brains optimize local segregation and global integration. Psychopathology often presents as a loss of this systemic efficiency.
- **Rich-Club Hubs:** Highly centralized nodes are disproportionately vulnerable to metabolic stress, acting as epicenters for disease onset.



Graph Theory Metrics

Quantifying Network Efficiency

Mathematical tools characterize how effectively information transfers across the network.

- **Path Length**: The average minimum steps required to traverse from any node to any other node.
- **Clustering Coefficient**: The likelihood that neighbors of a node are connected to each other (local integration).
- **Global Efficiency**: An inverse measure of path length, reflecting global parallel information transfer.

The Small-World Architecture

Healthy human brains exhibit **Small-World Organization**: a high clustering coefficient combined with low path length. This optimizes both specialized local computation and rapid global integration.

The Brain's Rich Club Network

A small set of highly connected brain regions form an elite, interconnected backbone.

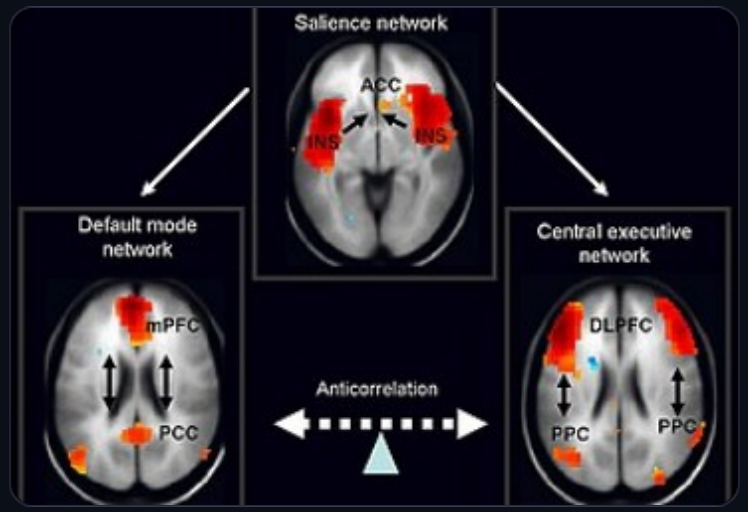
- **Hub Regions:** Areas like the precuneus, anterior cingulate, and thalamus possess extraordinarily high connectivity.
- **Rich Club Phenomenon:** High-degree hubs more interconnected with each other than by chance.
- **Clinical Vulnerability:** While the Rich Club optimizes routing, damage here triggers widespread cognitive collapse.

The Triple Network Model

The TNM Triad

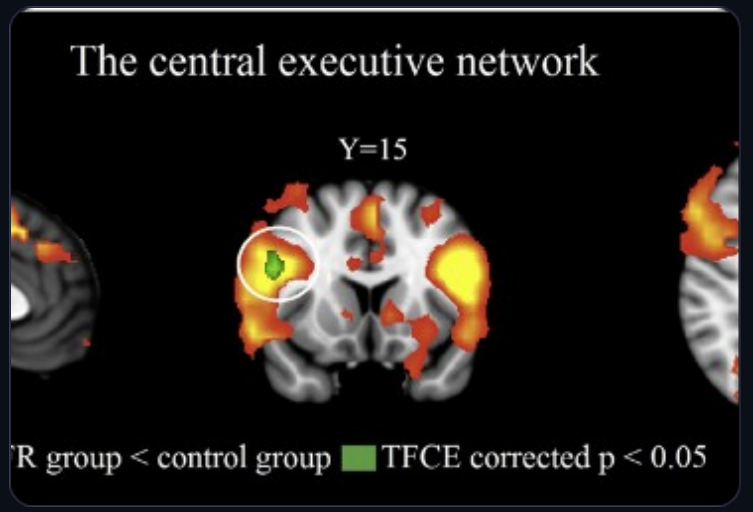
Default Mode (DMN)

Internal mentation & reflection



Salience (SN)

Threat detection & Switching

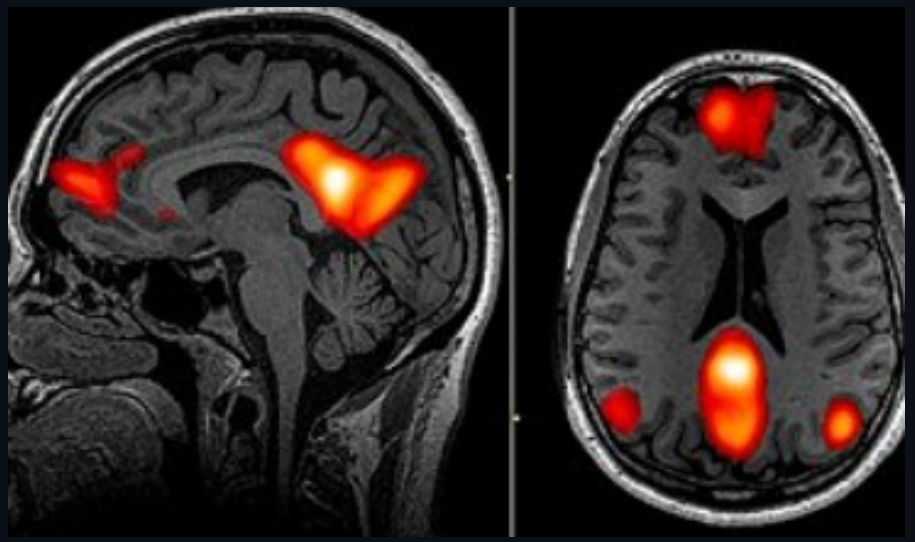


Central Exec (CEN)

Cognitive control & Focus

1: Default Mode Network (DMN)

- **Key Nodes:** Medial Prefrontal Cortex (mPFC), Posterior Cingulate Cortex (PCC), Precuneus.
- **Function:** Highly active during rest. Mediates self-referential thought, autobiographical memory, and spontaneous mind-wandering.
- **Symptom Correlate:** DMN **hyperconnectivity** is a highly replicated biomarker for depressive rumination. Patients fail to successfully deactivate the DMN during tasks, trapping them in negative self-focus.



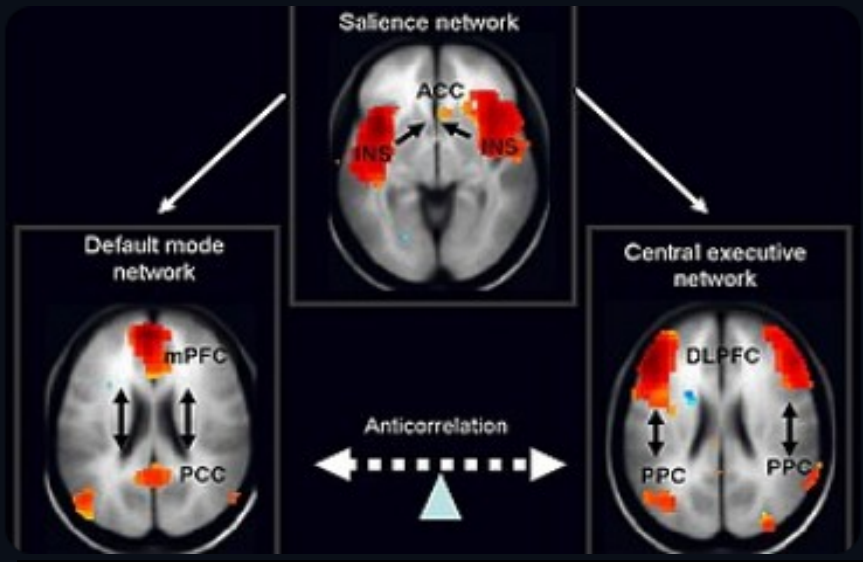
BJPsych Open. 2025 Jun 20;11(Suppl 1):S62–S63

