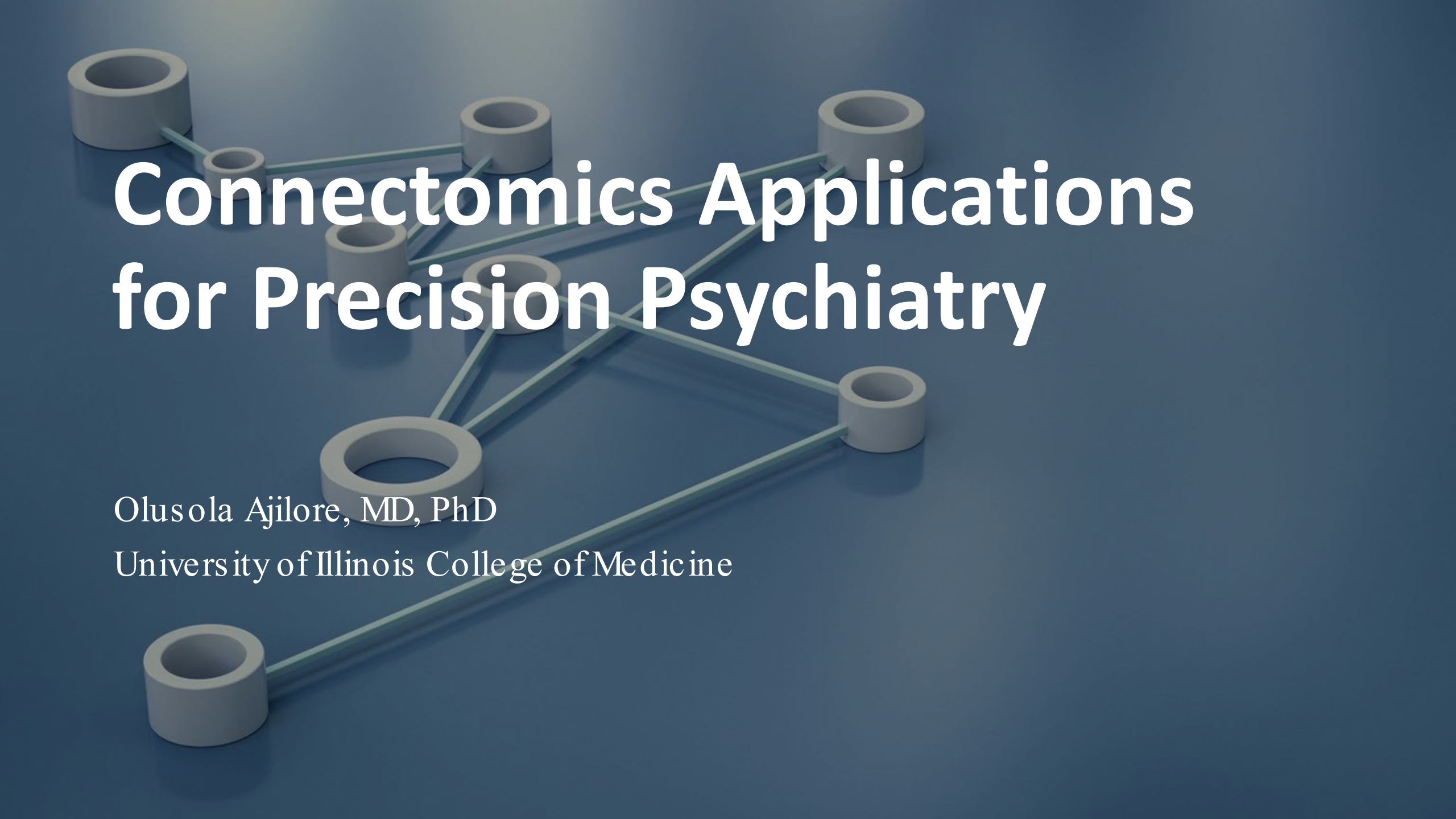


Connectomics Applications for Precision Psychiatry

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University of Illinois College of Medicine

Disclosures

- Advisory board: Embodied Labs, Blueprint, Novamind
- Co-Founder: KeyWise AI, Inc
- Funding
  - NIMH, NINDS, NCATS, Robert Wood Johnson Foundation



THE INSANITY

OF

Over-Exertion of the Brain;

BEING

THE MORISON LECTURES

DELIVERED BEFORE THE

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH,

Session 1894.

BY

J. BATTY TUKE, M.D., F.R.C.P.E., F.R.C.S.E.

WITH ILLUSTRATIONS AND DIAGRAMS.

EDINBURGH:
OLIVER AND BOYD, TWEEDDALE COURT.
LONDON:
SIMPKIN, MARSHALL, HAMILTON, KENT, AND CO., LIMITED.

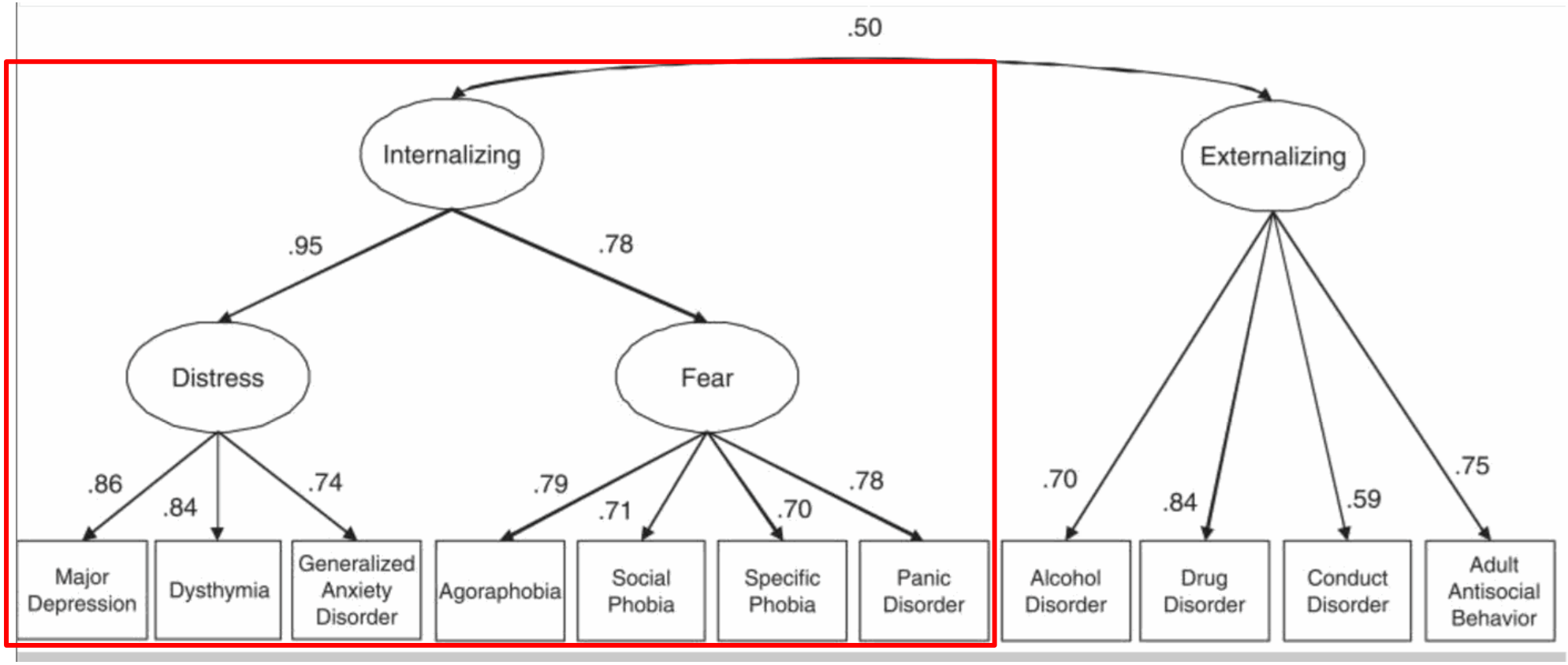
“As yet the chemistry and mechanics of psychical processes are matters of surmise and theory; all we can say is, that mental action is a function of connections…we have a right to infer that when the continuity of these connections is destroyed, interrupted or structurally impaired, modification of function must ensue.”

– *Sir John Batty Tuke, The insanity of over-exertion of the brain, 1894*

Precision Psychiatry

"The ***right treatment*** for the ***right person*** at the ***right time***"

Negative Valence Brain Targets and Predictors of Anxiety and Depression Treatment (PI: K. Luan Phan)



- RDoC: NIMH initiative to get away from DSM diagnostic categories
  - Focus on internalizing psychopathologies (IPs; e.g., anxiety, depression)
  - All have similar response to either CBT or SSRI, but choosing treatment is basically guess trial and error - disorders of emotion regulation
  - Identify DSM diagnosis agnostic biomarkers of disease burden or treatment response.

Connectome findings in mood/anxiety disorders

- Reduced global network efficiency in social anxiety and anxious temperament *(Markett et al, 2016; Zhu et al, 2017)*

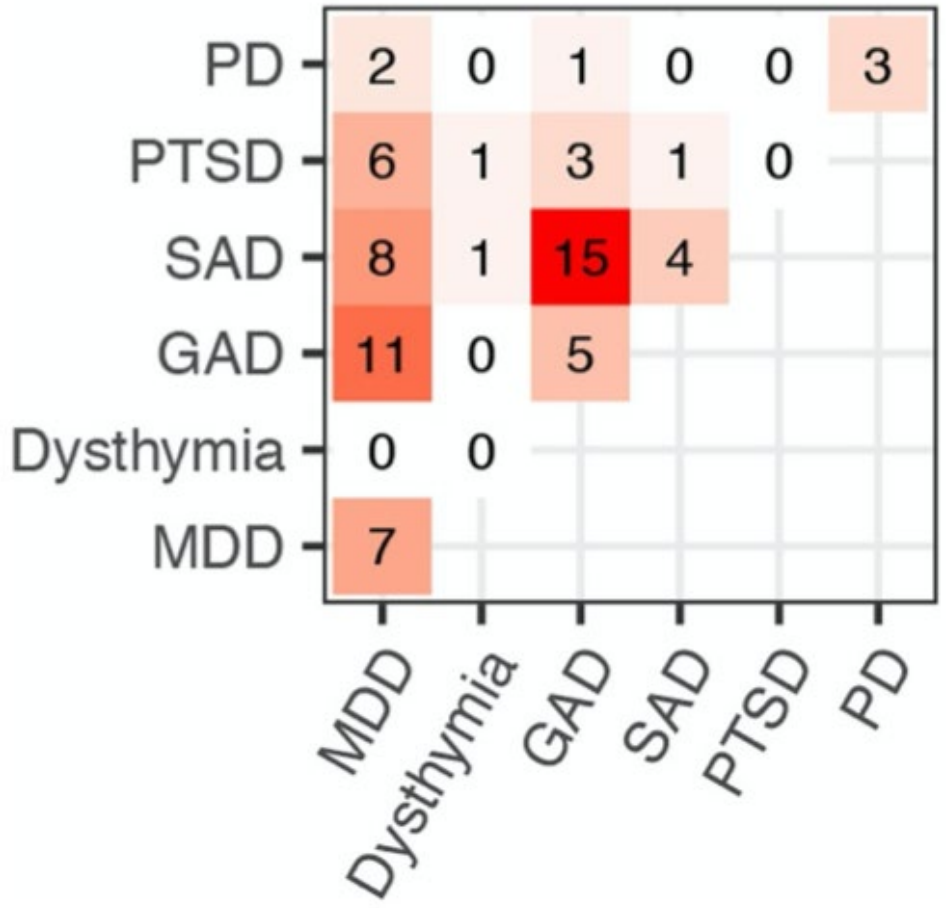
- Network efficiency reduced in mood disorders and correlates with symptom severity/processing speed *(Bai et al, 2012; Leow et al, 2013; Ajilore et al, 2014; Li et al, 2015)*

- Altered centrality in the DMN and limbic regions *(GadElkarim et al, 2012; Lim et al, 2013; Ajilore et al, 2014)*

Negative Valence RDoC Study sample

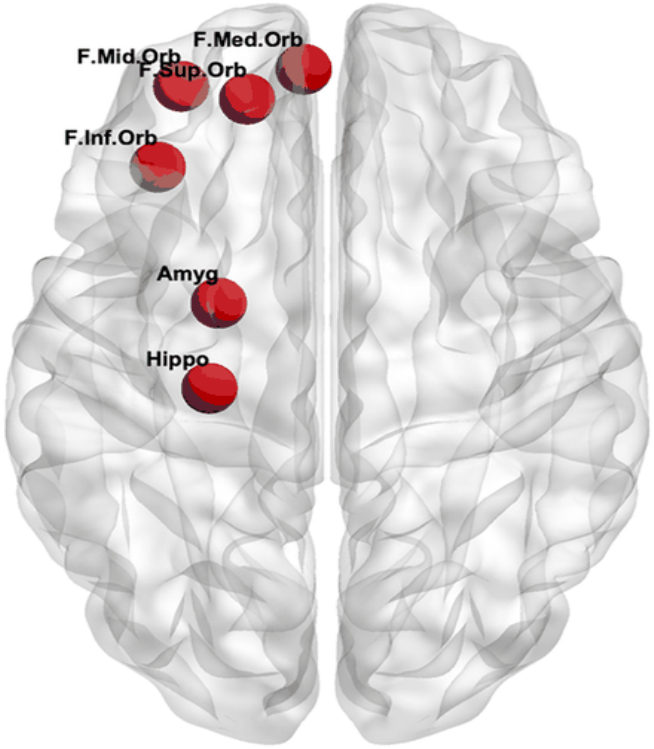


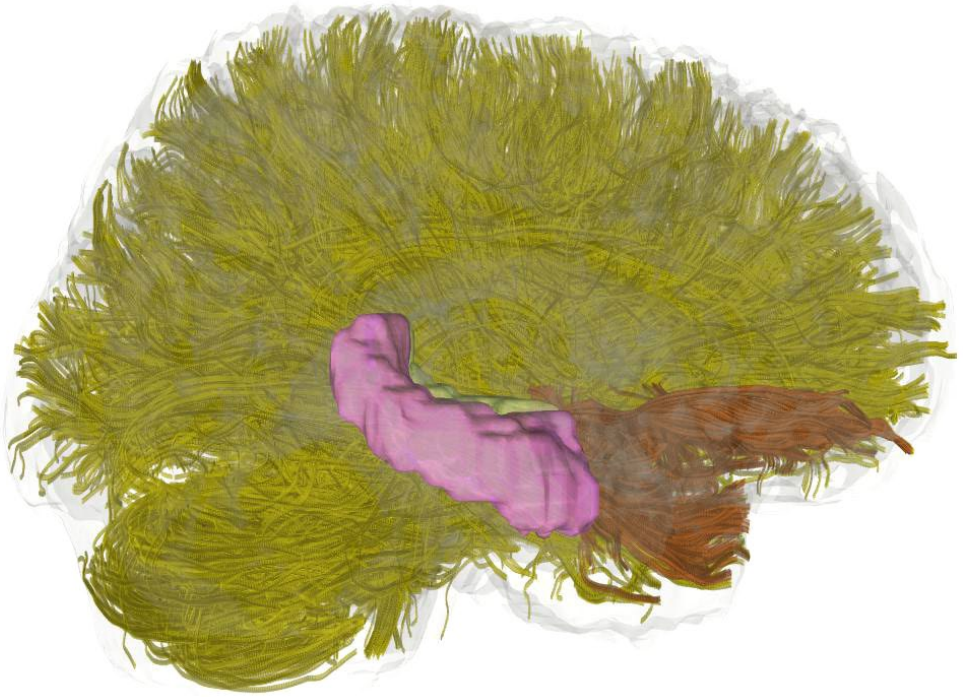
- Intentionally heterogeneous sample of IP patients (n = 69) and healthy controls (n = 24)
- Findings from previous studies on individual IPs more likely to overlap than be distinct
- Goal: identify brain network disruptions common in all IP PTs in sample relative to healthy controls (HC)
  - To study brain as a network, start with ***graph based metrics***
  - Features for each node (brain region) based on ***role in network***



Uncinate network





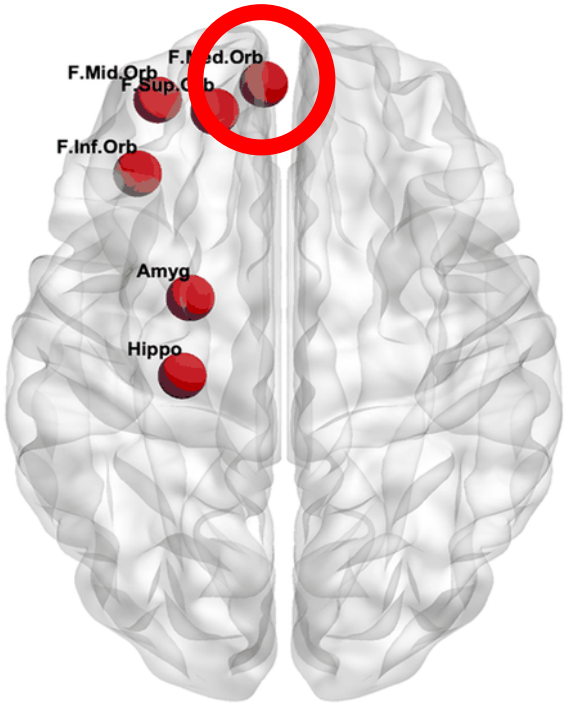


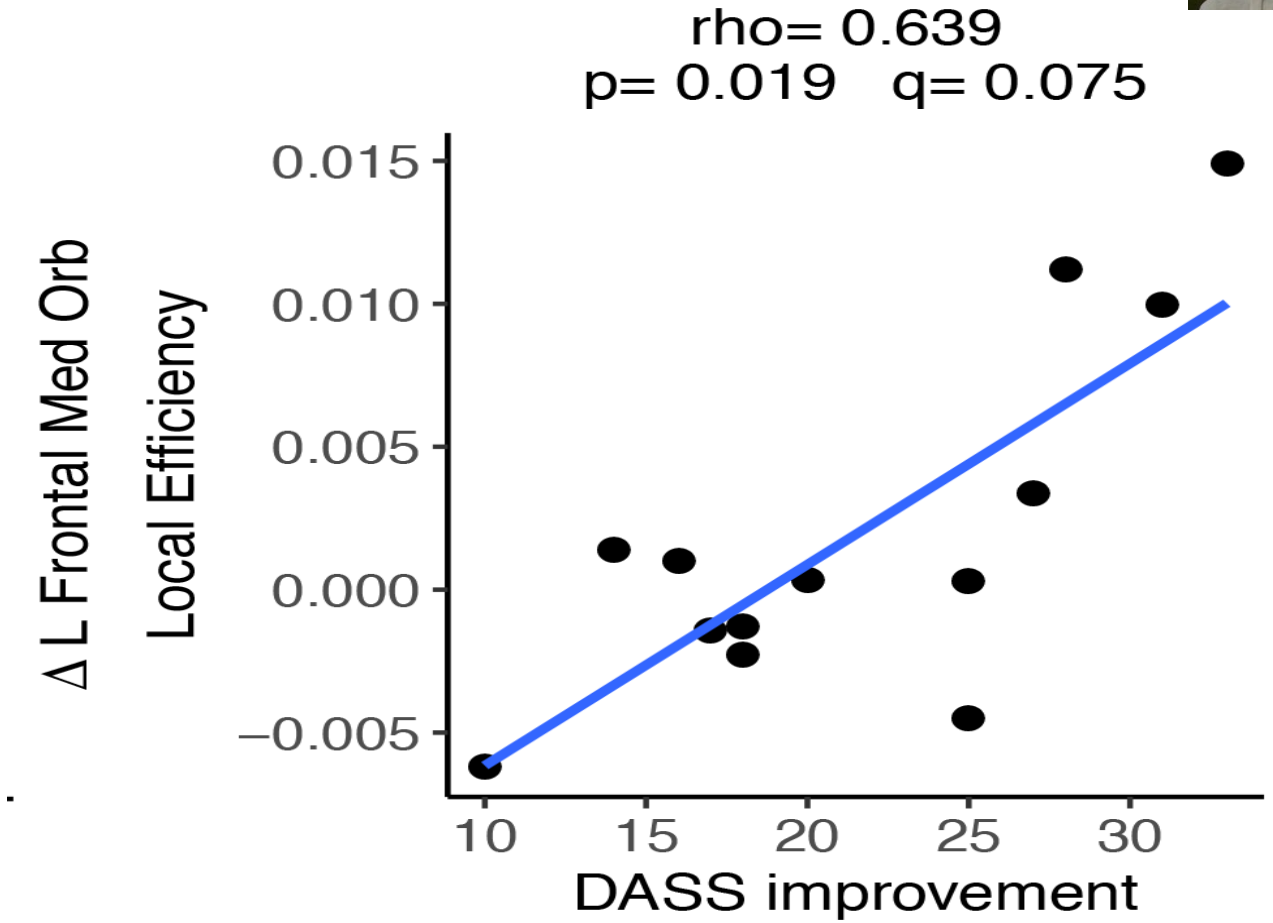
Uncinate fasciculus

- Increased WMH in late-life depression *(Sheline et al, 2008)*
- Associated with depression severity in the right UF *(Dalby et al, 2010)*
- Associated with functional connectivity in the left UF *(Steffens et al, 2011)*
- Fiber number of the right UF associated with depression severity *(Zhang et al, 2012)*
- Lower white matter integrity in LLD/adult MDD *(Charlton et al, 2014; Wen et al, 2014)*