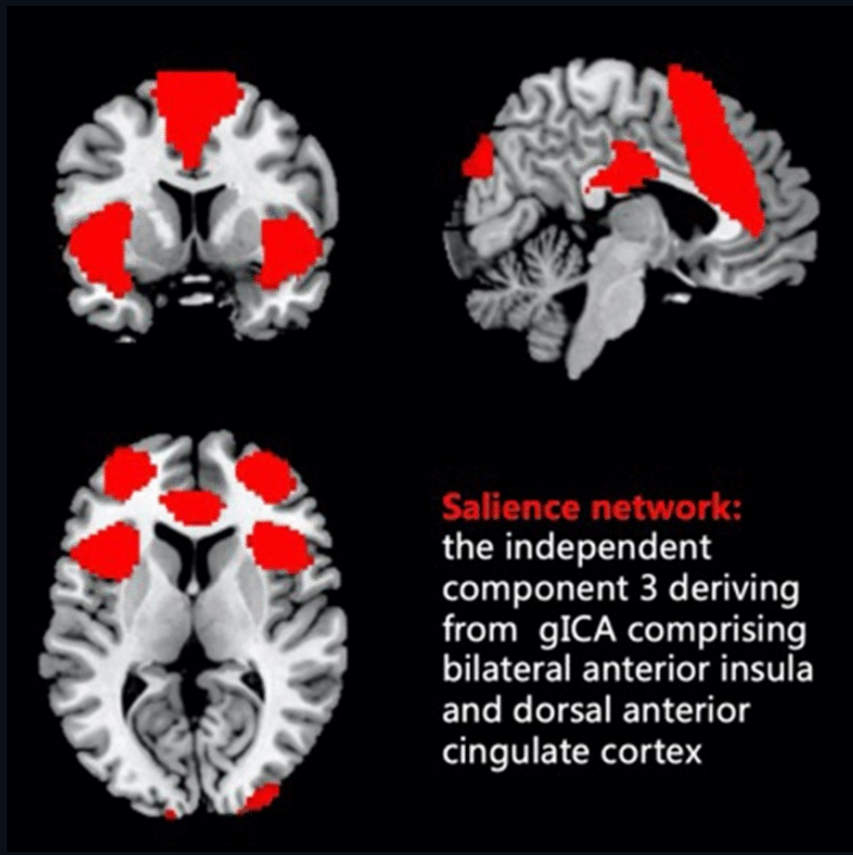
2: Salience Network (SN)

Key Nodes: Anterior Insula (AI), Dorsal Anterior Cingulate Cortex (dACC).

Function: Filters irrelevant information to isolate homeostatically important cues. Salient event/stimulus → the insula generates transient control signals that disengage the DMN and recruit executive networks to manage the stimulus.

Symptom Correlate: Aberrant salience attribution—where the SN fires inappropriately at neutral stimuli—is a core mechanism underlying delusions, hallucinations, and even disorganisation.





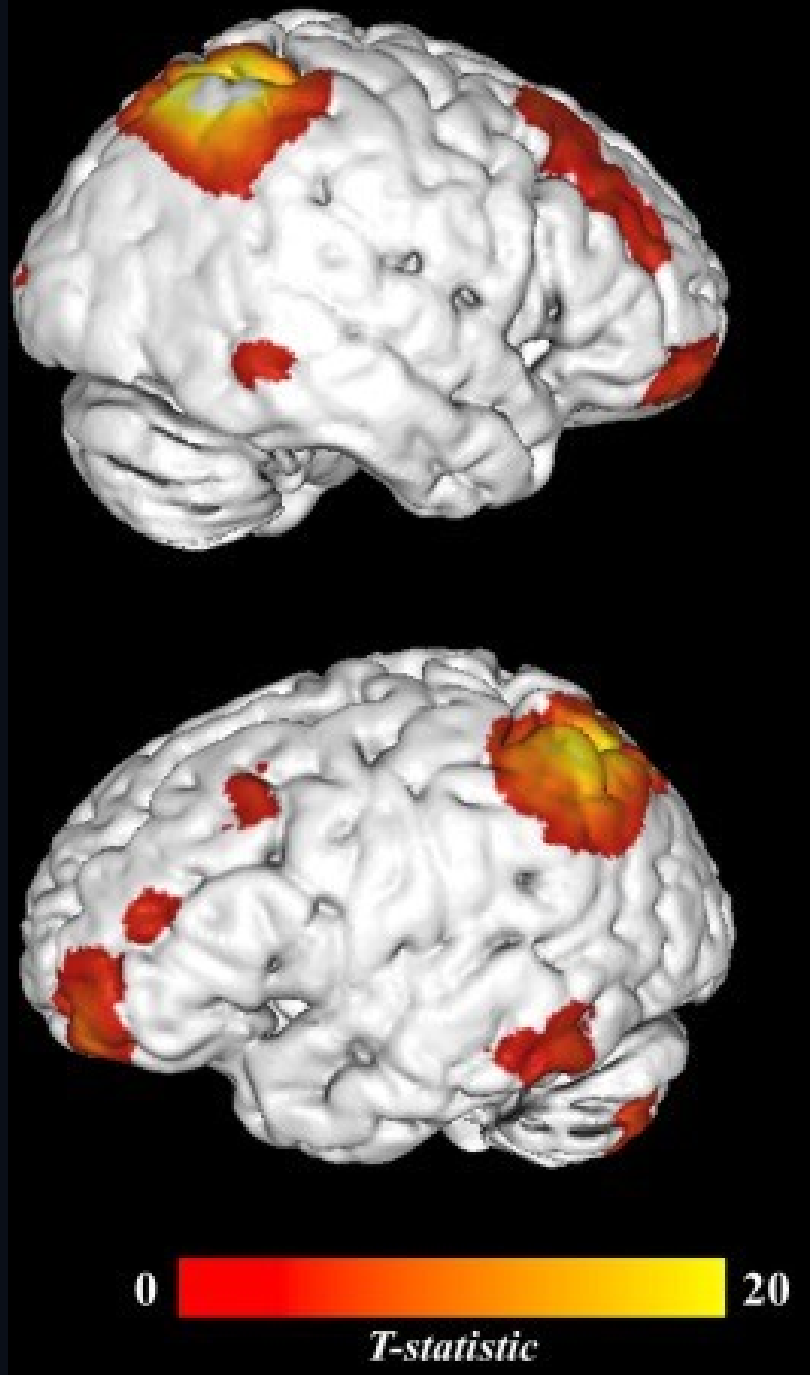
J Psychiatry Neurosci. 2012 Jan;37(1):17–27
Sci Rep 12, 11204 (2022)

3: Central Executive Network (CEN)

Key Nodes: Dorsolateral Prefrontal Cortex (dlPFC), Posterior Parietal Cortex (PPC).

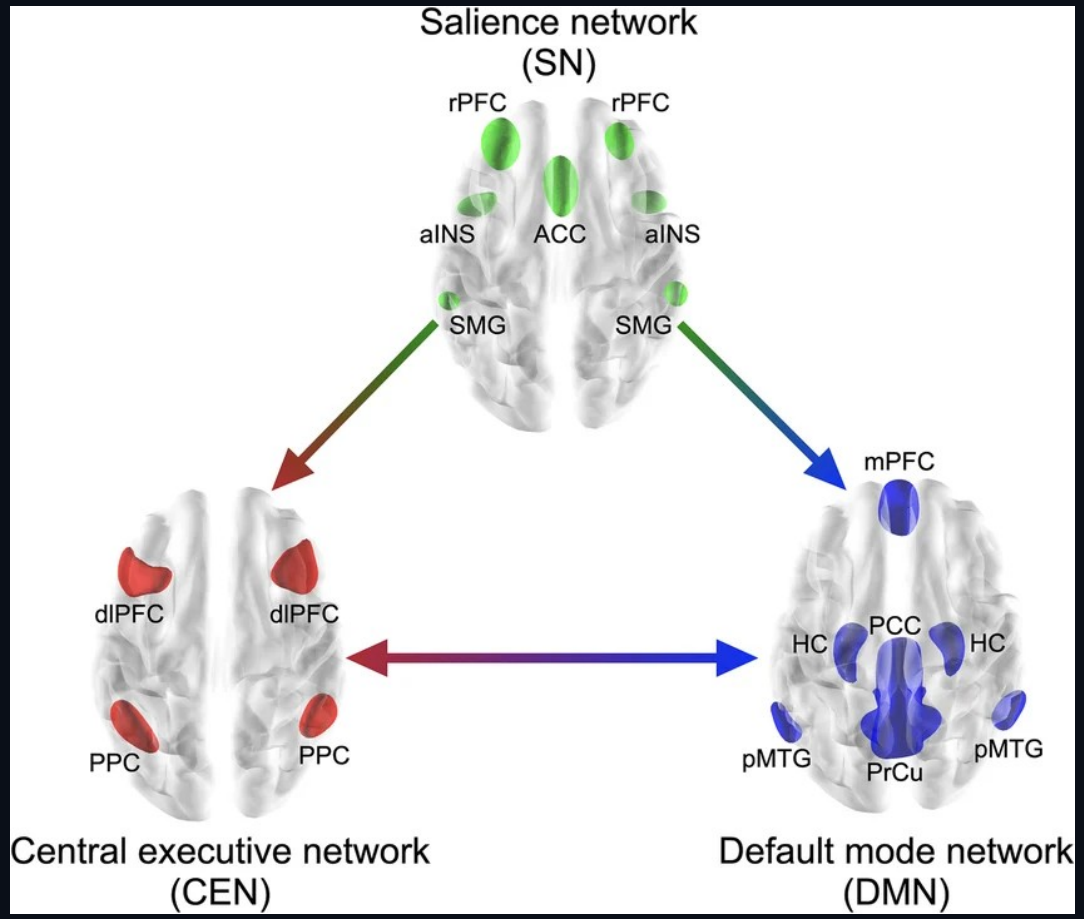
Function: Engaged during demanding tasks requiring working memory, planning, problem solving, and goal-directed behavior.

Symptom Correlate: CEN **hypoconnectivity** correlates directly with clinical disorganized thinking, poor working memory, and negative symptoms commonly observed in schizophrenia.



Medical Hypotheses 133 (2019) 109385

The Triple Network Model



A Unified Dynamic Engine

Key properties of TNM

- **Anti-Correlation:** The DMN (internal) and CEN (external) operate in a reciprocal balance.
- **Salience Control:** The SN arbitrates transitions, preventing cognitive lock-ups.
- **Unified Psychopathology:** Dysregulation in this tripartite system serves as a common driver for major mental health disorders.

Beyond the Triple Network

Extending connectomics to distinct sensory and reward dimensions.

Sensory & Motor interfaces

Visual Network

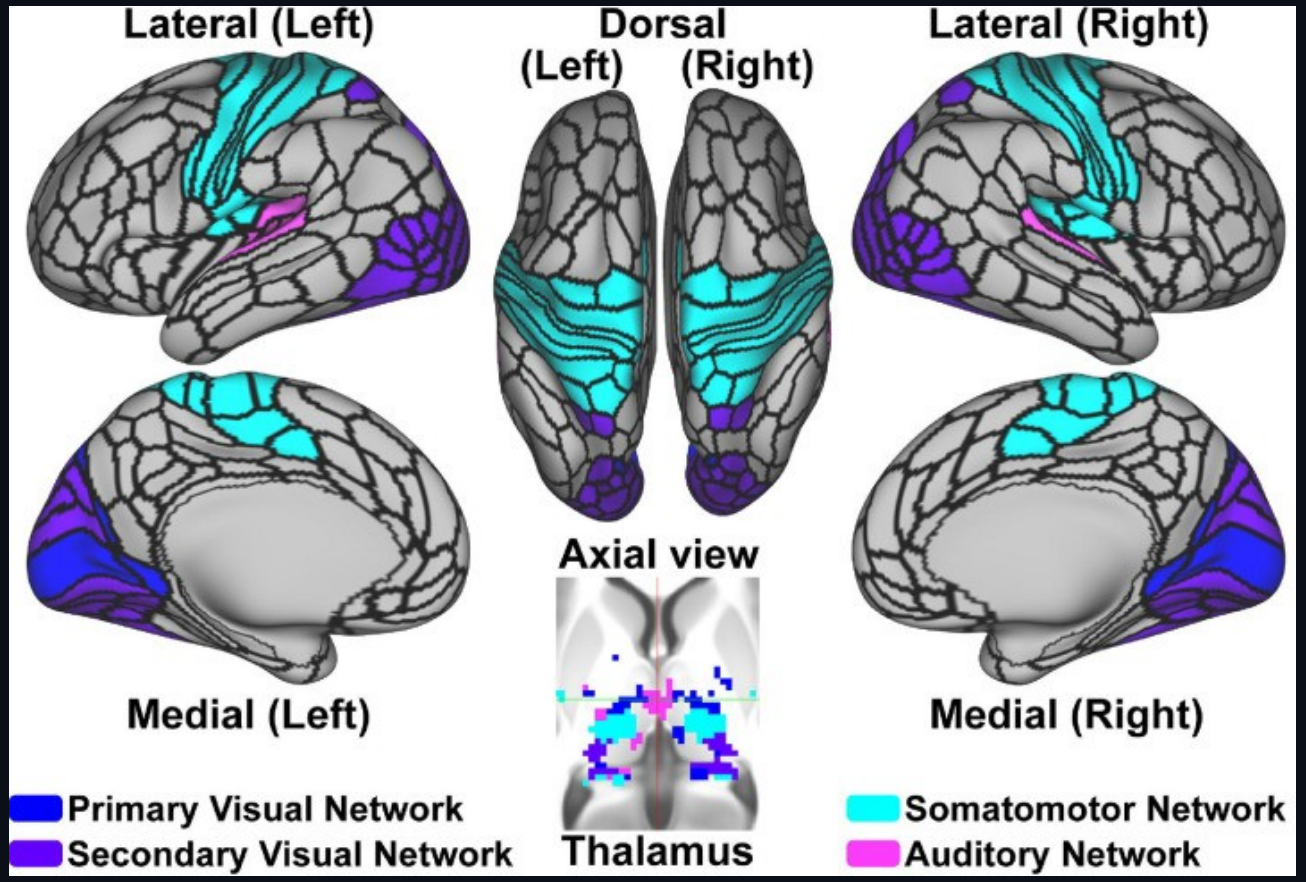
Spans primary and secondary occipital cortices. Processes early visual information and directs feature abstraction.