Connectome correlates of CBT treatment response

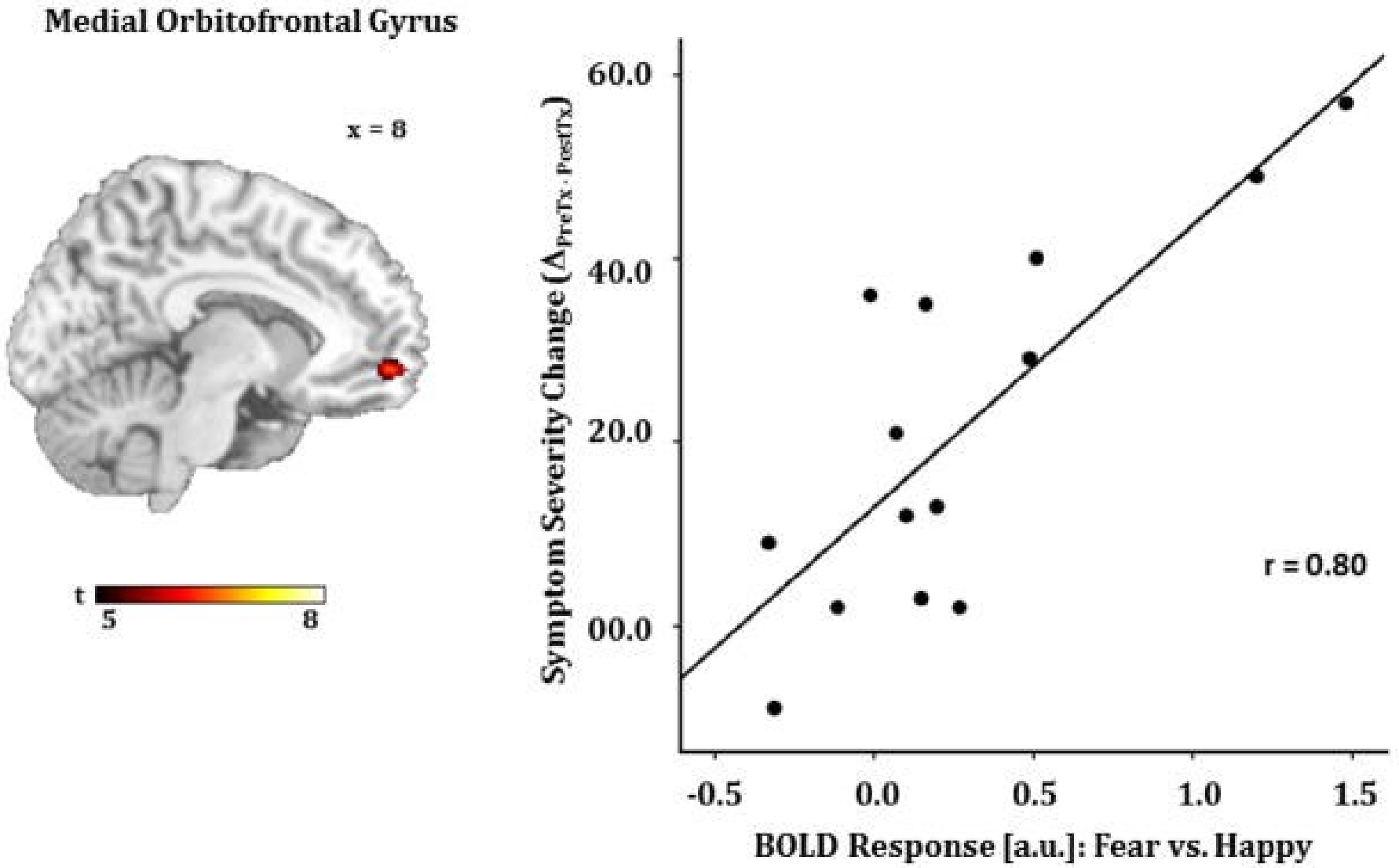






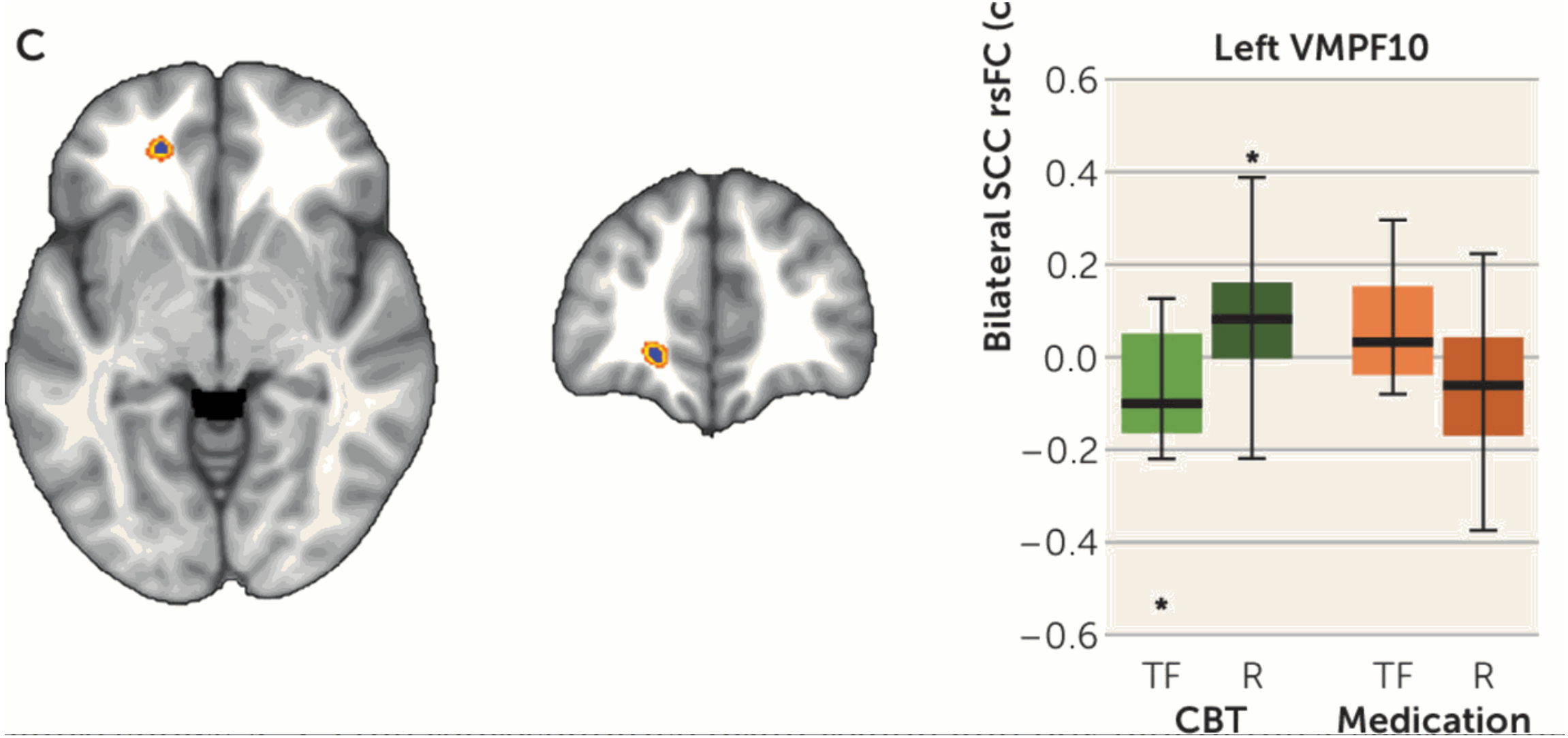
Thomas et al, Psych Res Neuroimaging 2020

Medial Orbitofrontal Response Predicts Symptom Change



Klumpp et al, 2014

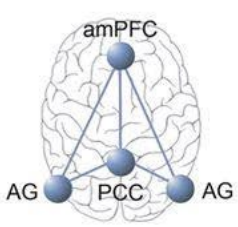
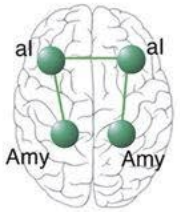
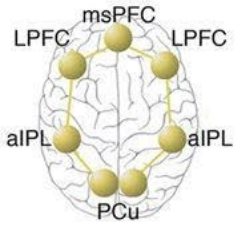
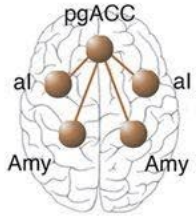
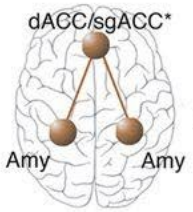
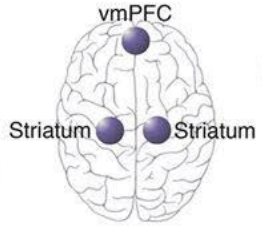
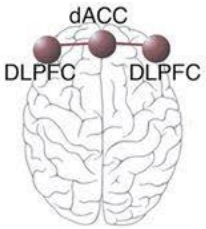
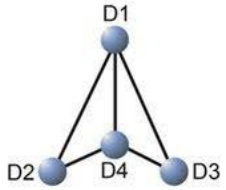
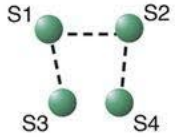
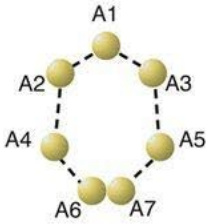
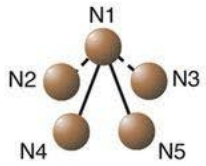
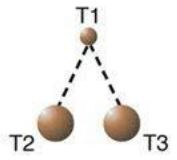
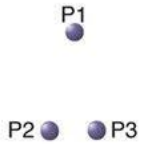
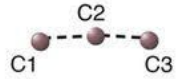
Subgenual Cingulate–VMPFC Connectivity Tracks CBT Response



Dunlop et al, AJP 2017

Why don’t we use connectome properties to inform treatment assignment?

Standardizing Circuit-Based Clinical Scores Across RDoC Domains

Condition	Intrinsic	Intrinsic	Intrinsic	Evoked by Sad Stimuli	Evoked by Threat Stimuli	Evoked by Happy Stimuli	Evoked by NoGo Stimuli
Circuit	Default Mode	Salience	Attention	Negative Affect - Sad	Negative Affect - Threat	Positive Affect	Cognitive Control
Standardizing Regions & Connections							
Quantifying Regional Circuit Clinical Scores							
Computing Global Circuit Clinical Scores	$(C_{D1,D2} + C_{D1,D3} + C_{D1,D4} + C_{D2,D4} + C_{D3,D4})/5$	$(-C_{S1,S3} - C_{S2,S4} - C_{S1,S2})/3$	$(-C_{A1,A2} - C_{A1,A3} - C_{A2,A4} - C_{A3,A5} - C_{A4,A6} - C_{A5,A7})/6$	$(A_{N1} + A_{N2} + A_{N3} + A_{N4} + A_{N5} - C_{N1,N2} - C_{N1,N3} + C_{N1,N4} + C_{N1,N5})/9$	$(-A_{T1} + A_{T2} + A_{T3} - C_{T1,T2} - C_{T1,T3})/5$	$(-A_{P1} - A_{P2} - A_{P3})/3$	$(-A_{C1} - A_{C2} - A_{C3} - C_{C1,C2} - C_{C2,C3})/5$

Activation

Hyper Typical Hypo

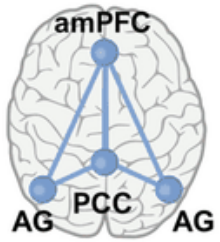
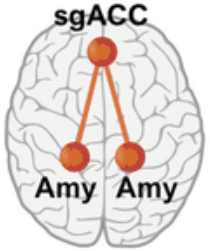
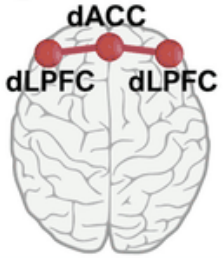
- Default Mode
- Salience
- Attention
- Negative Affect
- Positive Affect
- Cognitive Control

Connectivity

- Hyper-connectivity
- Hypo-connectivity

Goldstein-Piekarski et al, 2022

Biotype-Matched Treatment Improves Response and Remission Rates

A. Biotype Circuit	B. Defining Circuit Dysfunction	C. Treatment Predicted by Circuit Dysfunction	D. Treatment Success Rates	E. Improvement: Matched vs. Average
Default Mode 	↑ high score, anterior-medial subdivision	Sertraline	70% Matched 34% Average 16% Unmatched	**2.1** times higher remission rate
	↓ low score, posterior subdivision	Escitalopram	68% 48% 16%	**1.4** times higher response rate
		Venlafaxine	53% 29% 22%	**1.8** times higher remission rate
Negative Affect 	↑ high circuit score	Behavioral Therapy	63% 18% 10%	**3.5** times higher remission rate
	↓ low circuit score	Venlafaxine	41% 29% 14%	**1.4** times higher remission rate
Cognitive Control 	↑ high circuit score	Sertraline, Escitalopram, Venlafaxine	52% 42% 31%	**1.2** times higher response rate
	↓ low circuit score	TMS	41% 21% 16%	**2.0** times higher response rate

Ahn et al, 2025

METHODS: Two-Step C+/C- Stratification and Treatment Matching

Step 1. Screening

Cognitive Testing
Sensitive Behavioral Screen

- ✓ Measure behavioral manifestations of the cognitive biotype (C+)
- ✓ Enrich for potential C+ patients
- ✓ Allow high false positives (sensitivity) and oversampling

Scalable Platforms and Measures (WebNeuro)
Fully automated, rapid data collection and processing



Real-time test results for the **individual patient**, standardized to a healthy reference sample



Cognitive impairment defined as ≤ -0.5 SD



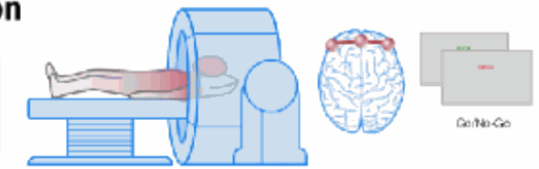
C+ candidates
(screen-positive)

Step 2. Precision Biotype Confirmation

Functional MRI Scans
Specific Biotype Confirmation

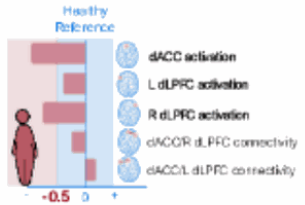
- ✓ Measure cognitive control circuit activity
- ✓ Provide mechanistic specificity of the C+ biotype

Scalable Platforms and Measures (EtCere)
Fully automated, rapid data collection and processing



EtCere

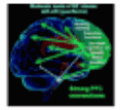
Real-time circuit scoring for the **individual patient**, standardized to a healthy reference sample



Circuit impairment defined as ≤ -0.5 SD



Confirmed C+
(biotype-validated)



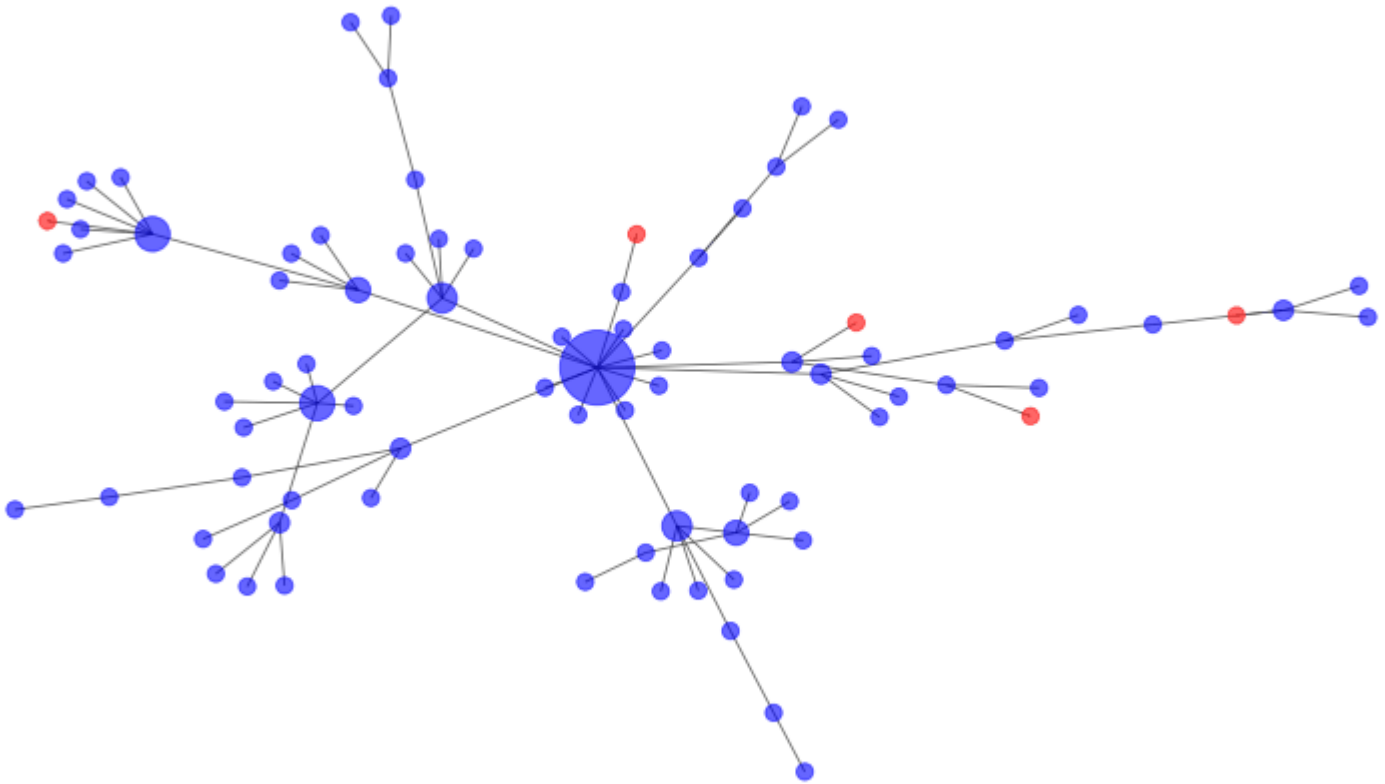
Arnsten et al. Molecular Psychiatry, 2023

Targeted Treatment
Guanfacine | Avoid standard SSRIs

Ahn et al, 2026

Data-driven methods for subnetwork discovery

How does something spread across a network?