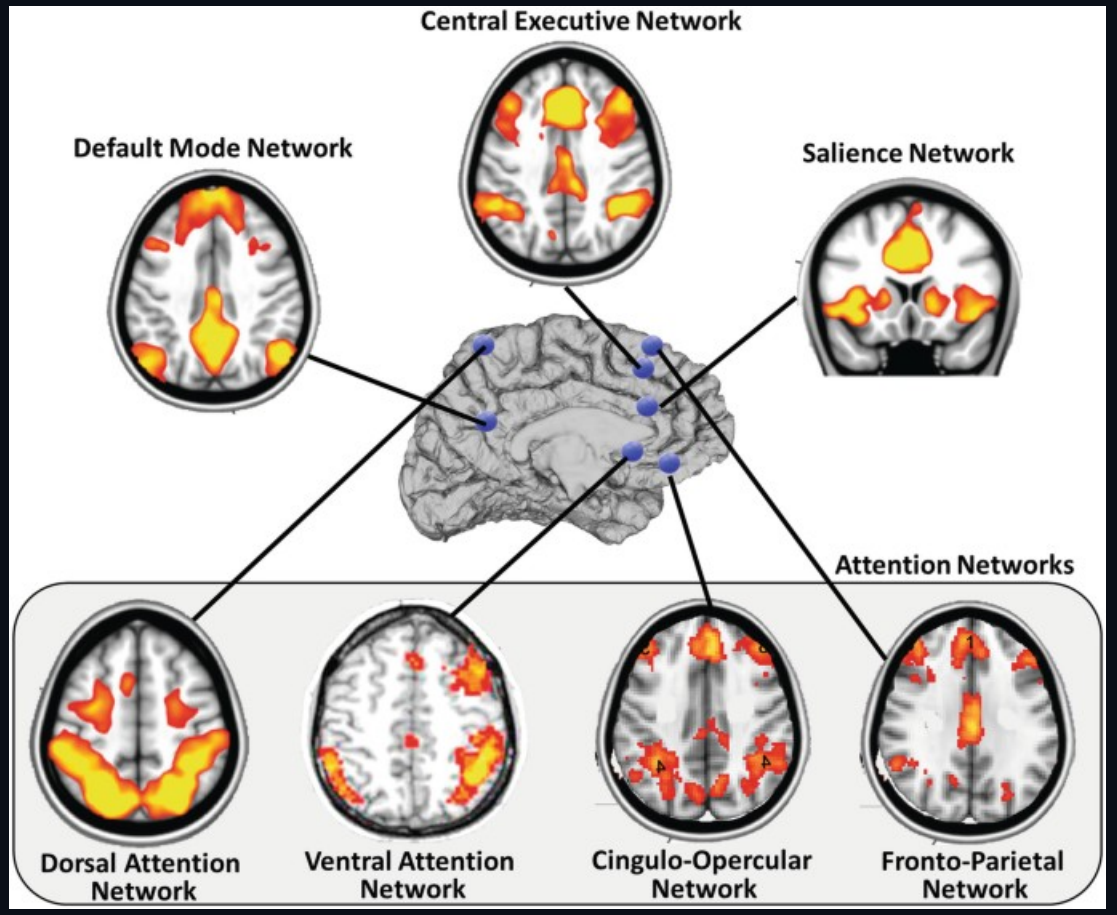
Auditory Network

Centered in Heschl's gyrus. Manages auditory inputs and provides structural speech feedback loops.

Somatomotor

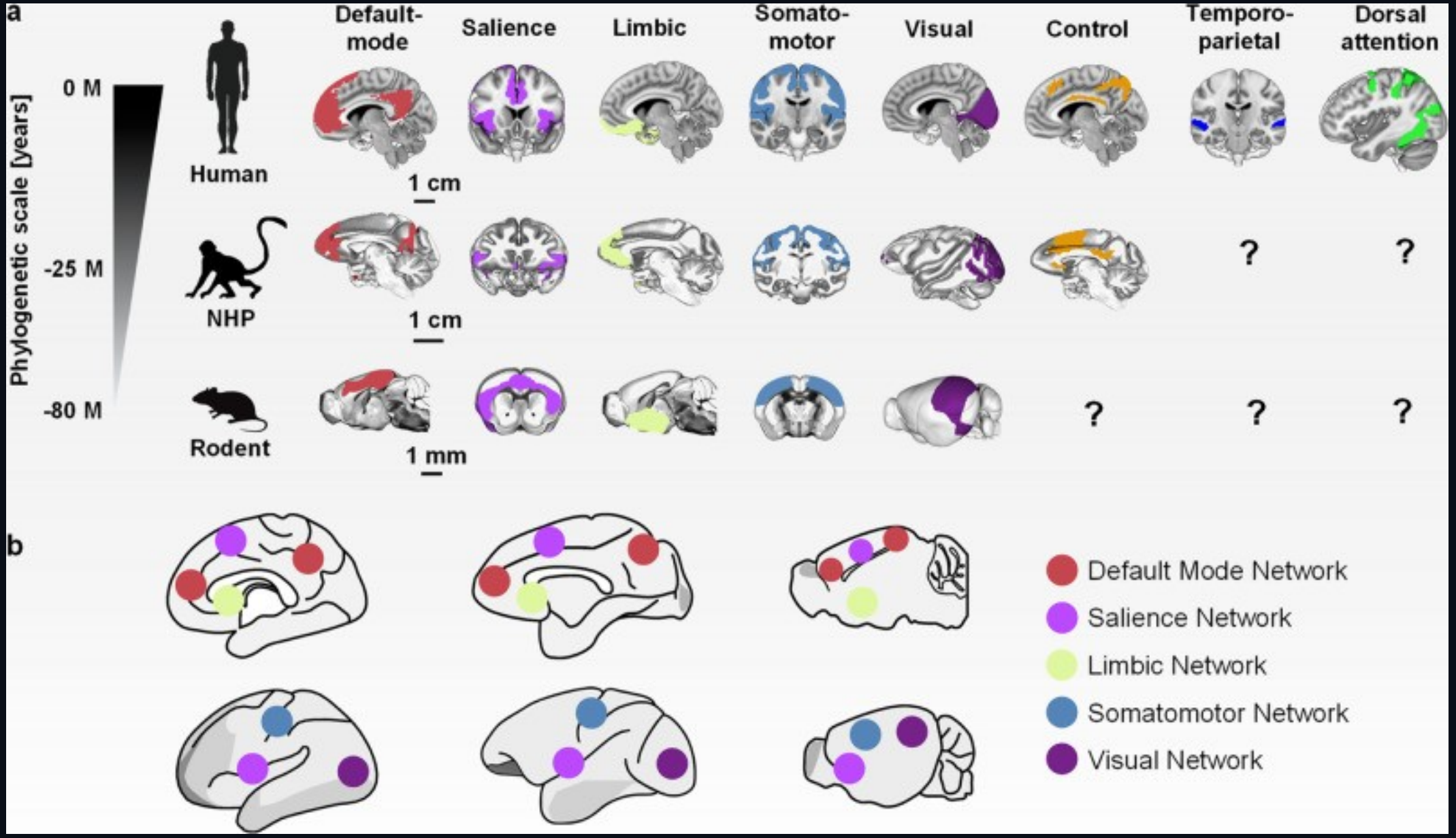
Spans the precentral and postcentral gyri. Handles motor output signals and direct tactile-sensory inputs.