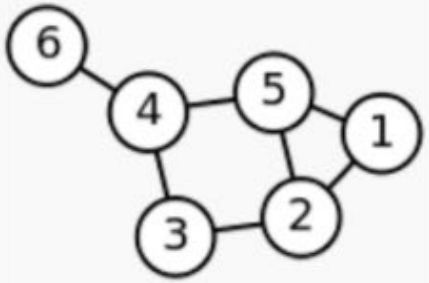


https://theconversation.com/how-to-flatten-the-curve-of-coronavirus-a-mathematician-explains-133514



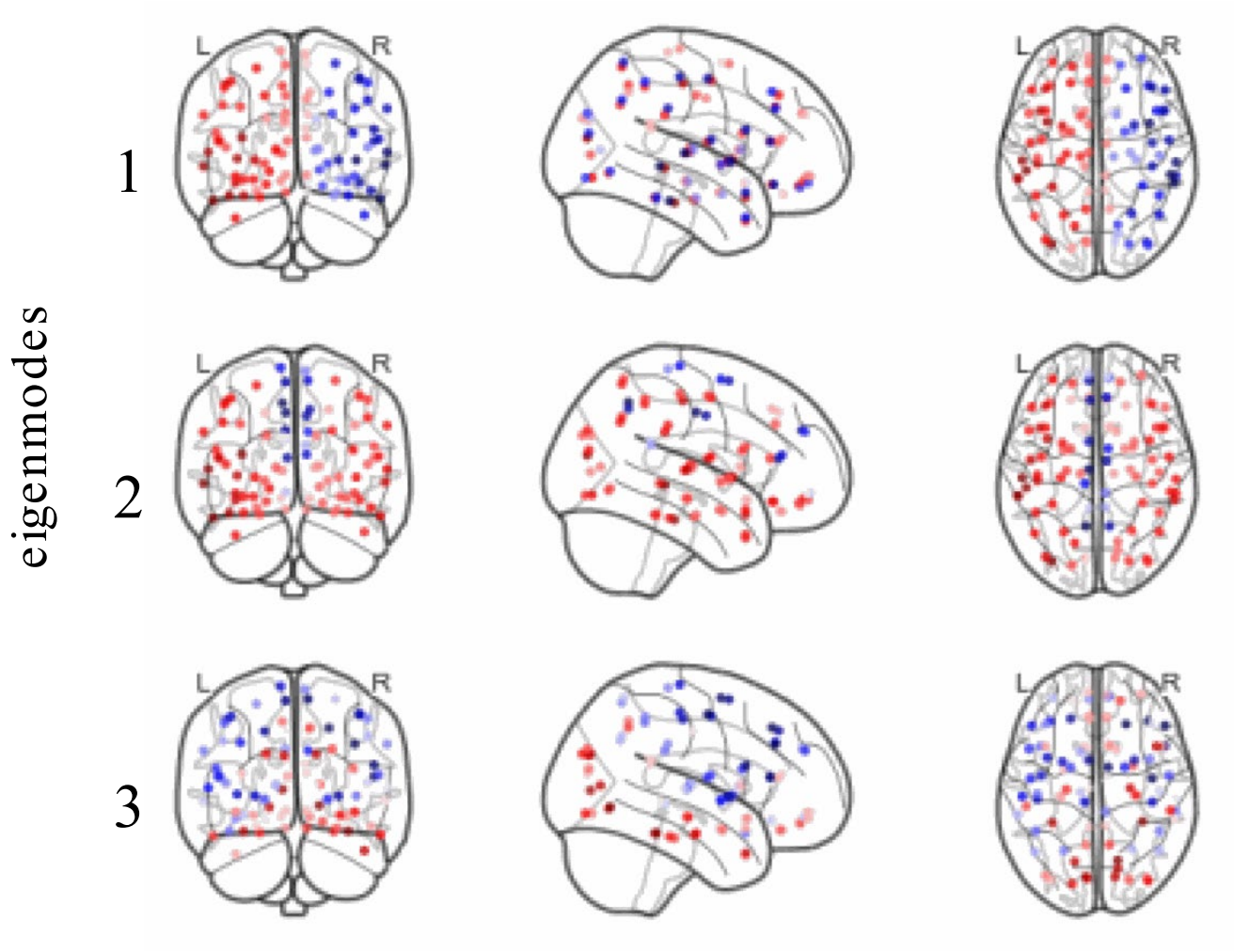
This Photo by Unknown Author is licensed under CC BY-SA

Network heat diffusion using the graph laplacian

Labeled graph	Degree matrix	Adjacency matrix	Laplacian matrix
	$\begin{pmatrix} 2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 3 & 0 & 0 & 0 & 0 \\ 0 & 0 & 2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 3 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$	$\begin{pmatrix} 0 & 1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 & 1 \\ 1 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \end{pmatrix}$	$\begin{pmatrix} 2 & -1 & 0 & 0 & -1 & 0 \\ -1 & 3 & -1 & 0 & -1 & 0 \\ 0 & -1 & 2 & -1 & 0 & 0 \\ 0 & 0 & -1 & 3 & -1 & -1 \\ -1 & -1 & 0 & -1 & 3 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 \end{pmatrix}$

- Can use network properties encoded by laplacian matrix to study diffusion in network over time
- Diffusion through an edge is proportional to edge weight

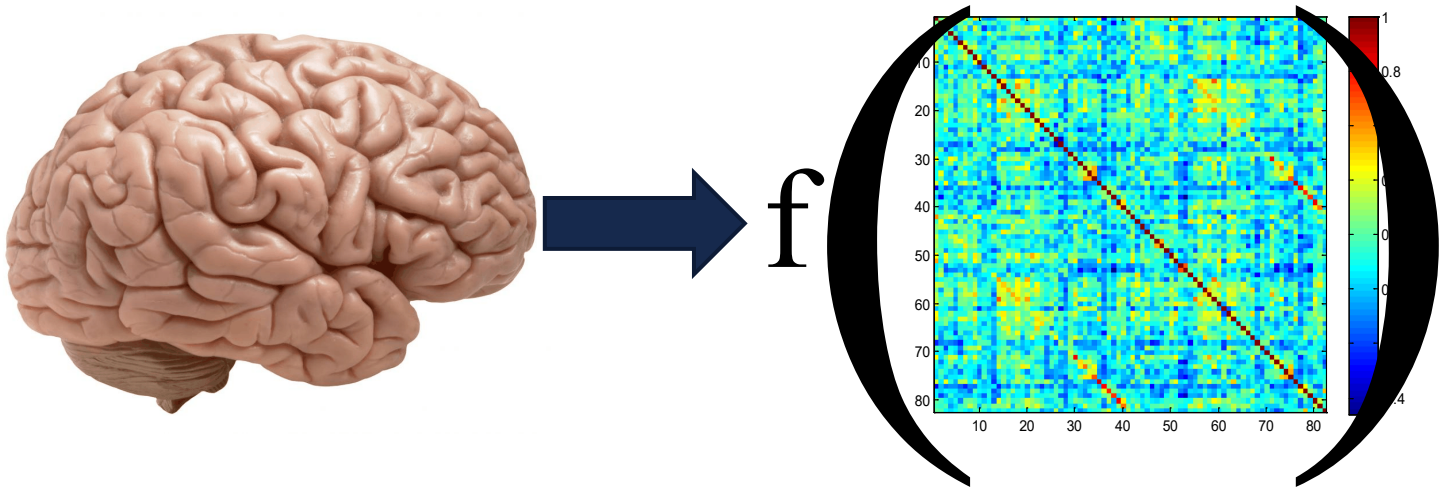
Brain eigenmodes in healthy controls



Redefining the structural connectome



- We can define a connectome based eigenmode embedding
- Connectome now reflects how easily information passes between nodes (network diffusion) rather than the strength of connection between nodes

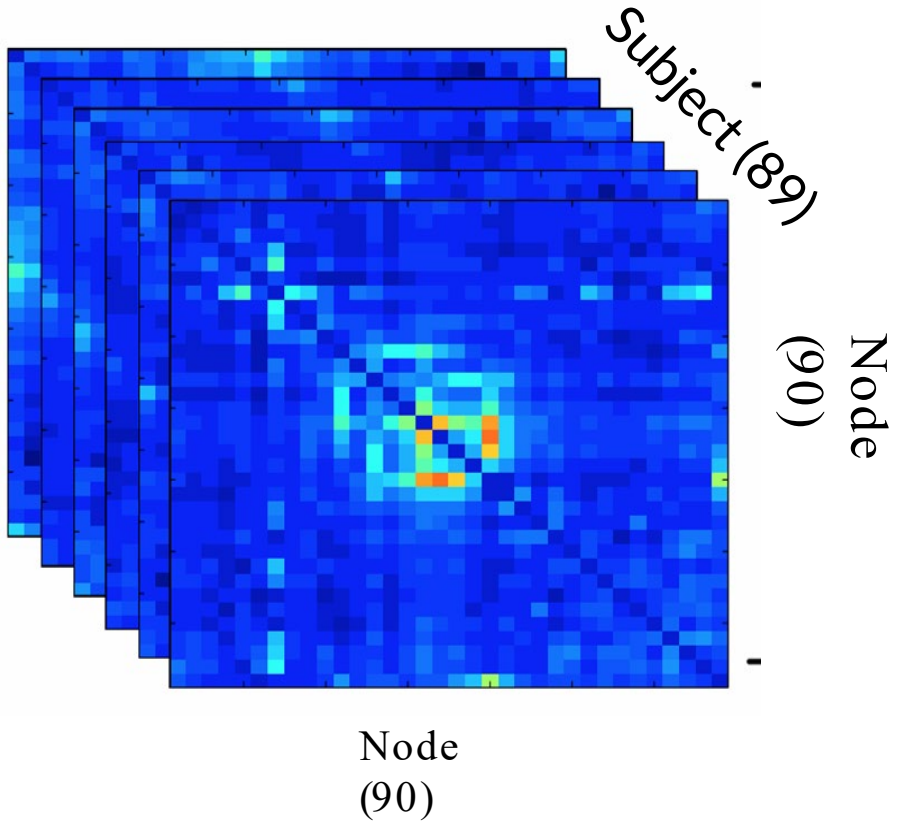


How to identify subnetwork with disrupted diffusion dynamics?

- Combine network diffusion approach with pre-existing method

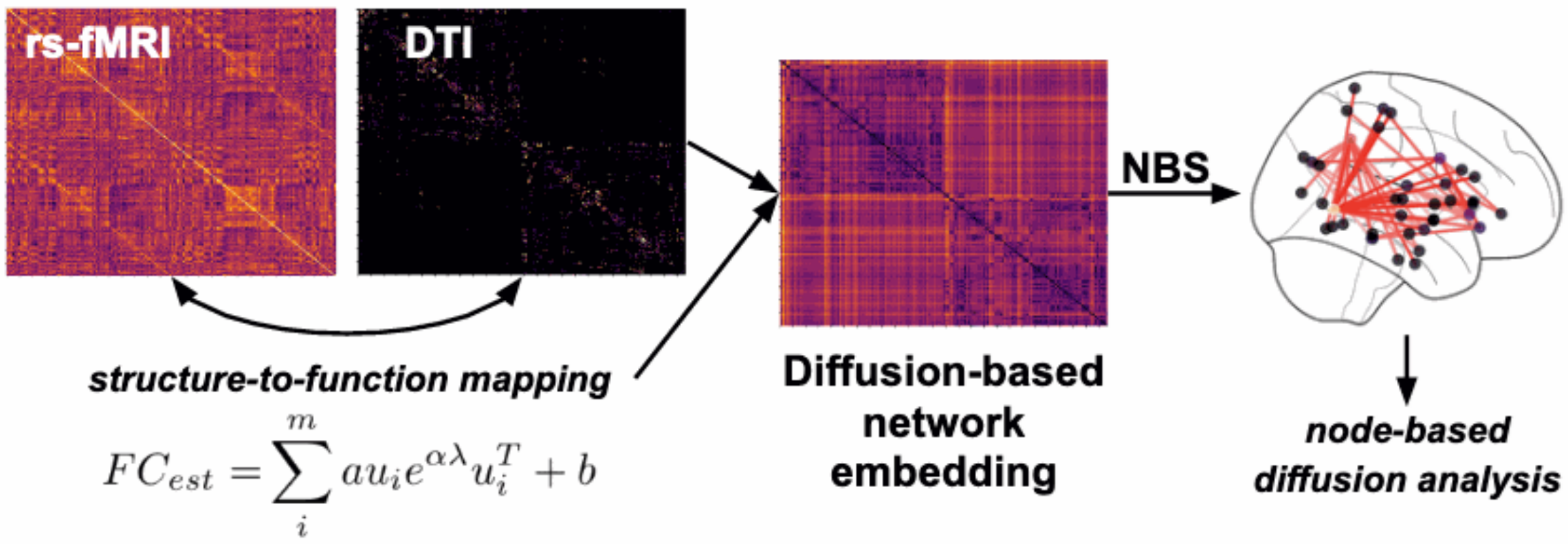
- Network Based Statistic (NBS)
  - Used extensively to identify brain subnetworks with relationship to clinical traits
  - Approach:
    - Perform correlation or t-test at each edge of connectome dataset
    - Set statistical values below a threshold to zero and identify connected components
    - Determine null distribution with permutation test
    - P-value is calculated as the number of times a null connected component is larger than the test component, divided by the number of permutations

  - Zalesky A, Fornito A, Bullmore ET (2010) NeuroImage 53:1197-207.



Method overview figure



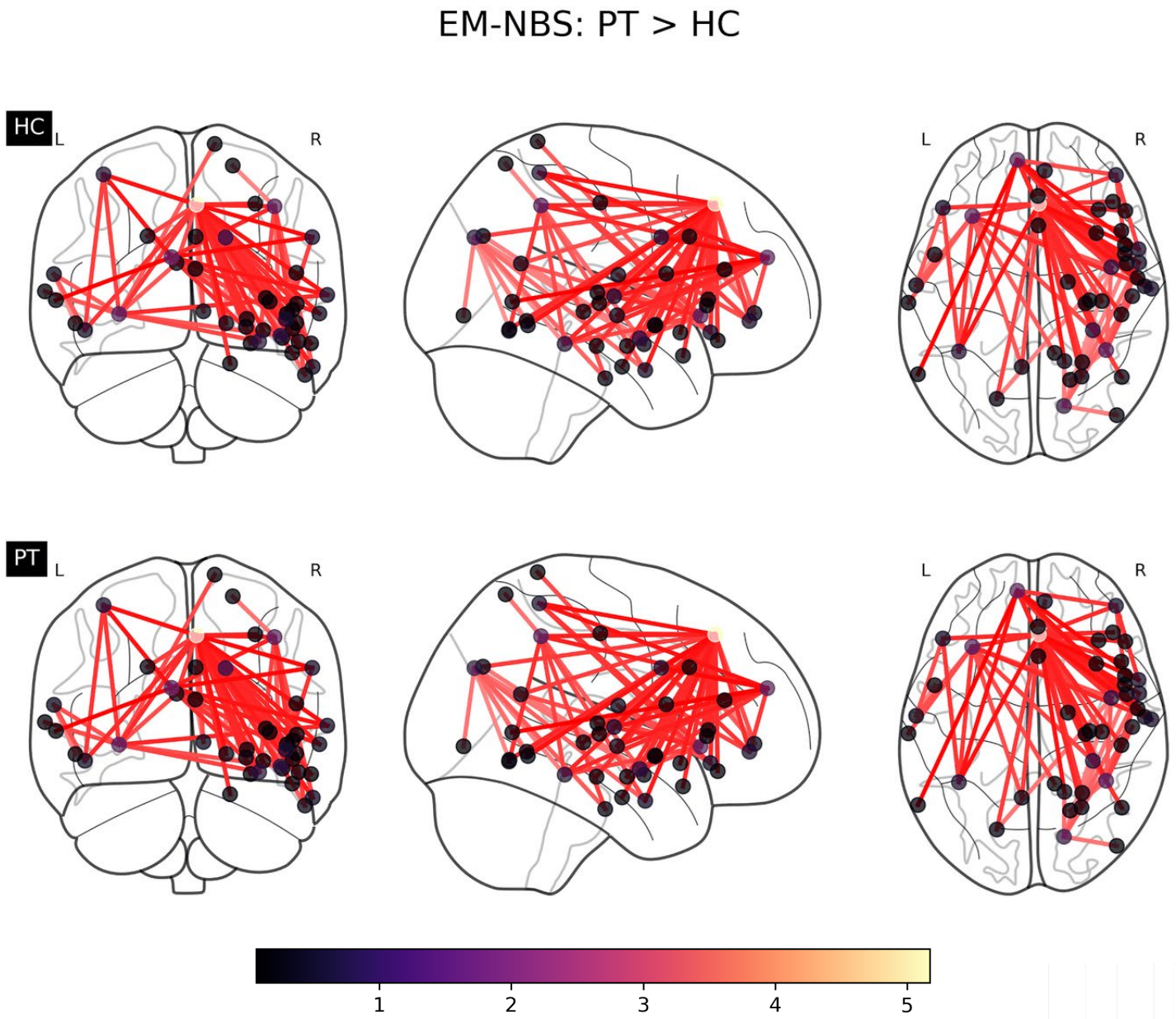


Thomas et al, Cerebral Cortex 2021

Subnetwork of Slower Diffusion in Patients vs. Controls

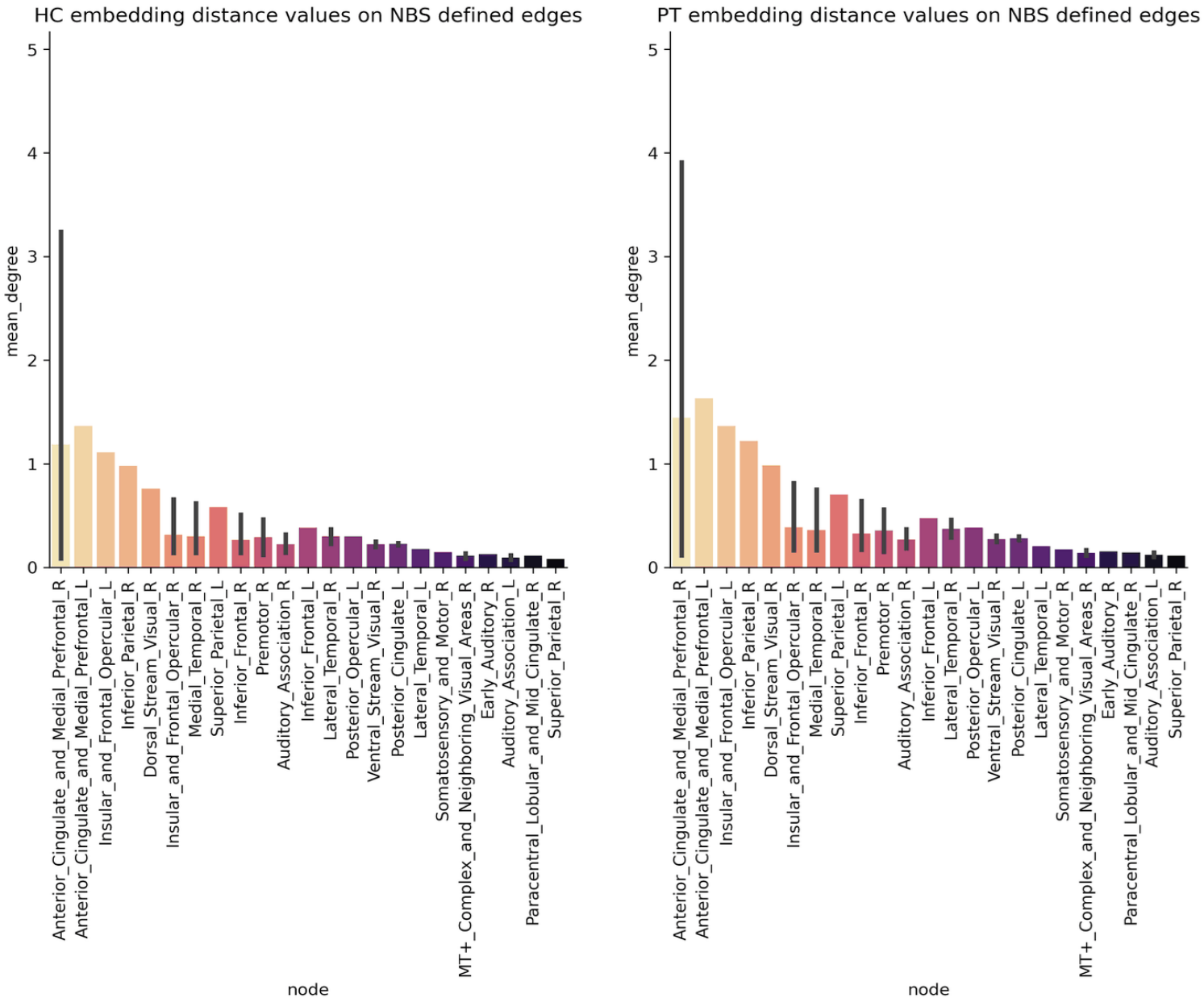
Subnetwork found via NBS on distance matrix connectomes (t statistic = 4).