medRxiv
[Preprint]. 2024 Sep 19:2024.06.14.24308836

https://link.springer.com/rwe/10.1007/978-981-15-2848-4_76-1



Commun Biol. 2023 Dec 7;6:1238

Psychopathology as Network Dysfunction

Schizophrenia: Dysconnectivity

A Disconnected Mind

- **Fronto-Temporal Uncoupling:** Poor synchronization between prefrontal control and sensory processing regions.
- **DMN Intrusion:** The DMN fails to suppress during tasks, causing internal dialogue to blend into external reality (hallucinations).
- **Thalamic Deficits:** The thalamus fails to gate sensory inputs, flooding the cortex with raw, unorganized information.

Limbic Dysregulation

Like in Bipolar Disorders, here too Limbic Dysregulation is seen. Mainly in context of paranoia, fear, hyperarousal etc. but at times also in context of emotional blunting.

https://doi.org/10.1016/j.schres.2017.02.026
https://doi.org/10.1002/wps.21159

Depression: Hyperactive DMN

The Loop of Rumination

Major Depressive Disorder is characterized by hyper-connectivity within default networks and hypo-connectivity in cognitive areas.

- **Overactive Self-Focus:** Pathological hyper-connectivity inside the default network locks attention on negative memories and rumination.
- **Cognitive Executive Deficits:** Reduced connectivity in executive control areas impairs decision-making and working memory.
- **Subcortical Reward Blunting:** Uncoupled connections between reward pathways and the prefrontal cortex foster anhedonia.

BJPsych Open. 2025 Jun 20;11(Suppl 1):S62-S63

Bipolar Network Instability

Mood State Oscillations

Fronto-Limbic Uncoupling: Prefrontal systems lose inhibitory control over subcortical structures (like the amygdala).

Dynamic Instability: Unstable, hyper-fluctuating functional connectivity tracks rapid shifts from mania to depression.

Striatal Hyperactivity: Elevates reward sensitivity during hypomanic/manic phases.

Limbic Dysregulation

In Bipolar Disorder, the structural and functional connections that normally allow prefrontal areas to dampen raw subcortical emotional signals are weak, leaving the emotional brain to swing between hyperactive states.

Acta Psychiatr Scand. 2025; 151(3): 192–209
Brain Imaging and Behavior 20, 84 (2026)

Anxiety & PTSD: Salience Drive

The Threat Hyper-Loop

In anxiety-related disorders, the brain is perpetually locked in a threat-response state. The salience network dominates processing resources, constantly calling upon executive centers to prepare for imaginary dangers.

- **Salience Hyperactivity:** An overactive salience system interprets benign internal and external stimuli as imminent dangers.
- **Impaired Fear Extinction:** Weak connections between prefrontal and amygdala pathways prevent safety cues from dampening threat signals.
- **Flashbacks:** Disrupted interactions between memory structures and the DMN trigger sudden, intrusive recollections.

Transl Psychiatry. 2020 Feb 10;10(1):61
Brain Sci. 2025 Sep 23;15(10):1025

ADHD: Task-Switching Deficits

- **Impaired Anti-Correlation:** The default network fails to quiet down when executive networks activate, causing internal thoughts to disrupt task focus.
- **Salience Signal Failure:** Deficits in the salience network impair its ability to signal proper transitions between rest and active work.
- **Striatal Dopaminergic Deficits:** Impairs reward-network coordination, driving a constant search for immediate dopamine spikes.

Inwards or Outwards?

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by a failure of task-positive networks to suppress task-negative ones.

Transl Psychiatry 9, 137 (2019).

Autism Spectrum Connectomics

Local Hyper-connectivity

Overdeveloped local wiring inside primary sensory networks supports intense specialization and sensory overstimulation.

Long-Range Hypo-connectivity

Underdeveloped pathways between distant regions limit the integration of social, cognitive, and sensory details into a cohesive whole.

Theory of Mind Deficits

Weak functional connectivity within social network hubs impairs intuitive social reasoning and perspective-taking.

Rev J Autism Dev Disord. 2025 Mar;12(1) 110-137

Transdiagnostic Connectivity

Disorder Type	DMN Status	CEN Status	SN Status	Core Pathology
Depression	**Hyper-connected**	Hypo-connected	Hypo-responsive	Intrusive negative rumination
Schizophrenia	Poorly Suppressed	**Uncoupled**	Aberrant Salience	Inner dialogue interpreted as reality
ADHD	Unsuppressed	Hypo-active	**Impaired Switch**	Failure of task-directed attention
PTSD	Hypo-connected	Weak Control	**Hyper-active**	Chronic state of perceived threat

FC Symptom Focus: Anhedonia

The Reward Circuit

Reward anticipation and consummatory pleasure rely on a circuit centrally involving the **Ventral Striatum (Nucleus Accumbens)** and Ventromedial PFC.

Striato-Cortical Deficits

distinct striatal iFC patterns involving the pregenual ACC, subgenual ACC, supplementary motor area, and supramarginal gyrus were associated with anhedonia severity.

J Am Acad Child Adolesc Psychiatry. 2013 Jun;52(6):628–41.e13

Limitations of Static FC

The brain is not frozen in time.

Why Static FC Falls Short

- **The Averaging Effect:** Static FC calculates a single matrix over an entire 15-minute scan, blurring distinct, evolving cognitive states into a single meaningless average.
- **Assumption of Stationarity:** It operates on the mathematically flawed assumption that network connections are rigid, contradicting the fluid nature of human cognition.
- **Missed Transience:** Critical, brief pathogenic states—such as a 10-second auditory hallucination or fleeting depressive rumination—are entirely washed out.

Critique I: Spatial Reductionism

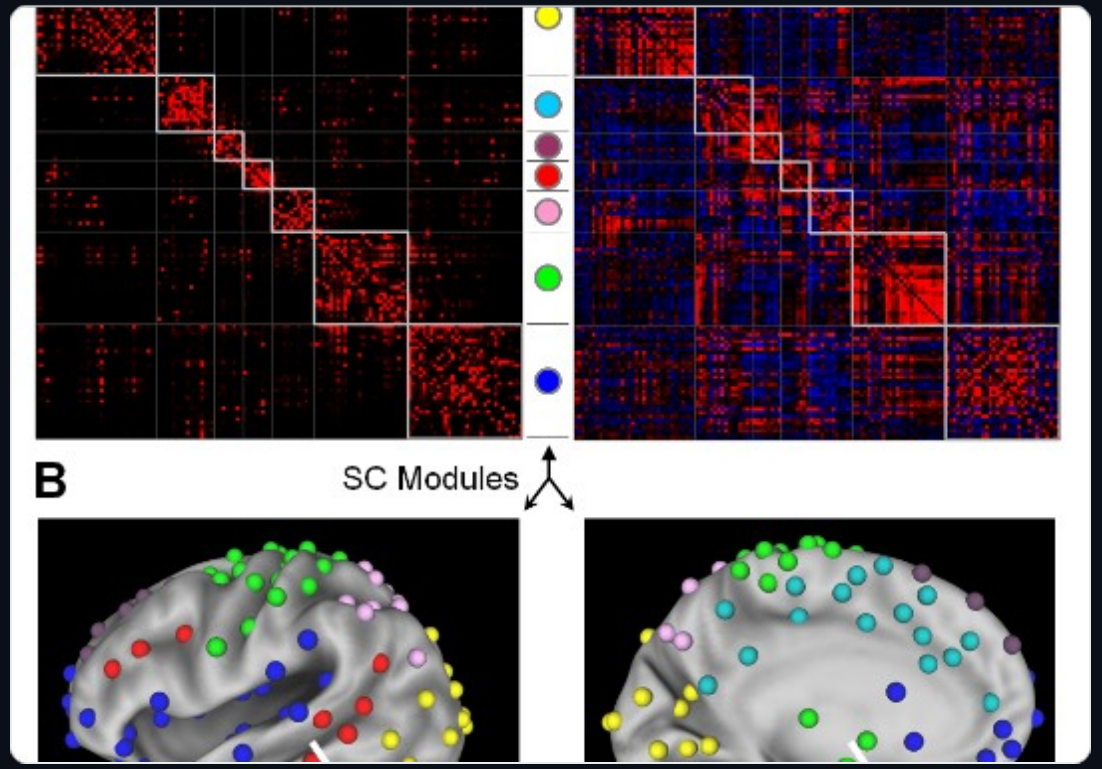
The Modular Trap

- **Sensory Exclusion:** Primary sensory and motor networks are treated as simple passive pathways rather than dynamic feedback controllers.
- **Limbic Omission:** Classical models leave out the orbitofrontal and temporal-polar limbic circuits that process emotional valence.
- **Artificial Borders:** Treating complex, continuous brain tissue as a small handful of isolated "blocks."

The Over-Simplification

Reducing the intricate biology of hundreds of highly unique anatomical and functional cortical areas down to just three major networks oversimplifies local processing boundaries and lateralized networks.

Critique II: Cortical Bias



Deep Brain Blindspots

Early fMRI research focused on the cortex, leaving deep brain structures out of canonical network models.

- **Thalamic Gatekeeping:** The thalamus actively controls the flow of information to the cortex; uncoupling here is a core feature of schizophrenia.
- **Striatal Gating:** Striatal connections are crucial for managing habit formation and reward seeking.
- **The Cerebellum:** Long dismissed as purely motor-focused, the cerebellum coordinates cognitive processing speed.

Critique III: The Stationarity Assumption

Averaging Out Real-Time Signals

Traditional functional connectivity averages neural communication patterns over a 5-to-10-minute fMRI session.

- **Loss of Real-Time Activity:** It assumes connections are steady and constant, ignoring rapid reconfigurations occurring second-by-second.
- **Artifact Vulnerability:** Averaging over time risks masking brief, pathological brain states or transition errors.
- **The Solution:** Moving toward frameworks that track connections as highly fluid, dynamic mathematical systems.

Critique IV: Specificity Deficits

The Transdiagnostic Biomarker Problem

Deficits in DMN, CEN, and SN are remarkably similar across diverse diagnoses, complicating their use as clinical biomarkers.

- **Diagnostic Overlap**: The exact same network deficit can appear in schizophrenia, depression, and ADHD.
- **Patient Heterogeneity:** Two patients sharing the exact same diagnosis can display completely different connectivity profiles.
- **Clinical Stagnation:** Understanding general system failure has not yet translated into precise, individualized treatment targets.

The Missing Link

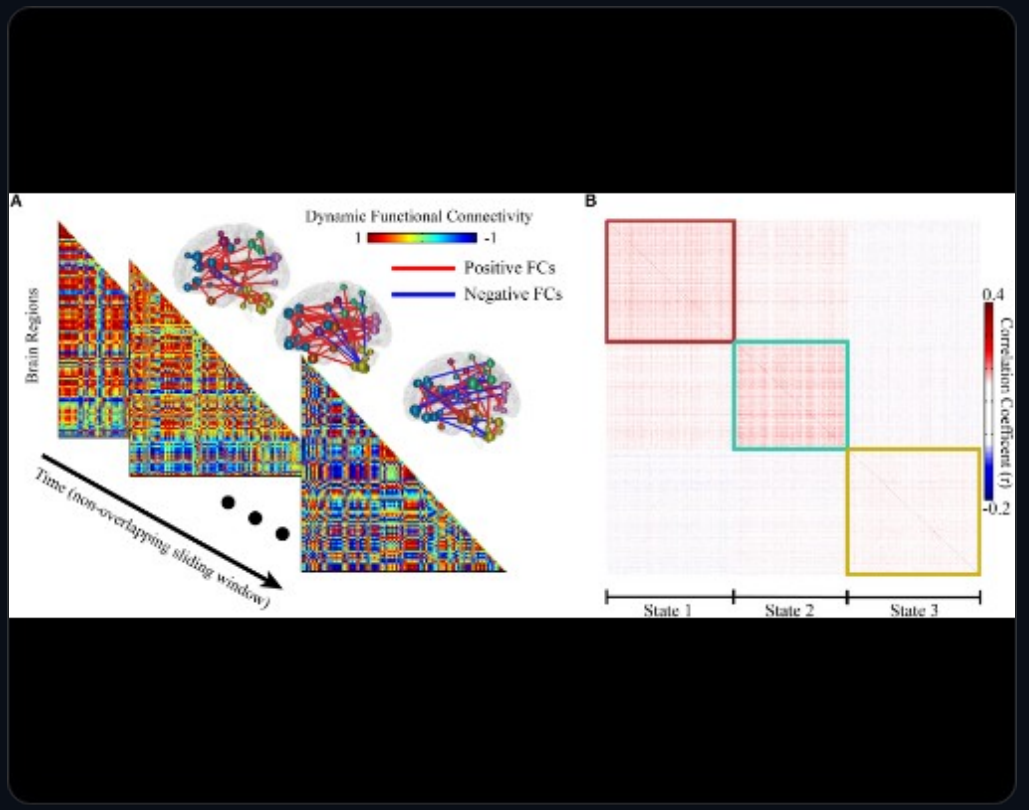
Because these network changes are shared across many conditions, they likely reflect a general risk for psychopathology (the 'p-factor') rather than the unique features of any single disorder.

Beyond Static Functional Connectivity (dFC)

Capturing the transient landscape of brain states.

Understanding dFC

- **Sliding Windows:** Rather than one long average, dFC computes connectivity across short, overlapping temporal windows (e.g., 30 seconds).
- **Microstates:** Unsupervised clustering algorithms identify recurring, time-varying matrices known as dynamic "states" or "microstates".
- **Clinical Metrics:** dFC enables the measurement of fractional dwell time (time spent in a state) and transition probabilities between specific states.