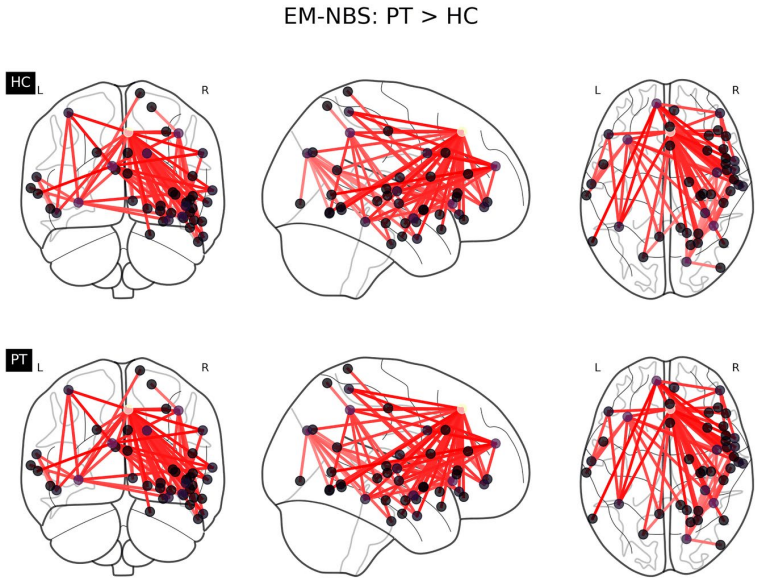
Found with one-sided t-test such that all significant edges indicate a greater distance in PT relative to HC - i.e., slower diffusion.



Thomas et al, Cerebral Cortex 2021

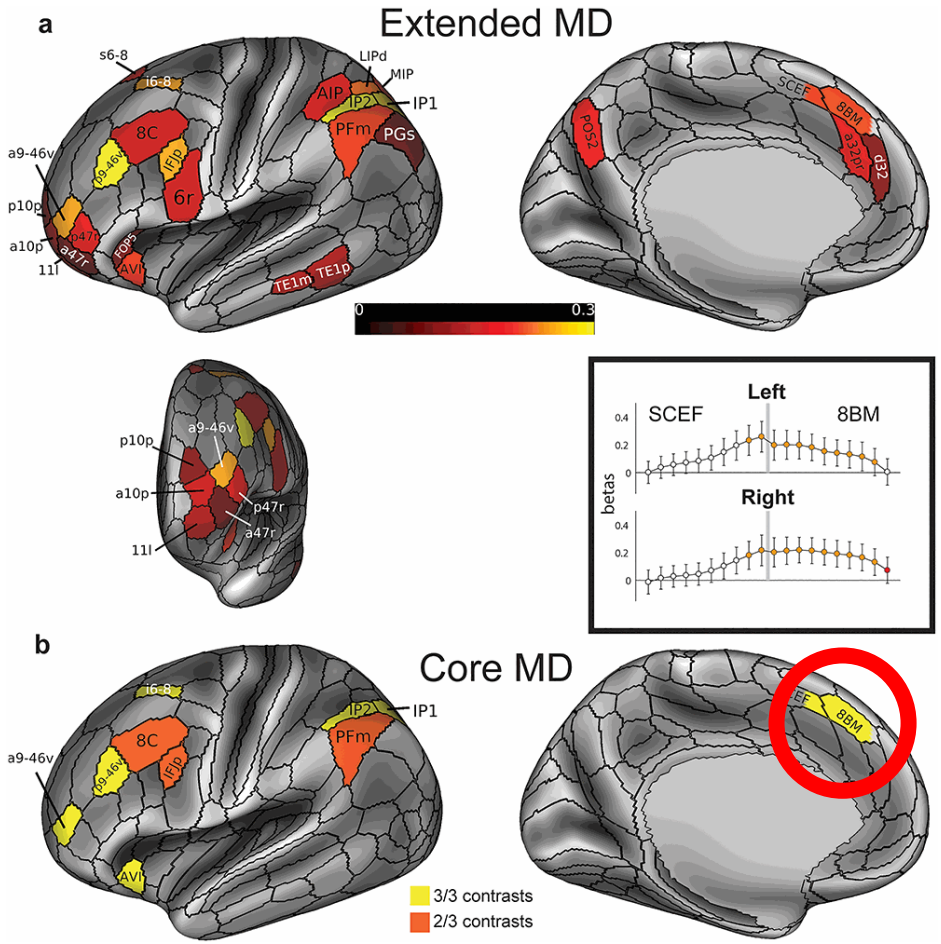
Subnetwork Hub Regions: Anterior Cingulate / Medial PFC





Subnetwork hubs are anterior b/l anterior cingulate/medial prefrontal regions

Overlap with the Multiple Demand (MD) System

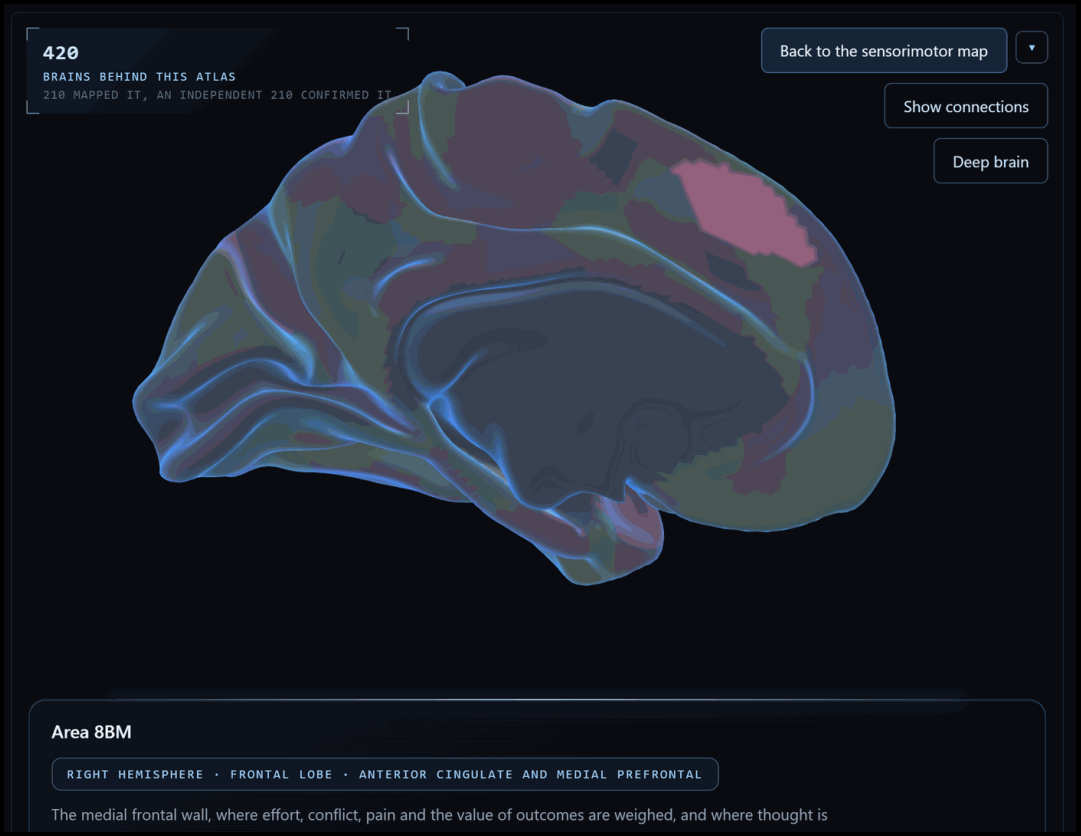


MD system – frontoparietal regions co-activated across a number of cognitively demanding tasks

Assem et al Cereb Cortex, Volume 30, Issue 8, August 2020, Pages 4361–4380, https://doi.org/10.1093/cercor/bhaa023

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Area 8BM

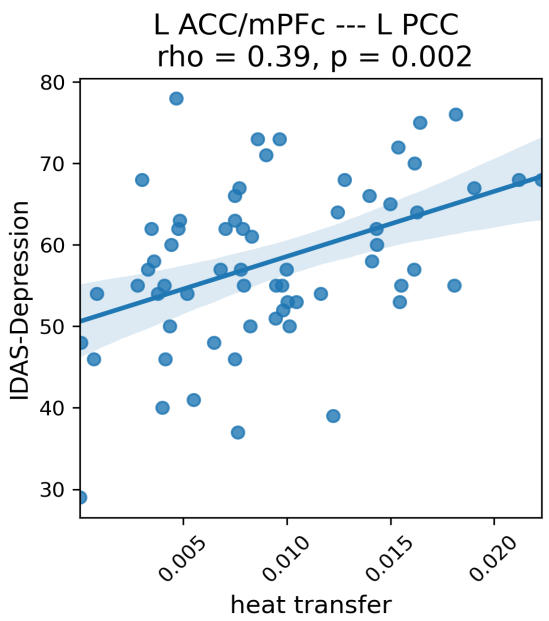


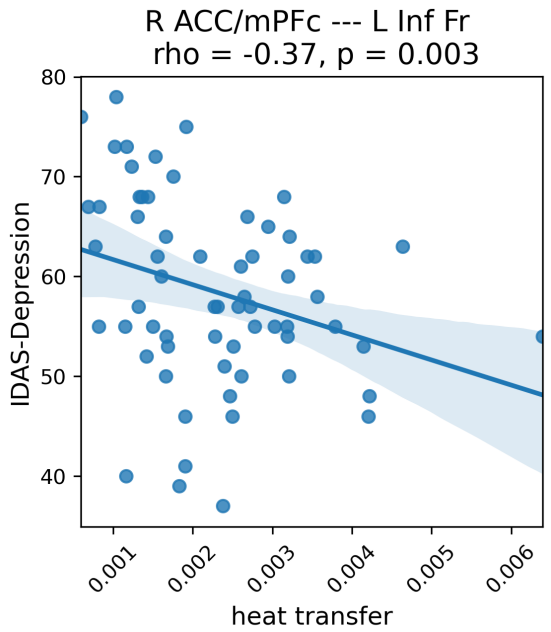
https://amyleesterling.github.io/human-brain/somatotopy.html

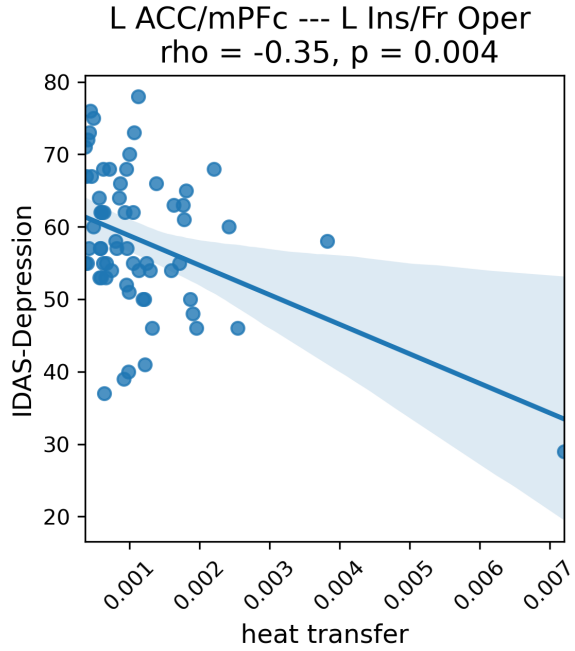
Information transfer correlates of baseline symptom severity

BASELINE: correlates of baseline idas_depression in PT only.

Negative correlation indicates that less heat transfer between nodes is associated with higher idas_dep.





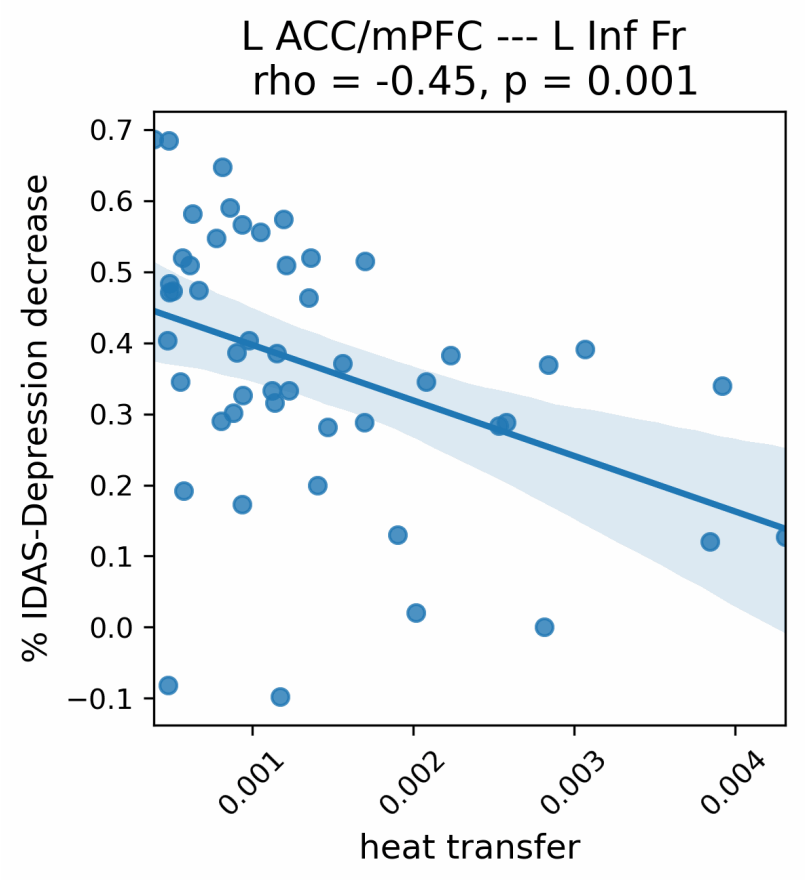


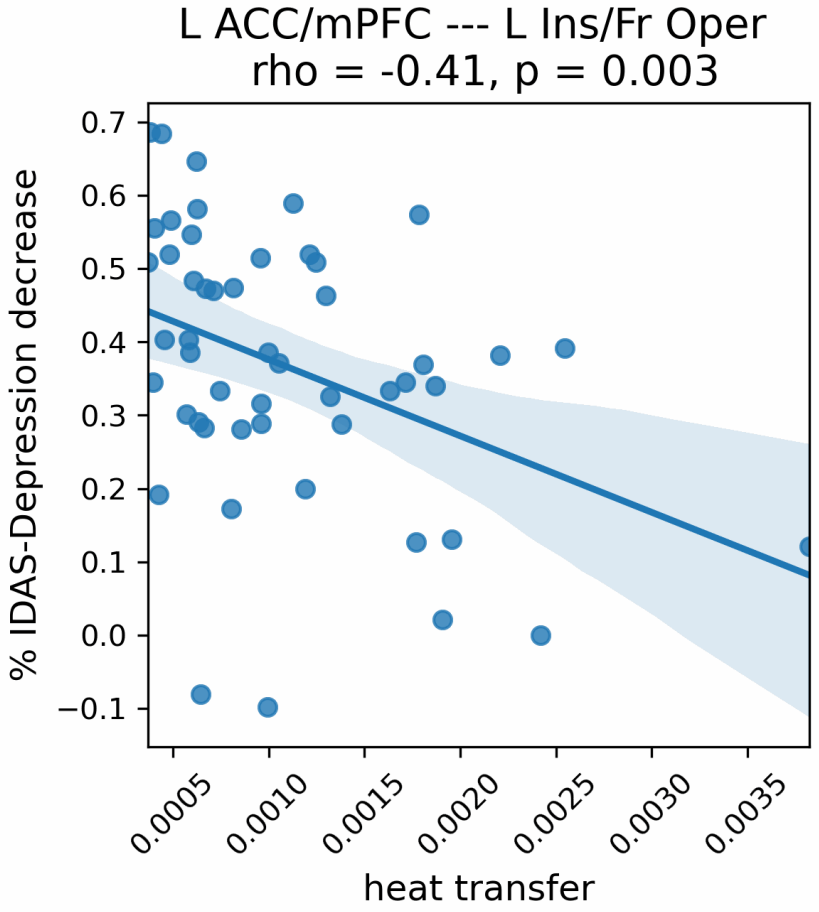
Thomas et al, Cerebral Cortex 2021

Information transfer symptom correlates of overall treatment response

ALL PT: correlations of percentage decrease in idas depression with heat transfer between nodes.

Negative correlation indicates that less heat transfer between nodes at baseline is associated with higher treatment response



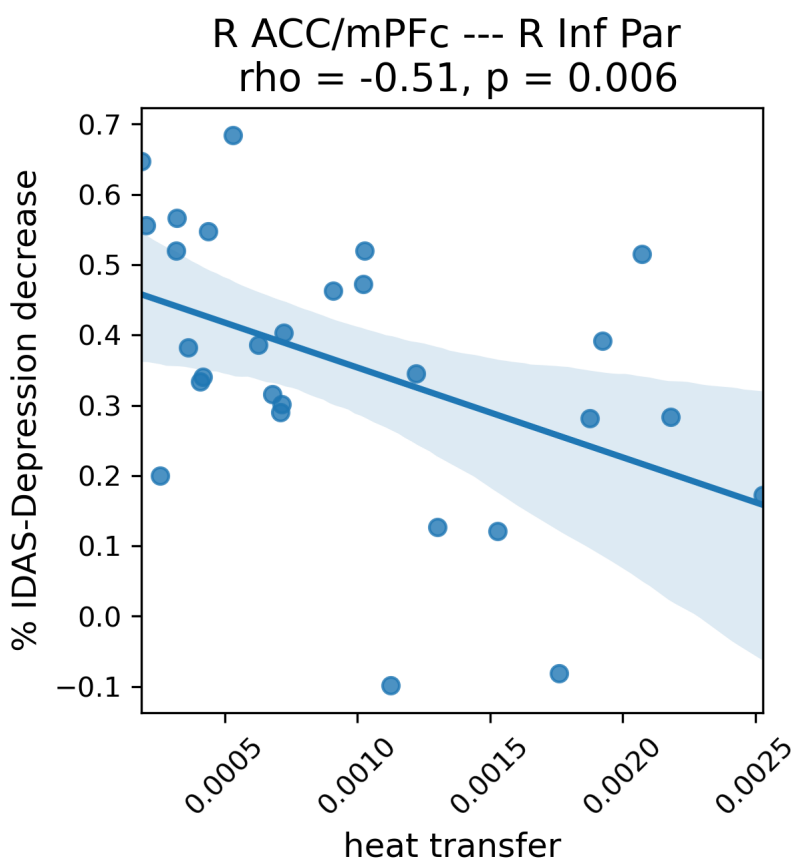


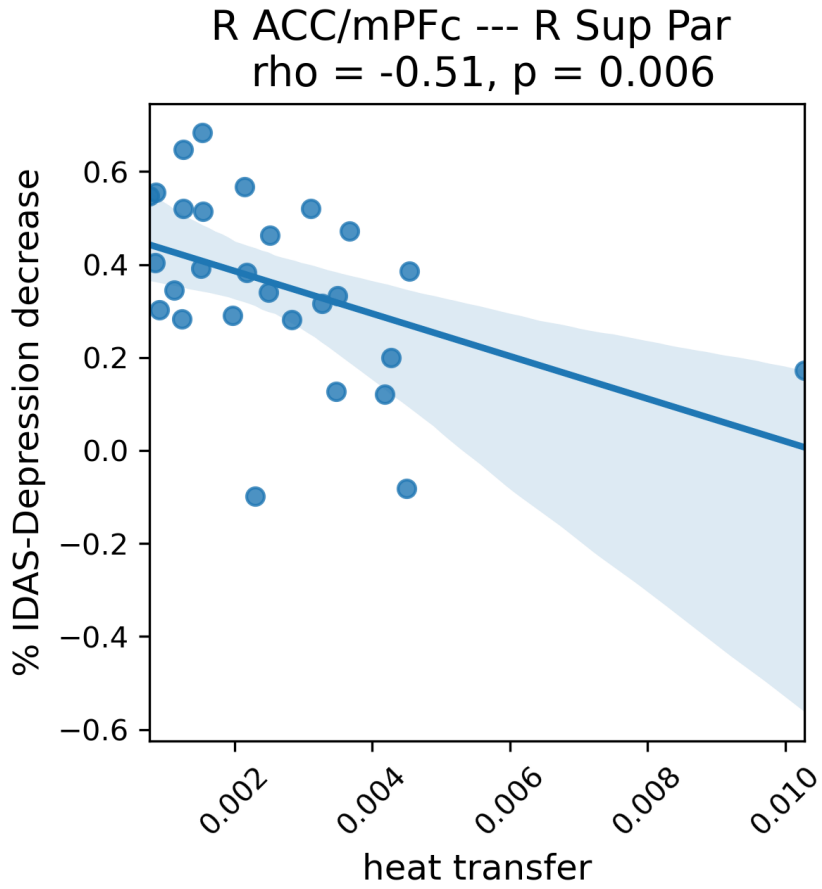
Thomas et al, Cerebral Cortex 2021

Information transfer symptom correlates of CBT treatment response

CBT: correlations of percentage decrease in idas depression with heat transfer between nodes.

Negative correlation indicates that less heat transfer between nodes at baseline is associated with higher treatment response



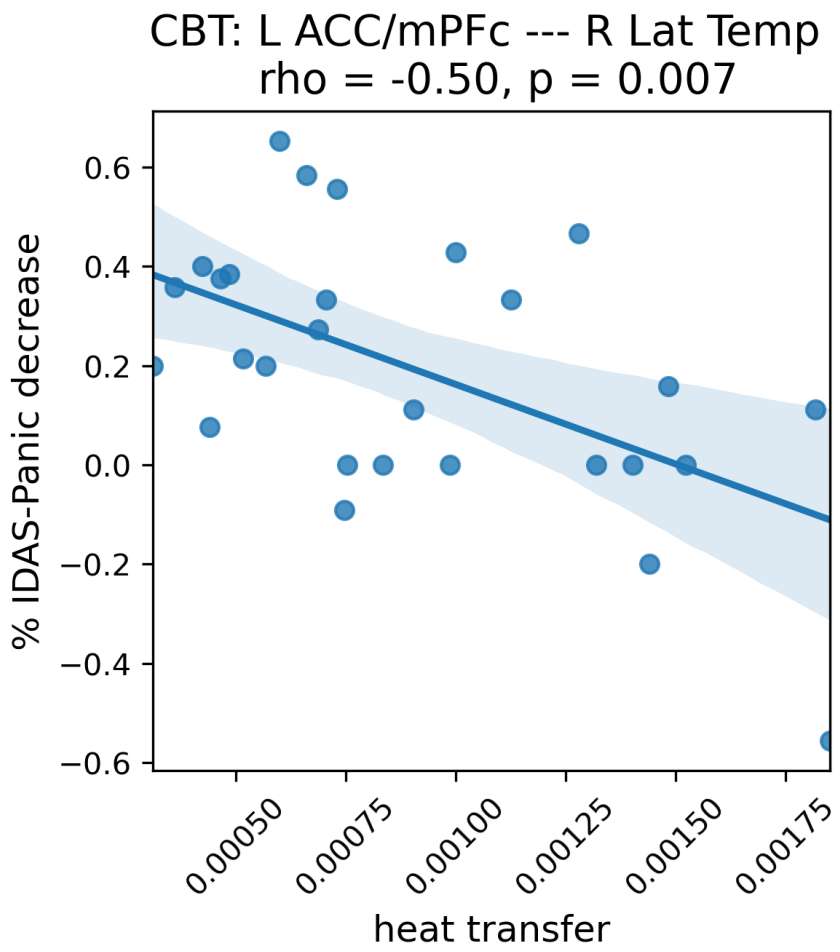


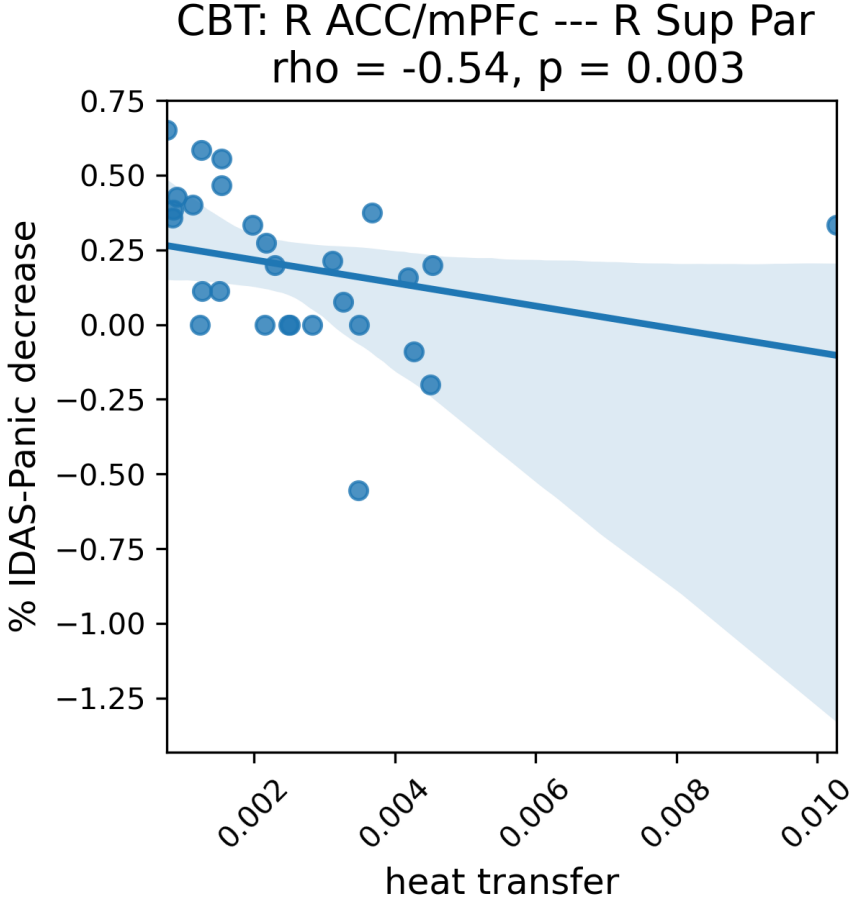
Thomas et al, Cerebral Cortex 2021

Information transfer symptom correlates of CBT treatment response

CBT: correlations of percentage decrease in idas panic with heat transfer between nodes.

Negative correlation indicates that less heat transfer between nodes at baseline is associated with higher treatment response



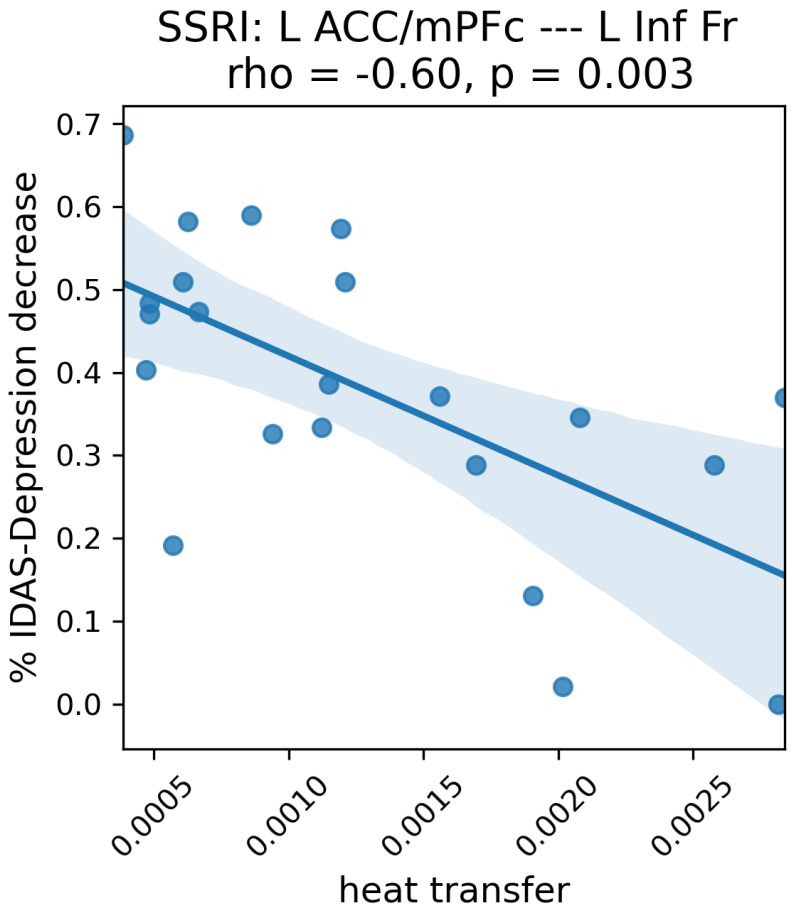


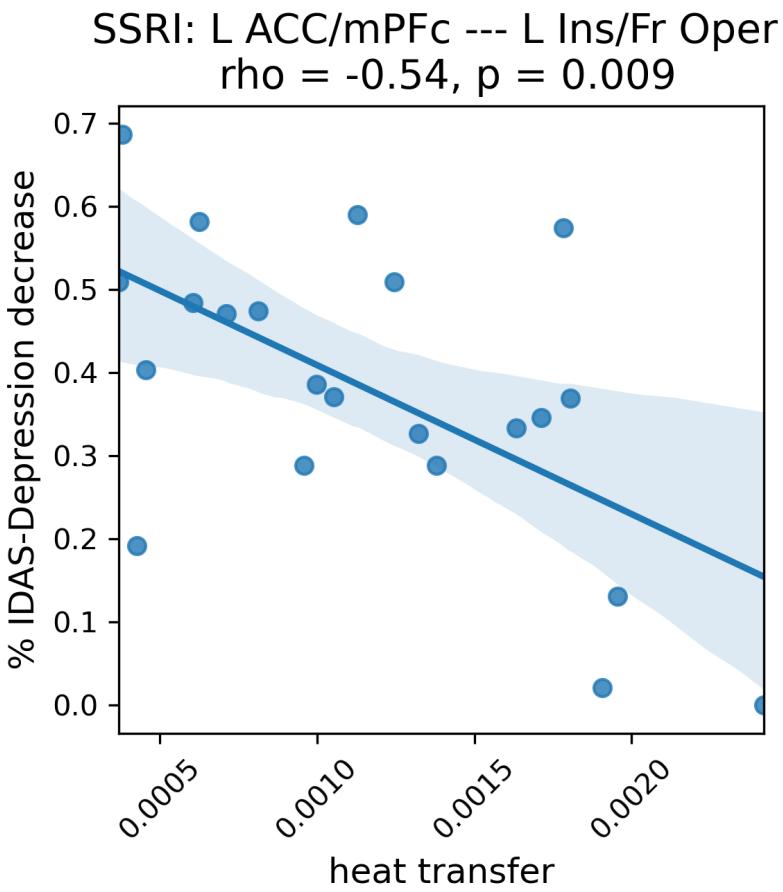
Thomas et al, Cerebral Cortex 2021

Information transfer symptom correlates of SSRI treatment response

SSRI: correlations of percentage decrease in idas depression with heat transfer between nodes.

Negative correlation indicates that less heat transfer between nodes at baseline is associated with higher treatment response





Thomas et al, Cerebral Cortex 2021

Network diffusion are associated with treatment response to CBT and SSRI treatment

Can we use it to model neuromodulation treatments like rTMS?

Where to add heat to correct diffusion pattern?

Simple approach: take advantage of characteristics of the heat kernel.

Objective is to ***find a node at which some constant value of heat will best 'normalize' the heat diffusion of the network, we can identify a set of constant values to add to each PT's heat kernel that are derived from adding heat to a single node.***

Thomas et al, Cerebral Cortex 2021

Where to add heat to correct diffusion pattern?

Do this as follows for a given i^{th} subject:

HC’ = average heat kernel for healthy controls
PT^i = heat kernel for a subject

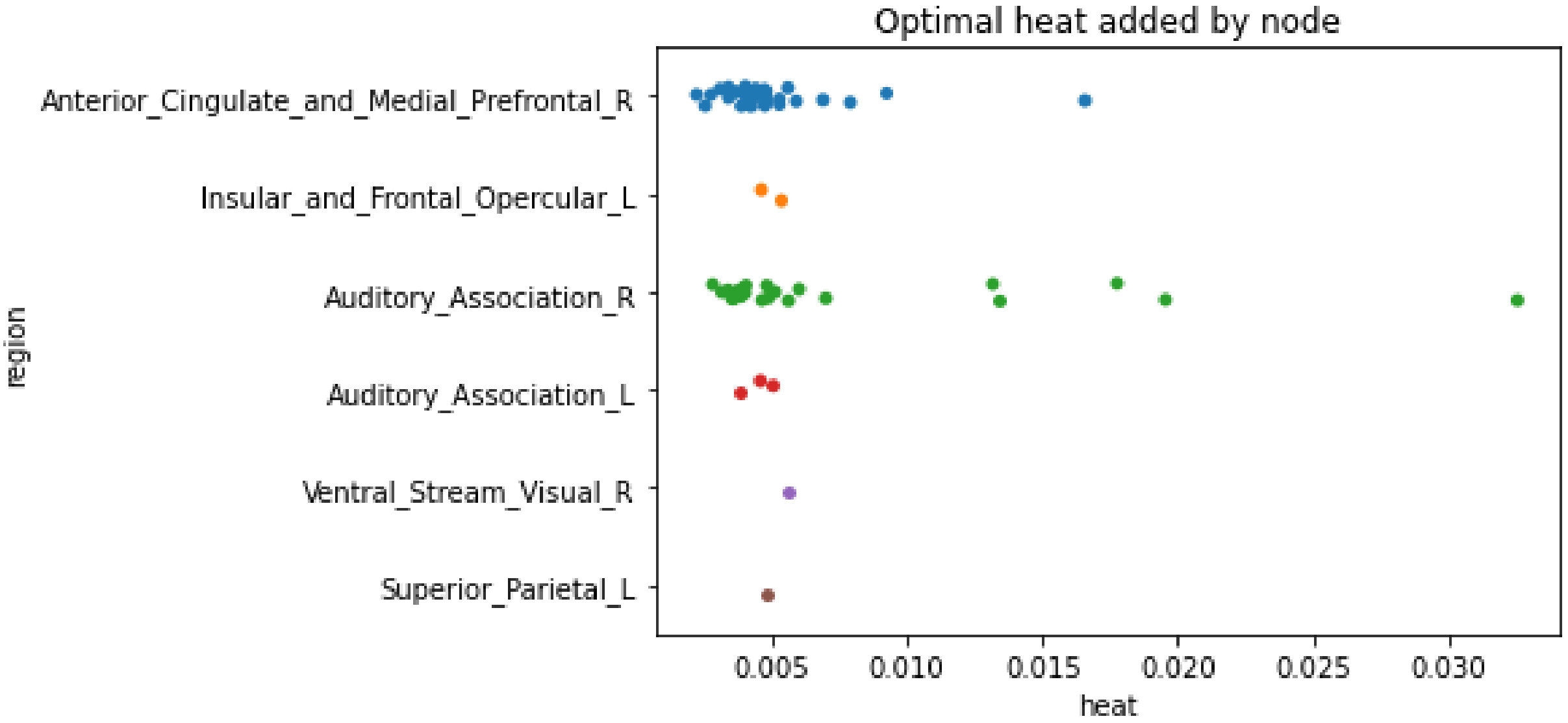
Then define $X^i = HC' - PT^i$

We want to minimize: $||X^i - \mathbf{c}_i Y_i||_2$ w.r.t. **c**, where $Y_i = \mathbf{1}PT^i[j,:]^T$ where j is the j^{th} node, **1** is the all ones vector and Y would then be a matrix with repeating rows that represent that amount of heat, c, transferred from node j to all other nodes.

We then choose the j^{th} node with where good normalization occurs by adding the least amount of heat, **c**, to the network. In our case, we just enumerate over all possible j’s, as the total number of nodes is not high enough to prevent such a strategy.