Beyond TNM: Dynamic Connectivity

Sliding-Window Correlation

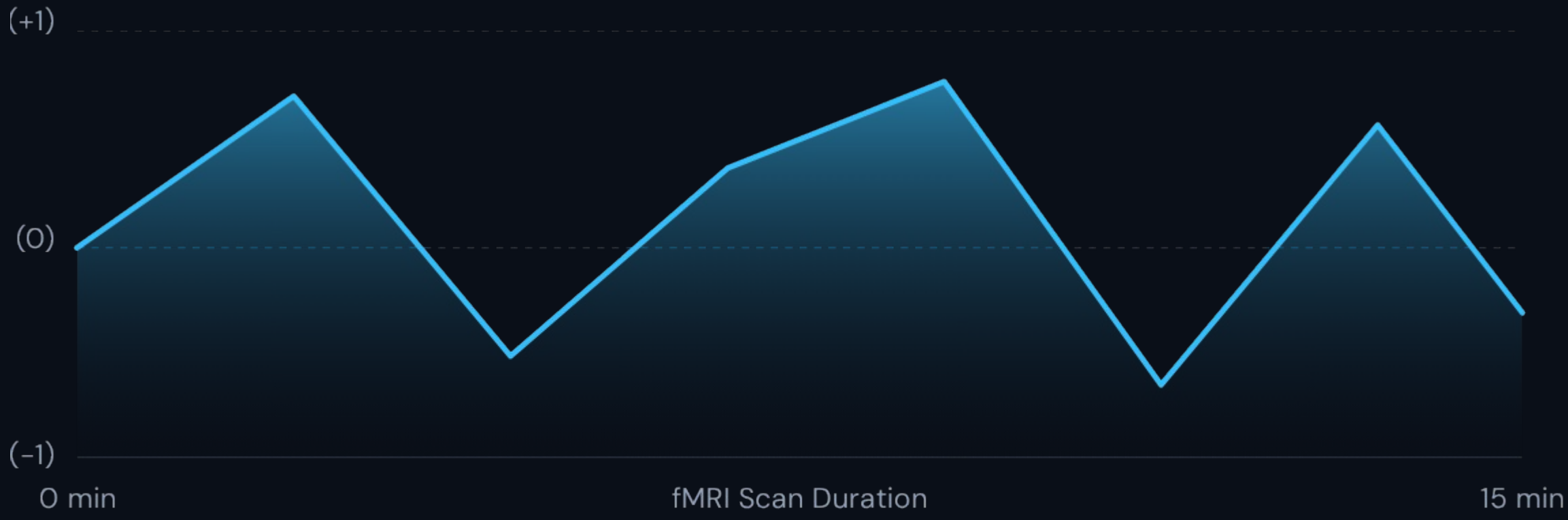
Instead of static snapshots, modern models calculate correlation within overlapping windows of time ( ).

$$r_{xy}(t) = \frac{\sum_{\tau=t}^{t+W-1} (x(\tau) - \bar{x}_t)(y(\tau) - \bar{y}_t)}{\sqrt{\sum_{\tau=t}^{t+W-1} (x(\tau) - \bar{x}_t)^2} \sqrt{\sum_{\tau=t}^{t+W-1} (y(\tau) - \bar{y}_t)^2}}$$

Dynamic States

This equation maps the ebb and flow of synchronization between brain regions. Rather than viewing the brain as statically wired, we can now track its rapid transition through fleeting, micro-scale brain states.

Fluctuating Connectivity In Vivo



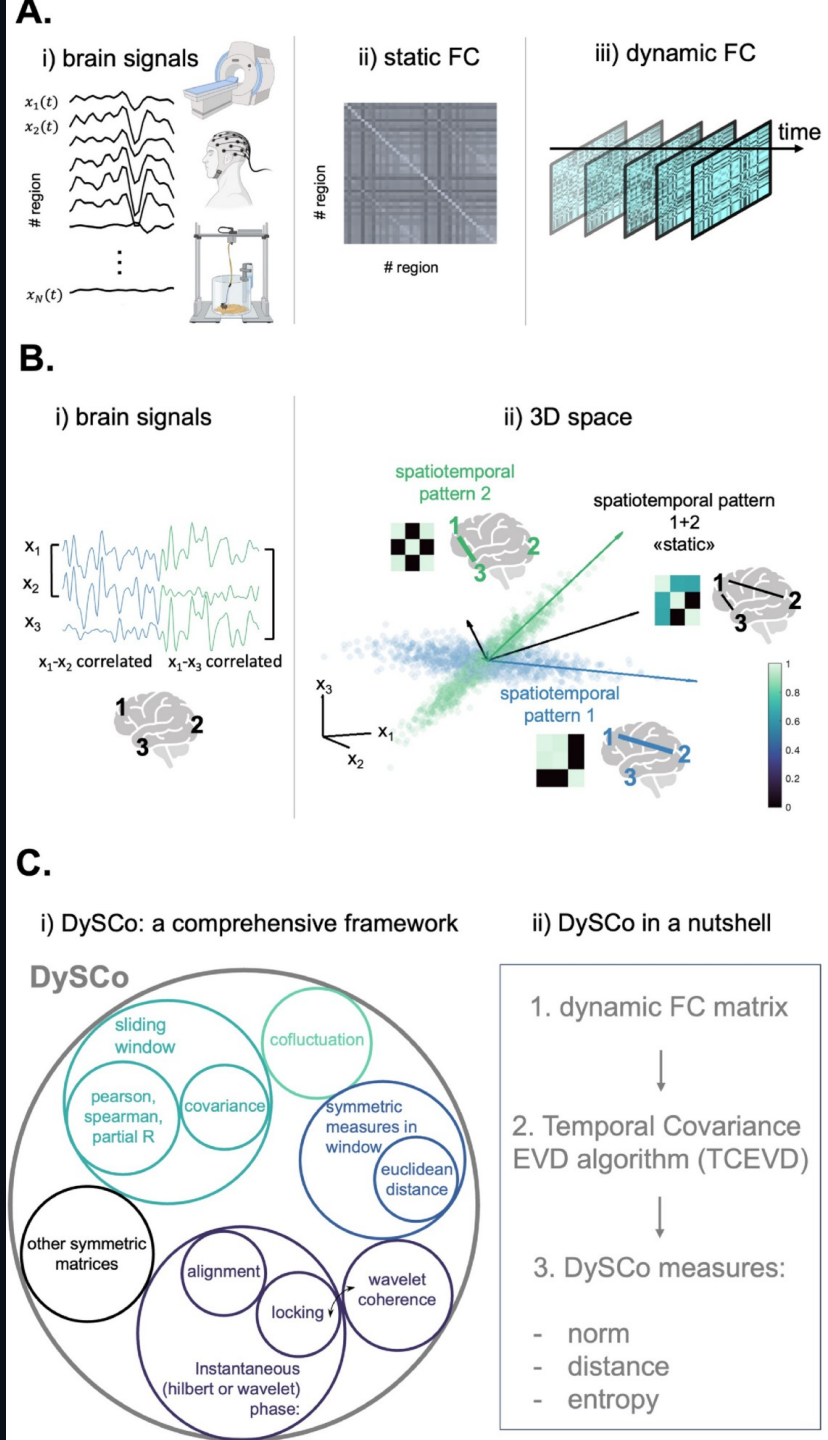
Connections (e.g., Amygdala to mPFC) dynamically shift between engaged coupling and strong anticorrelation over minutes, predicting mood lability.