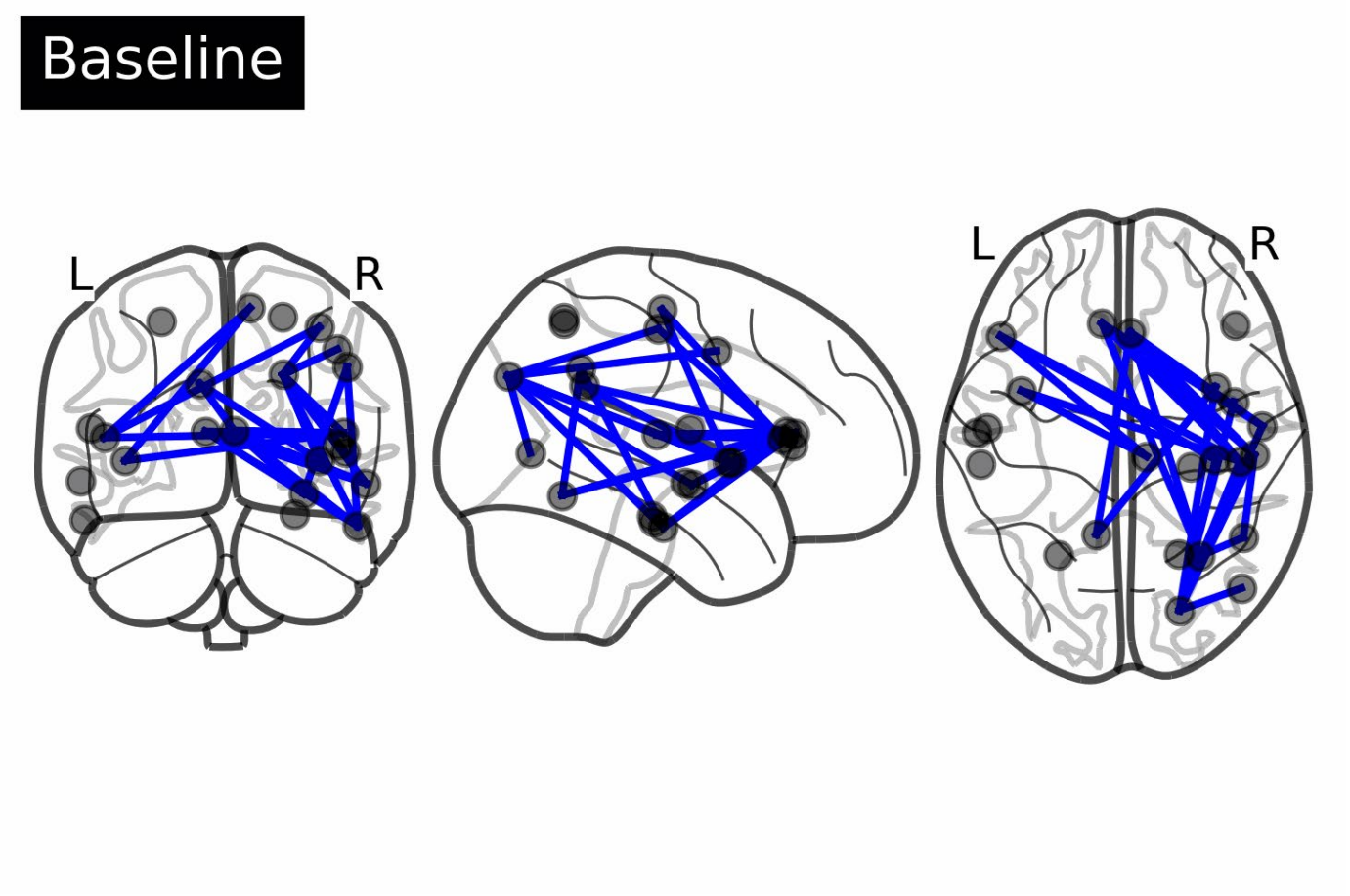
Thomas et al, Cerebral Cortex 2021

Where to add heat to the network



Thomas et al, Cerebral Cortex 2021

Where to add heat to the network

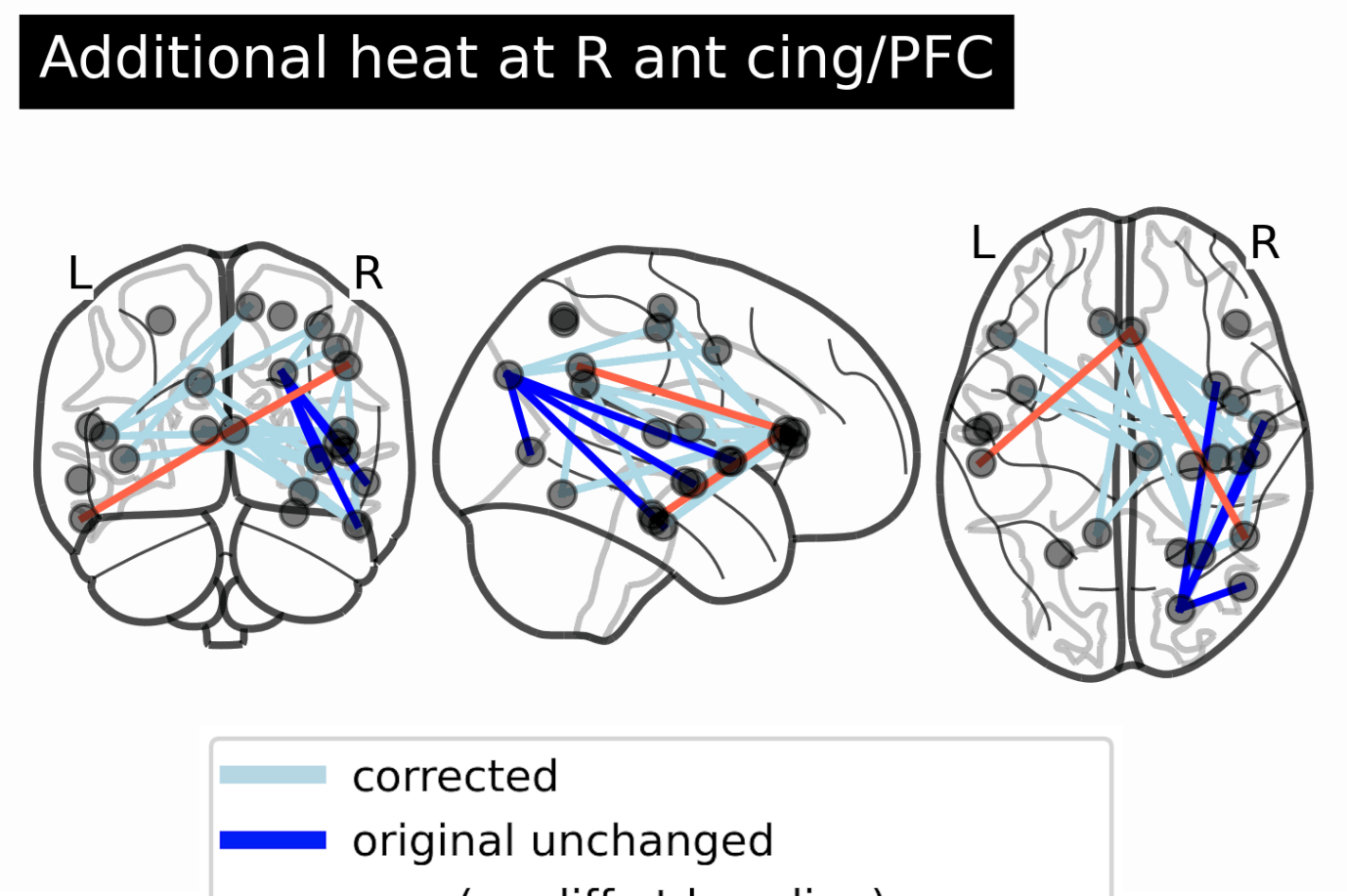


These are significant edges via t-test that survived FDR between nodes in the NBS subnetwork conducted on the edges of each subject's heat kernel.

In other words, a post-hoc t-test was conducted at every unique edge in the NBS subnetwork (n=253) to determine baseline significance for comparison after the heat was applied.

Thomas et al, Cerebral Cortex 2021

Where to add heat to the network



Only significant edges ($q < 0.05$) are shown and are colored as in the legend. These are after heat was placed at the R anterior cingulate/prefrontal region - the same region with the greatest strength in the NBS subnetwork. As the objective was to find the node to which the smallest amount of heat can be added that will normalize each PT's subnetwork HK values to the average HC.

As you can see, the 'overcorrection' edges (orange and red) both emanate from the anterior cingulate, which would be expected.

Thomas et al, Cerebral Cortex 2021

Summary

- In internalizing psychopathologies, network diffusion is selectively impaired in a prefrontal subnetwork with a hub in the bilateral anterior cingulate (area 8BM), a core component of the MD system
- Network diffusion deficits at baseline are correlated with symptom severity and predict treatment response to CBT and SSRI treatment
- Network diffusion deficits may inform as patient-specific targets for intervention

Future directions/Unanswered questions

- Is neurostimulation of a node (i.e. rTMS) the same as “adding heat” in the model?

Perhaps

  - Studies based on network control theory suggest structural network topology can inform stimulation targets to effect desired, predictable behavioral effects on cognitive performance *(Stisso et al, Cell Rep 2019; Beynetl et al, J. Neurosci 2020)*

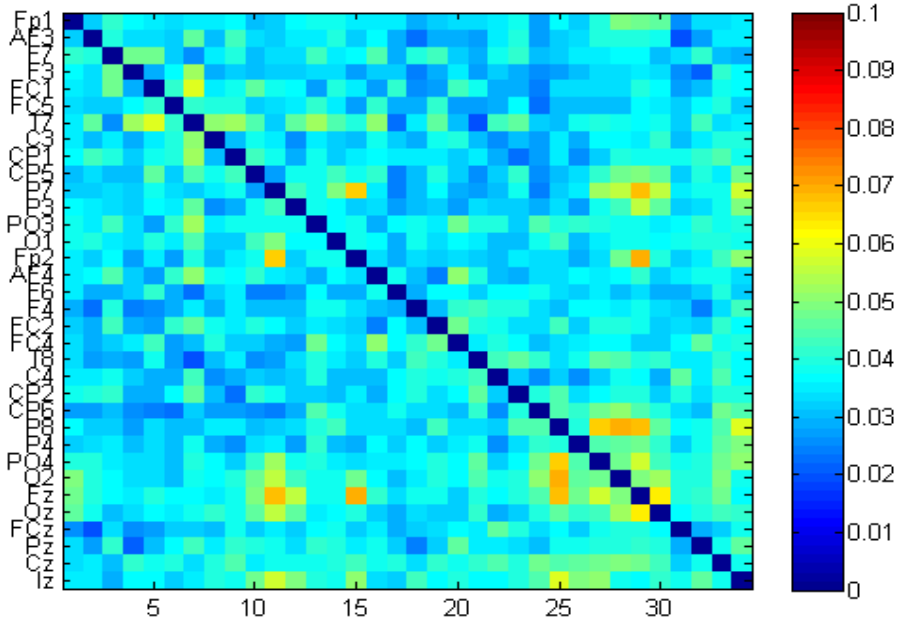
  - Structural connectivity predicts TMS propagation *(Momi et al, Neuroimage 2021)*

  - *Will test empirically with the B-SMART rTMS data (Williams & Phillip)*

- ***Can connectomics be used to determine individual targets for neuromodulatory “correction” of network-based deficits in internalizing psychopathologies?***

EEG connectome

- Method: Weighted phase lag index (WPLI)
- Solution: paired wise relation for every two channels.



34 * 34 * 130

Channel Channel Time

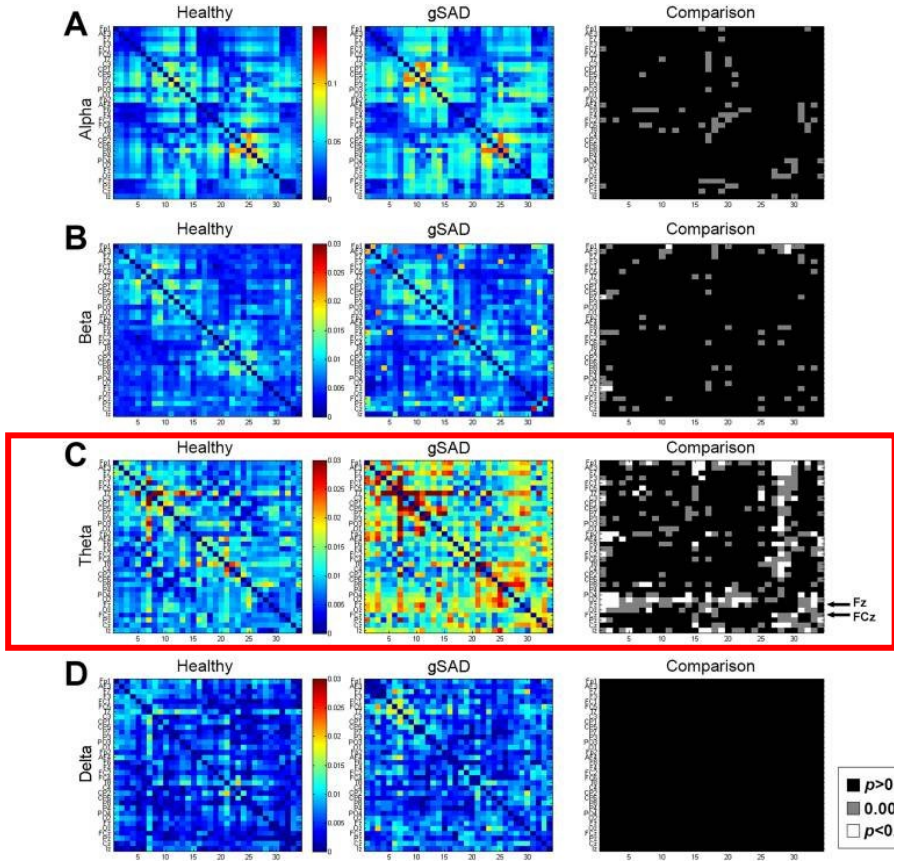
EEG Connectivity:

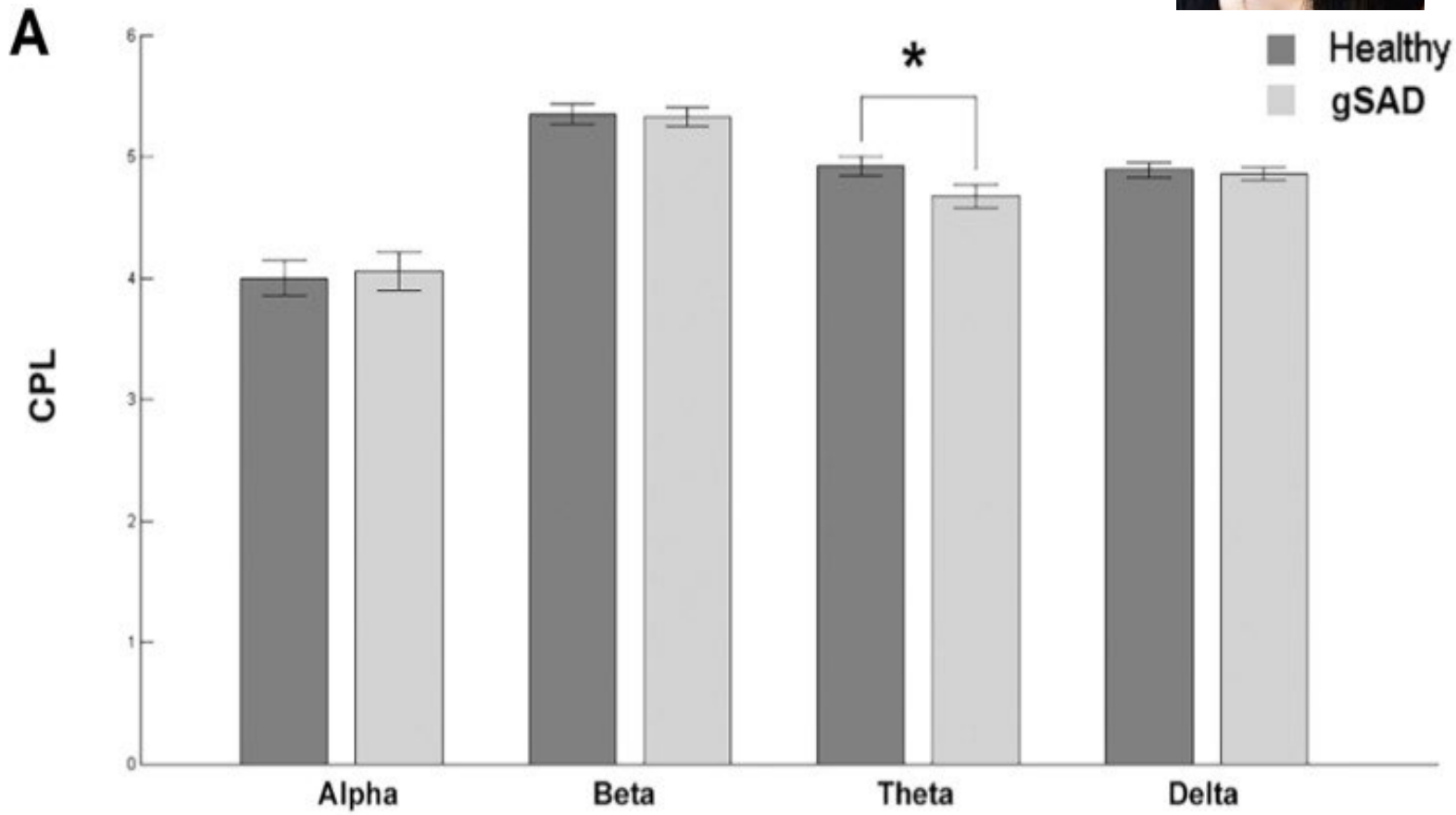
0<WPLI<1

Weak Strong

Theta network connectivity is increased in social anxiety

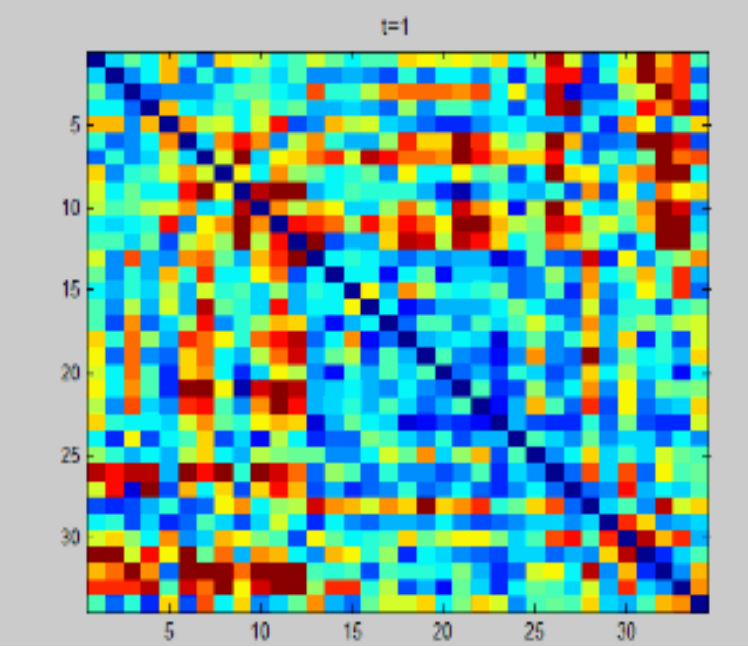






Xing et al, Neuroimage Clin 2016

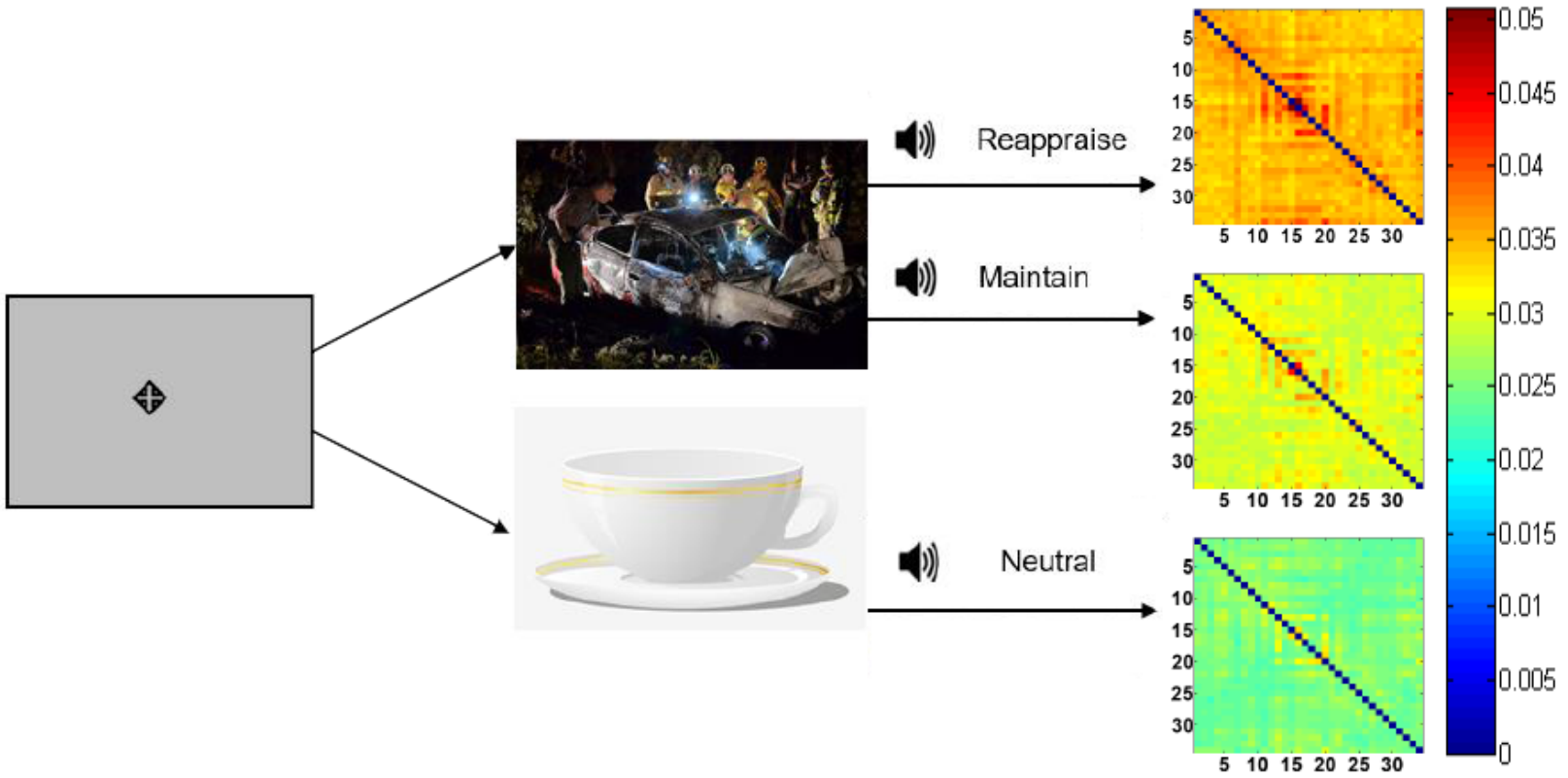
Dynamic EEG network changes - “Chronnectome”



- Altered dynamic FC between the MPFC and DMN and insular cortex in unmedicated MDD *(Kaiser et al, 2016)*
- Frontoinsular and DMN regions show altered network dynamics associated with rumination in adolescent depression *(Ajilore et al, 2016; Kaiser et al, 2019)*
- Dynamic FC between the MPFC and PCC in bipolar disorder associated with reduced processing speed and executive function *(Nguyen et al, 2017)*