The DySCo Framework

DySCo: A general framework for dynamic functional connectivity

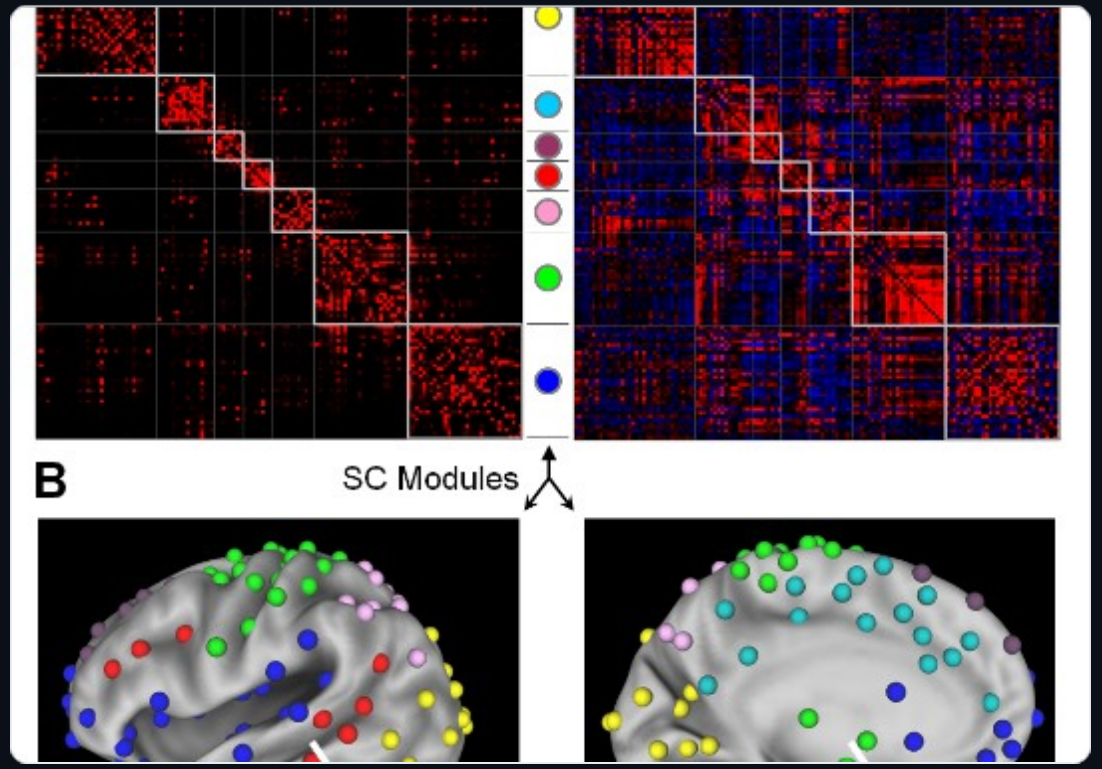
Giuseppe de Alteriis

DySCo is a framework that presents the most commonly used dFC measures in a common language and implements them in a computationally efficient way. This allows the study of brain activity at different spatio-temporal scales, down to the voxel level.



Future directions

Beyond TNM: Brain Gradients



Continuous Spatial Hierarchies

Instead of grouping brain tissue into rigid, separate networks, modern connectomics maps continuous functional spectrums.

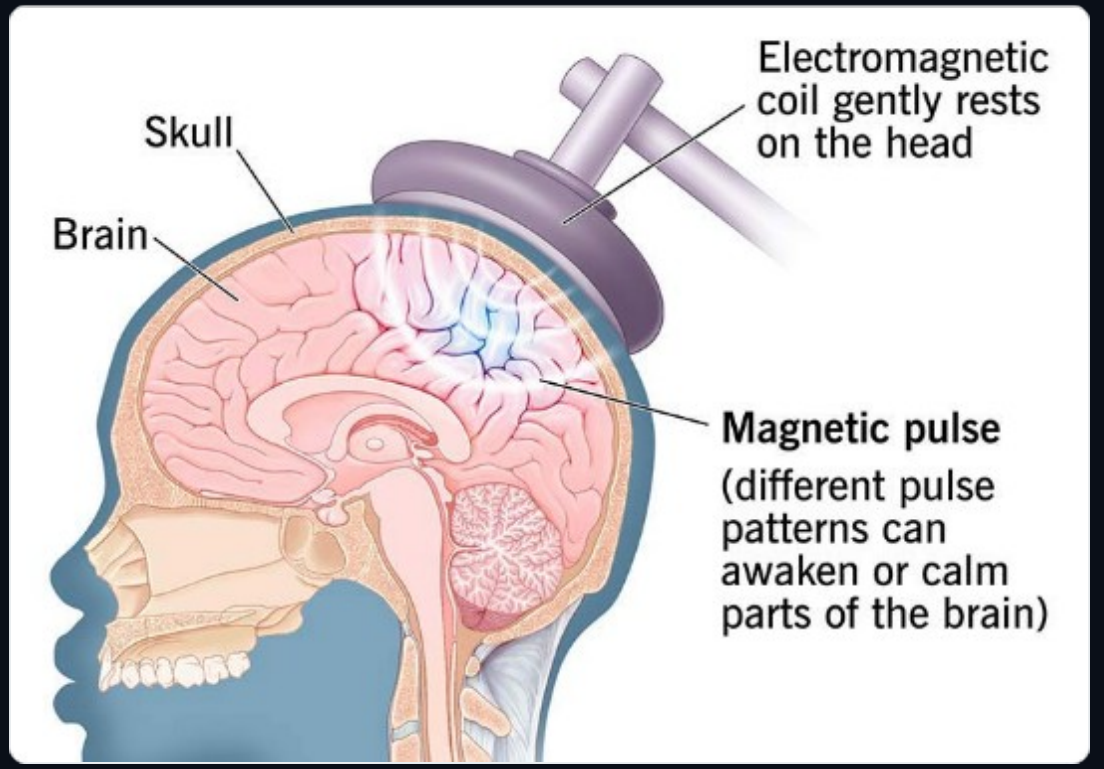
- **The Principal Gradient:** A smooth transition running from primary sensory areas to high-order default networks.
- **Hierarchical Collapse:** Underlies major psychiatric disorders, where the distinction between sensory input and internal thought blurs.
- **Continuous Phenotypes:** Captures subtle, individual variations better than rigid diagnostic categories.

Network-Targeted Therapeutics

Modifying Dynamic Systems

Modern clinical treatments focus on directly altering large-scale network dynamics rather than isolated local areas.

- **Personalized TMS:** Targets stimulation coordinates based on a patient's individual fMRI functional map.
- **Psychedelic Desynchronization:** Compounds like psilocybin disrupt rigid default mode structures, facilitating adaptive retraining.
- **Closed-Loop Neuromodulation:** Detects aberrant local rhythms in real time to deliver targeted, corrective stimulation.



Fin.