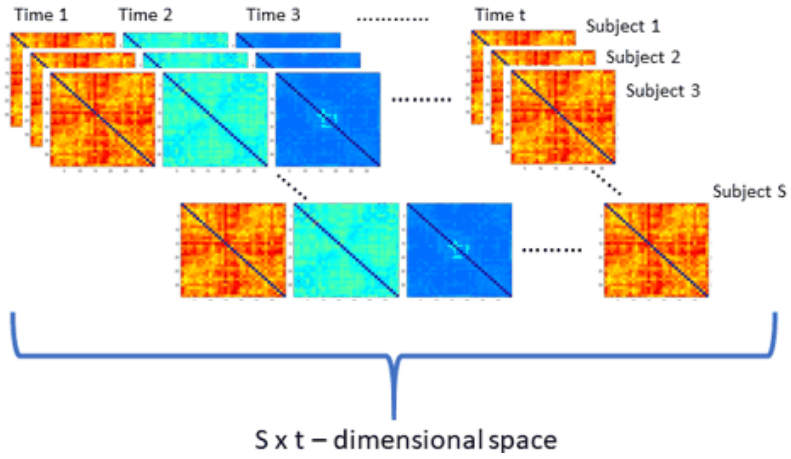
ERT EEG Connectome

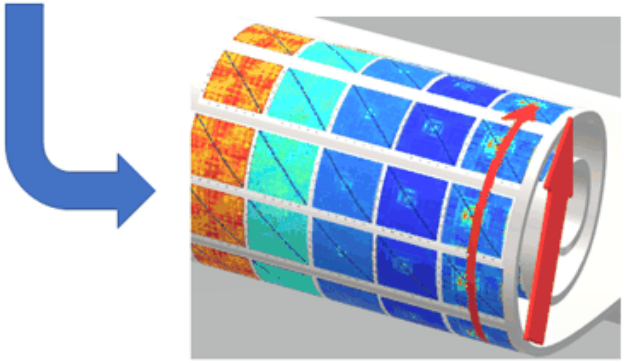




Dynamic network properties in emotion regulation







Visualize in 3-D space

Xing et al, NeuroImage 2019

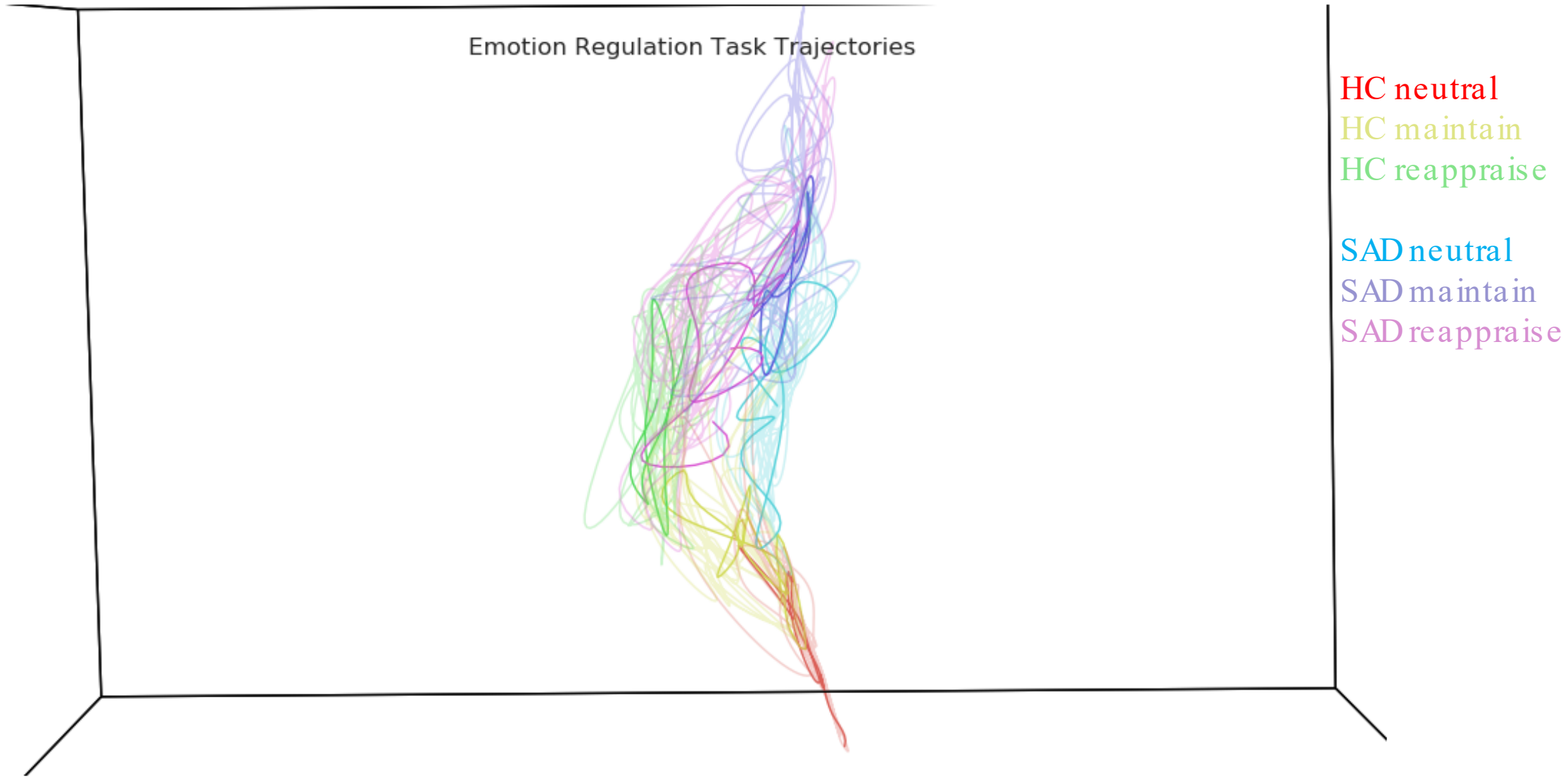
Emotion Regulation Trajectories — Front View



HC neutral
HC maintain
HC reappraise

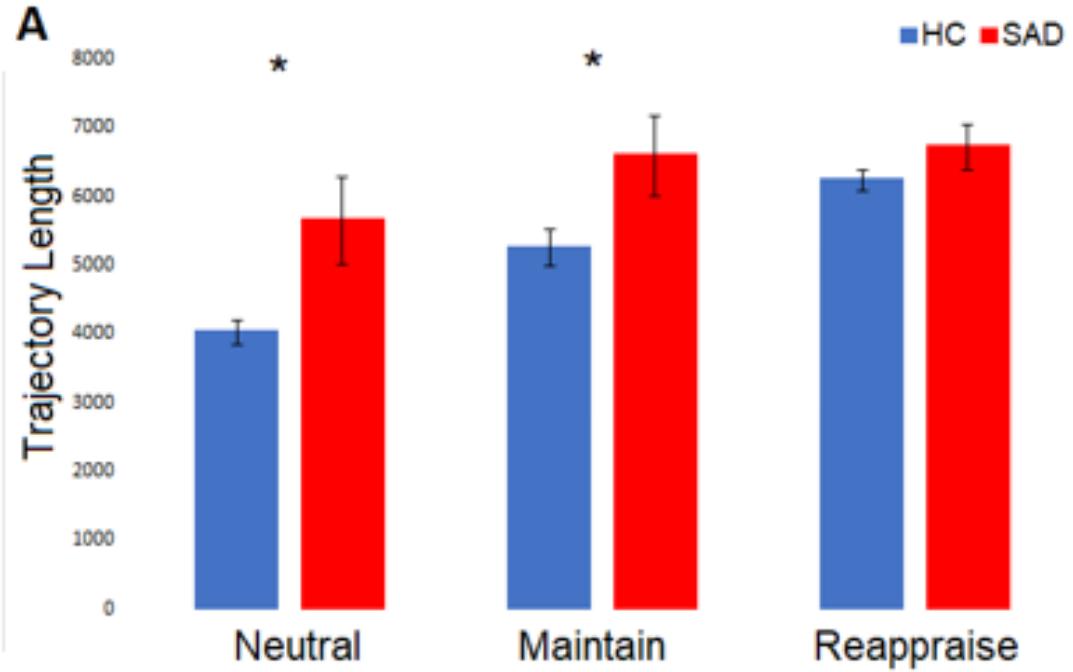
SAD neutral
SAD maintain
SAD reappraise

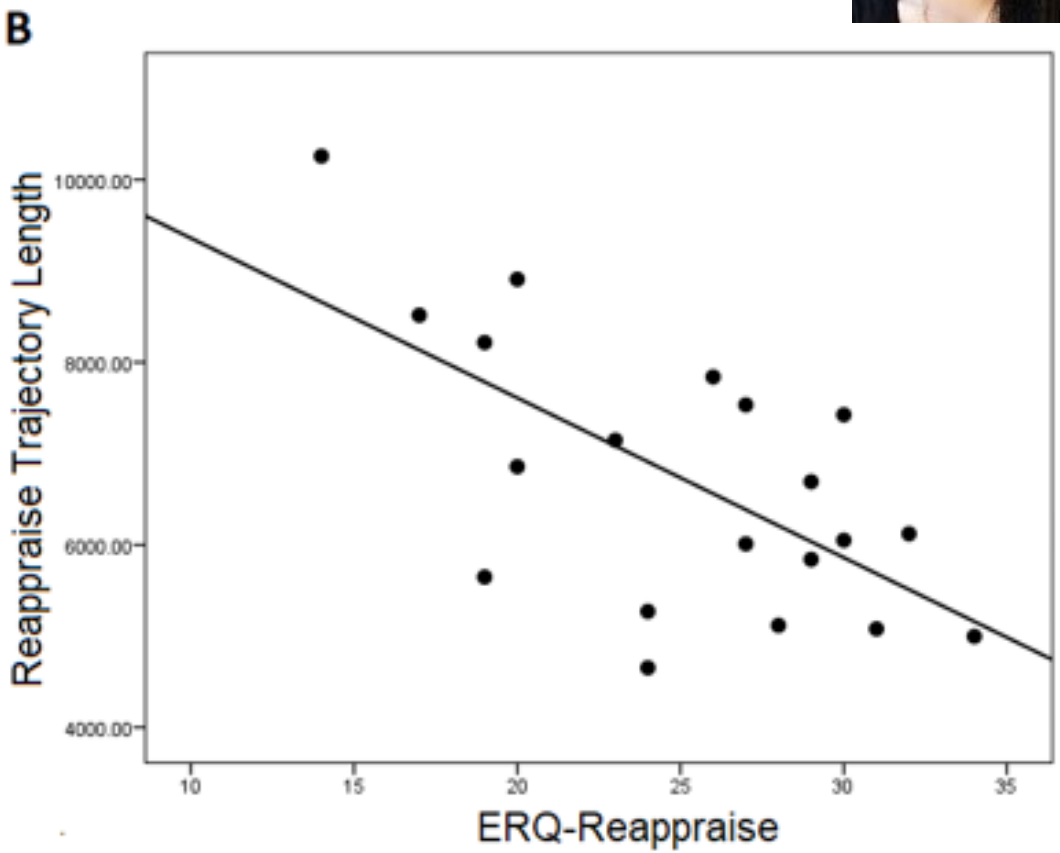
Emotion Regulation Trajectories — Rotated View



Dynamic network properties of emotion regulation

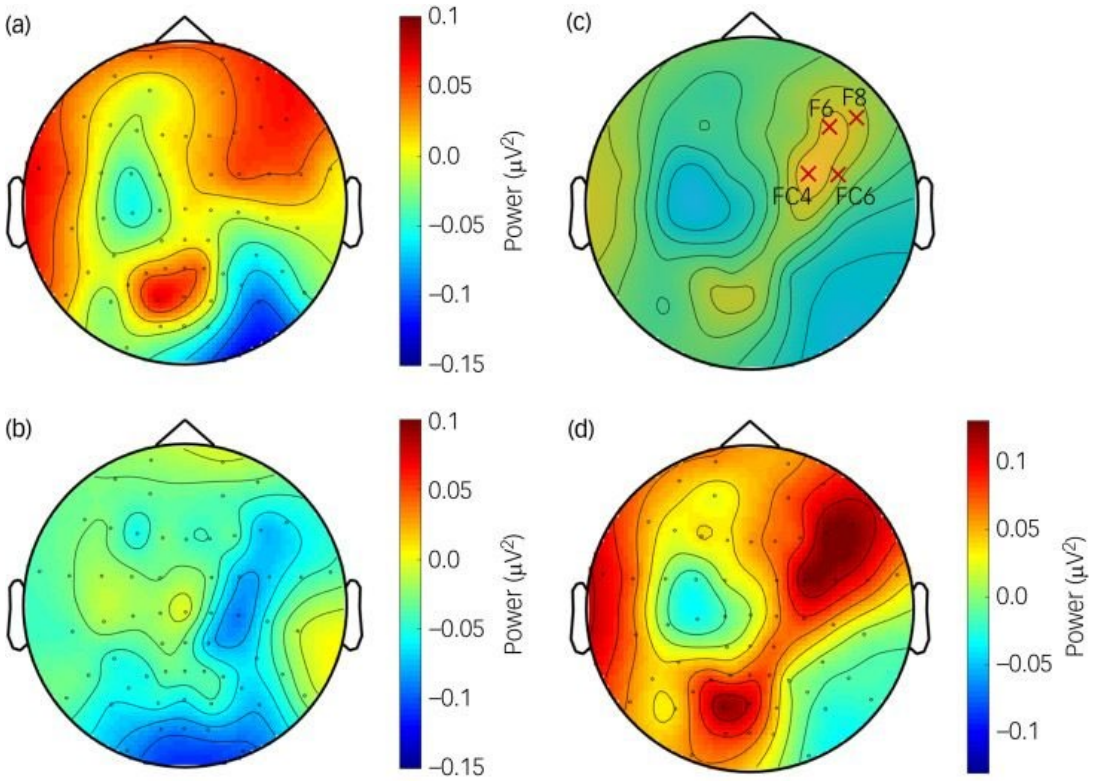


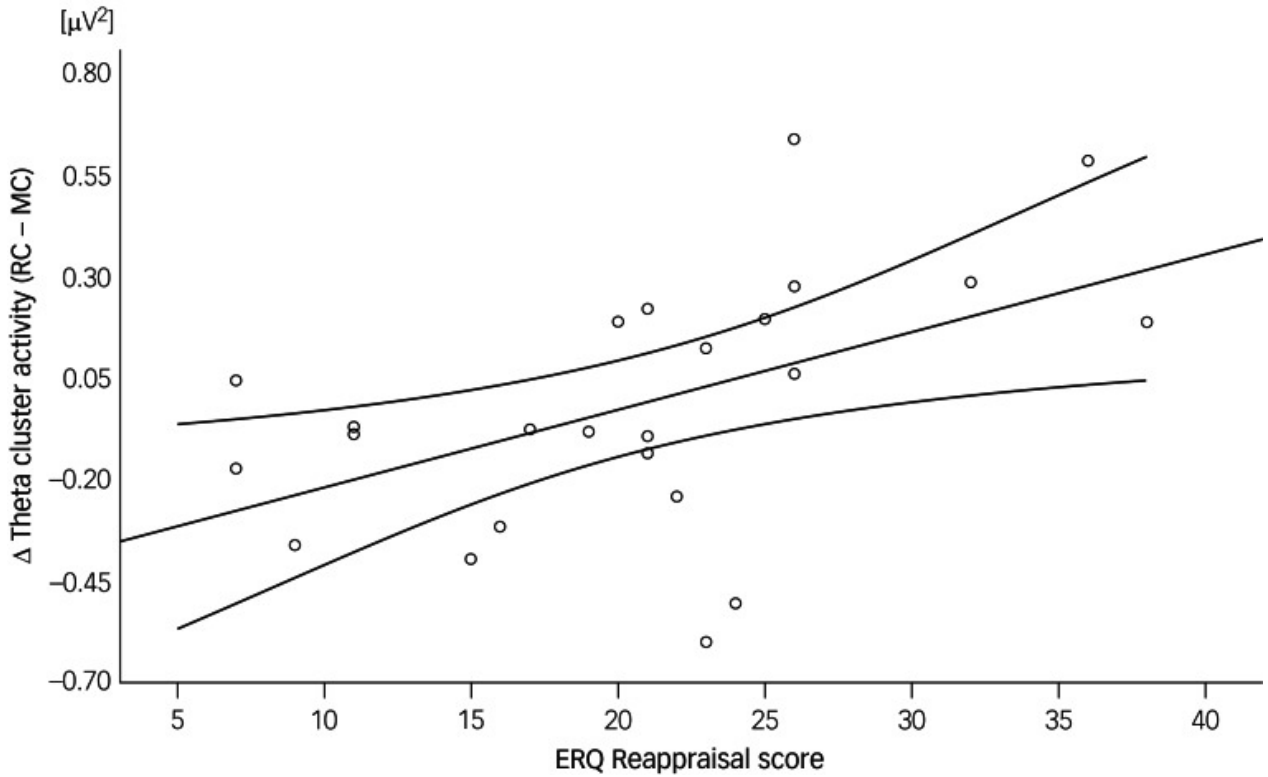




Xing et al, NeuroImage 2019

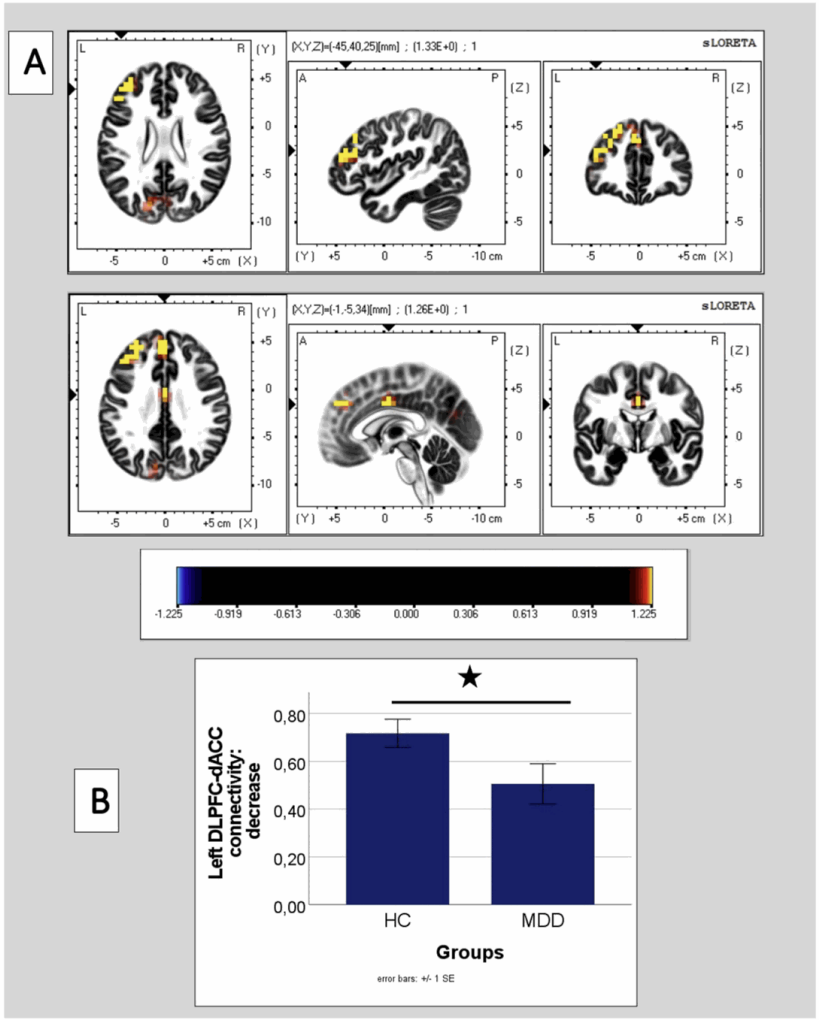
Reduced reappraisal frontal theta in BPD vs Controls

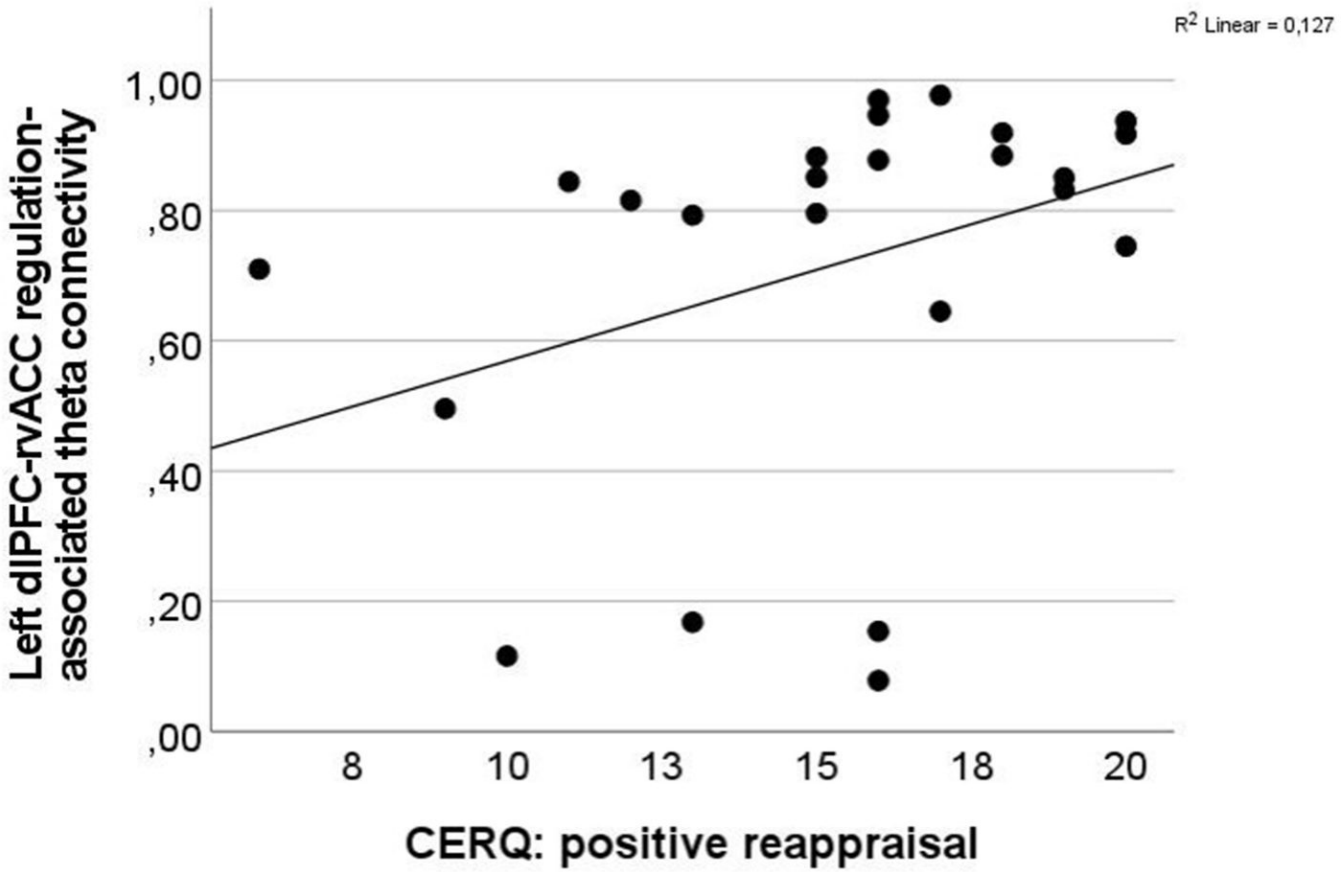




Haaf M, Polomac N, Starcevic A, Lack M, Kellner S, Dohrmann AL, Fuger U, Steinmann S, Rauh J, Nolte G, Mulert C, Leicht G. Frontal theta oscillations during emotion regulation in people with borderline personality disorder. BJPsych Open. 2024 Mar 4;10(2):e58. doi: 10.1192/bjo.2024.17. PMID: 38433600; PMCID: PMC10951849.

Reduced frontocingular theta synchrony in MDD vs Controls





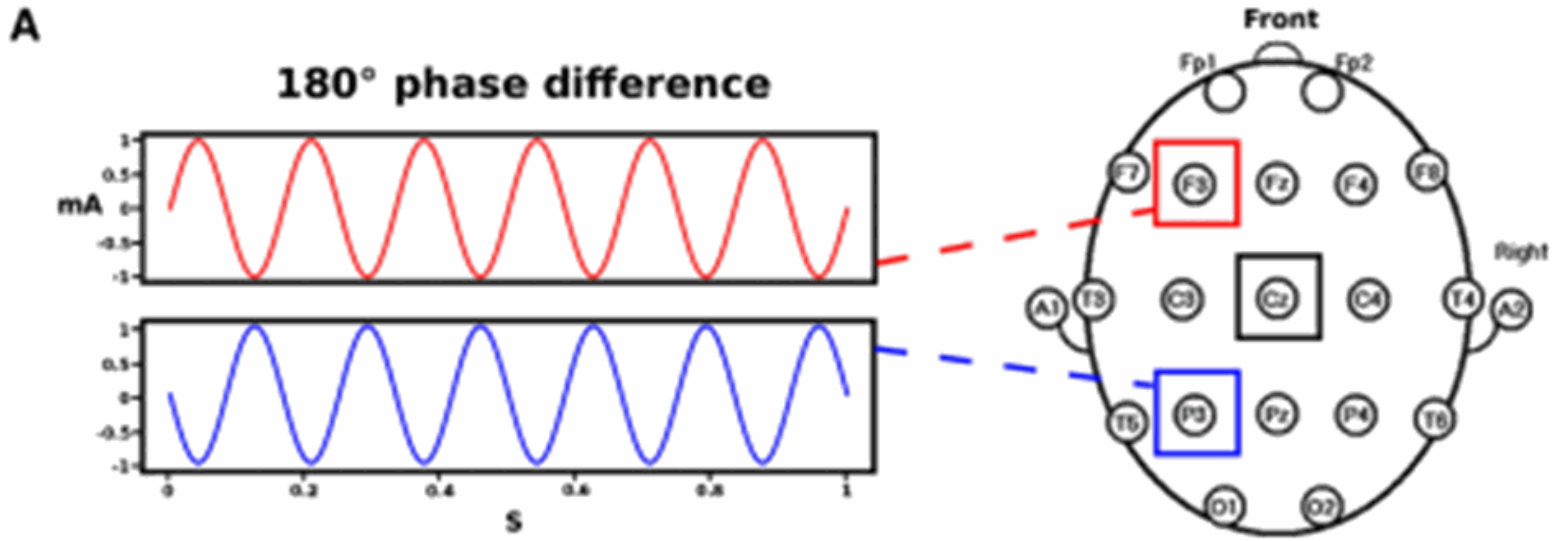
Steinmann S, Tiedemann KJ, Kellner S, Wellen CM, Haaf M, Mulert C, Rauh J, Leicht G. Reduced frontocingulate theta connectivity during emotion regulation in major depressive disorder. J Psychiatr Res. 2024 May;173:245-253. doi: 10.1016/j.jpsychires.2024.03.022. Epub 2024 Mar 21. PMID: 38554620.

Theta, Anxiety and Emotion Regulation

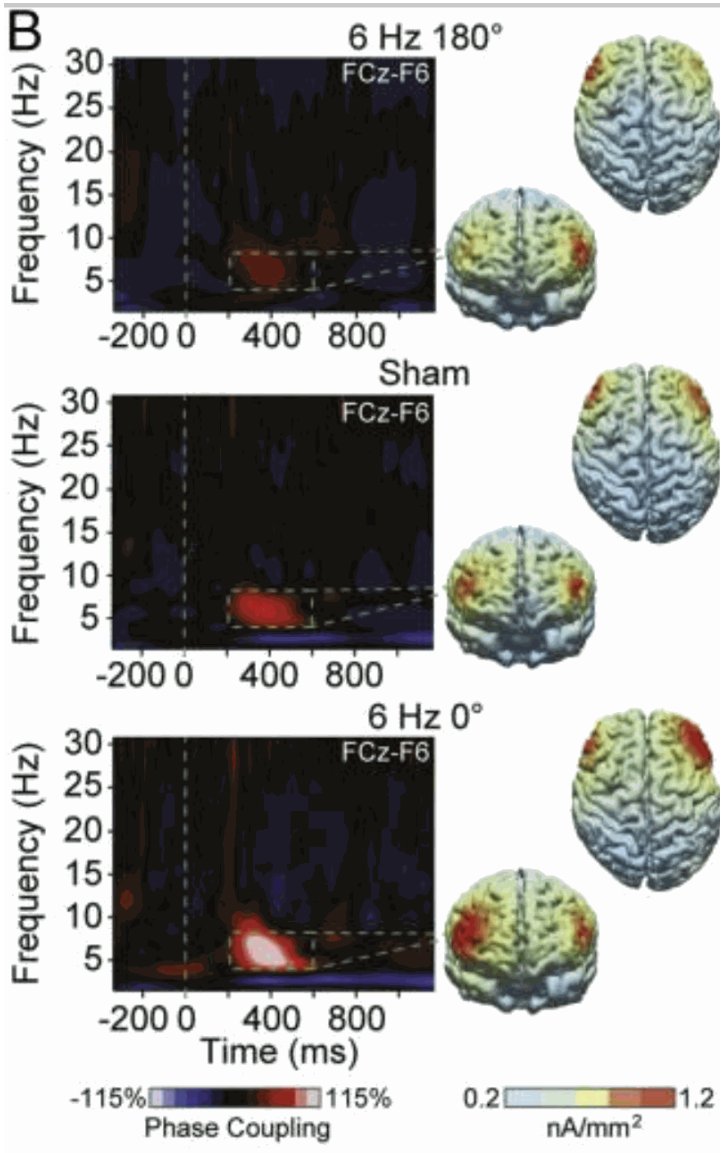
- Altered theta-band network properties associated with anxiety
- Altered theta-band network dynamics may represent cognitive effort during emotion regulation
- Ramping up theta is needed for successful emotion regulation
- Could these altered theta-band network properties serve as a target for intervention?

Transcranial Alternating Current Stimulation (TACS)

- Sinusoidal electrical current
- Frequency-specific
- Shown to alter synchrony and frequency
- Can be applied “onset”/ “in-phase”/ 0° or “offset”/ “out-of-phase”/ 180° phase shifted

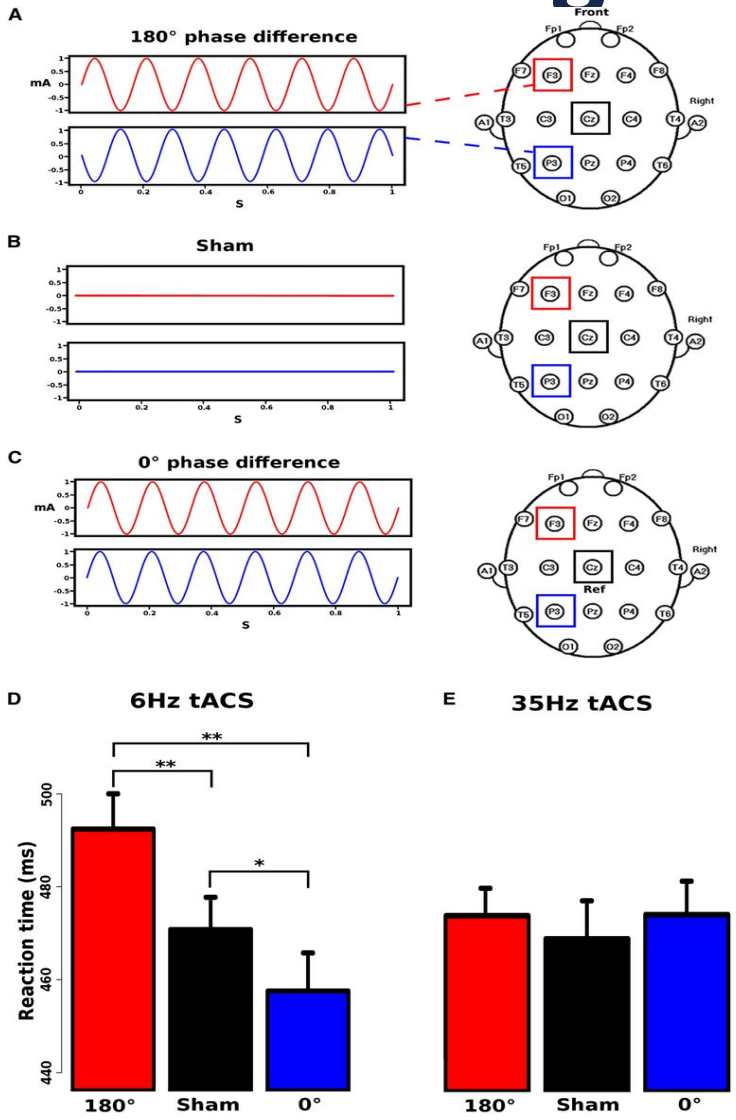


Offset TACS can decouple frequency oscillations….



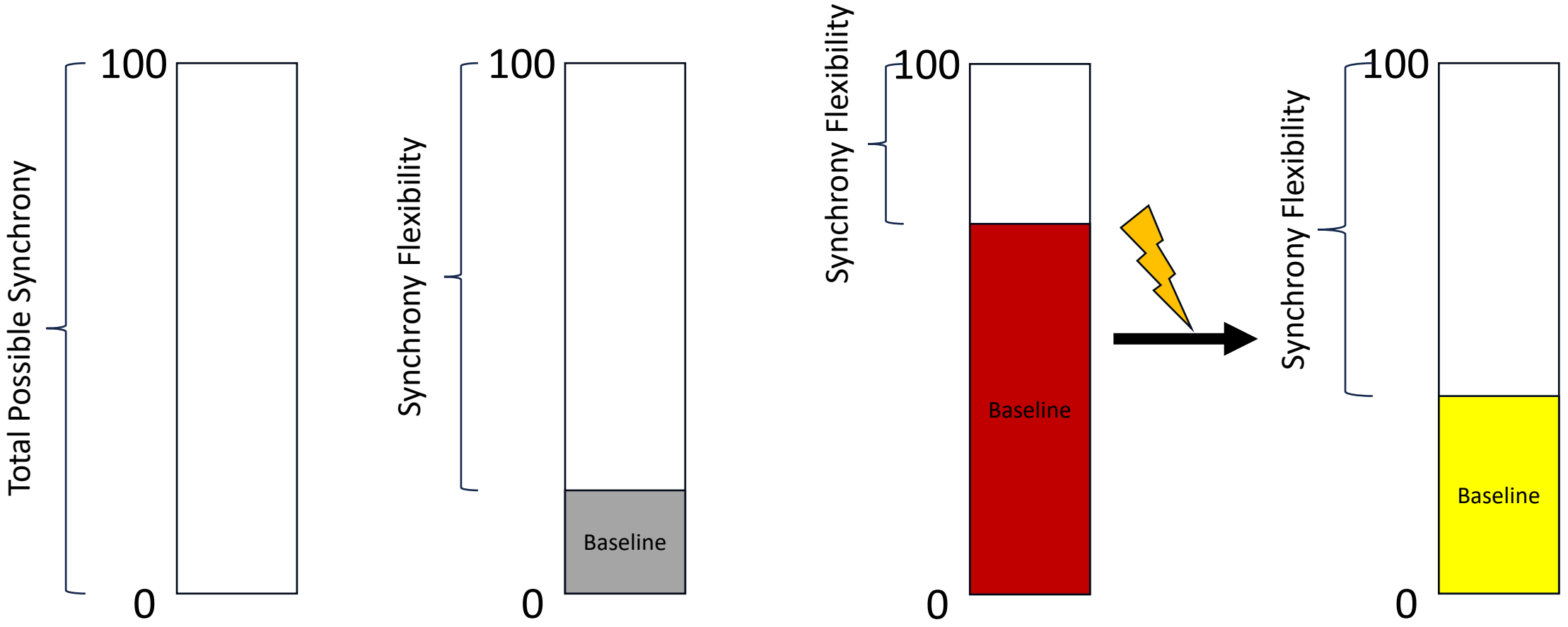
Reinhart RMG. Disruption and rescue of interareal theta phase coupling and adaptive behavior. Proc Natl Acad Sci U S A. 2017 Oct 24;114(43):11542-11547. doi: 10.1073/pnas.1710257114. Epub 2017 Oct 9. PMID: 29073084; PMCID: PMC5664527.

Offset TACS can decouple frequency oscillations….and affect cognition

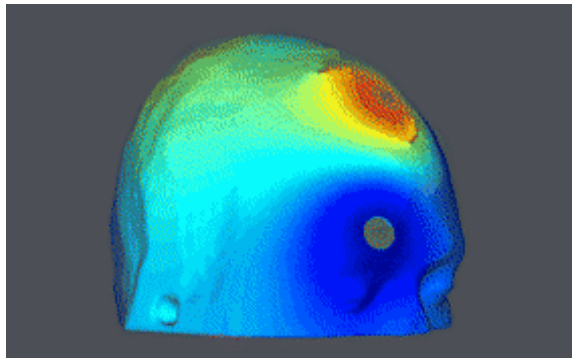


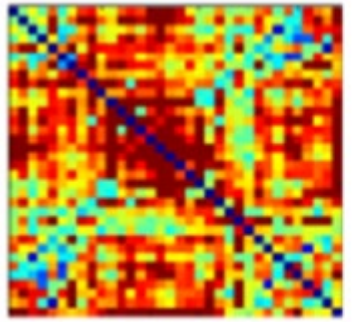
Polanía R, Nitsche MA, Korman C, Batsikadze G, Paulus W. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol. 2012 Jul 24;22(14):1314-8. doi: 10.1016/j.cub.2012.05.021. Epub 2012 Jun 7. PMID: 22683259.

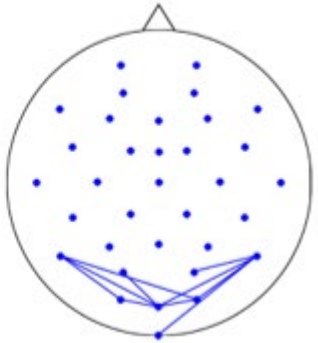
Synchrony Flexibility: The Rationale for tACS



EEG Connectome-guided transcranial alternating current stimulation (tACS)



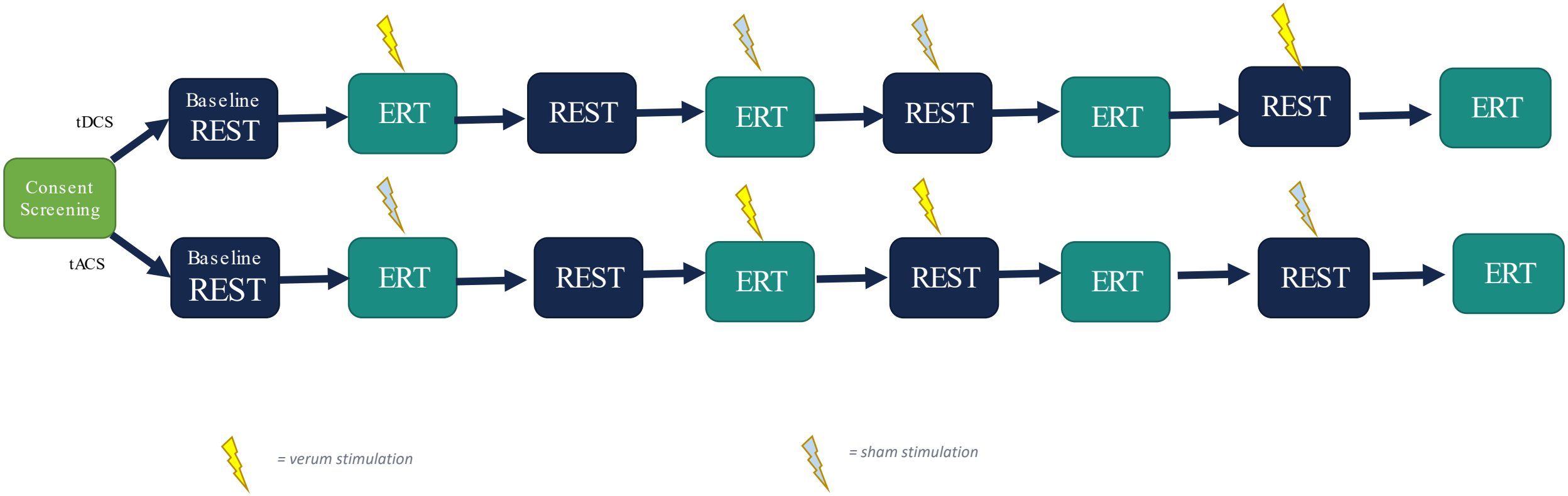








Study Design



Subject Characteristics

	tACS	tDCS	*t*	*p*	*SE*
N	16	17			
DASS Depression	22.0 +/– 9.2	23.8 +/–9.3	0.548	0.587	3.219
DASS Anxiety	21.1 +/– 8.2	23.2 +/– 10.7	0.617	0.542	3.325
DASS Total	34.6 +/– 9.6	37.3 +/–10.5	0.779	0.442	3.509
Age	30.0 +/– 12.1 years	34.4 +/– 12.0 years	1.016	0.318	4.344
Sex	***n***	***n***	0.202	0.842	0.125
Female	12	15			
Male	2	2			
Education	***n***	***n***	0.07	0.945	0.422
Less than high school or GED	0	1			
High School or GED	5	2			
Associates	1	4			
Bachelor's	4	8			
Masters	4	2			
Ethnicity	***n***	***n***	0.202	0.842	0.125
Hispanic/Latino	2	2			
Not Hispanic/ Latino	12	15			
Race	***n***	***n***	0.363	0.719	0.238
American Indian	1	0			
Asian	1	1			
Black or African American	4	4			
White	8	11			
Other	0	1			

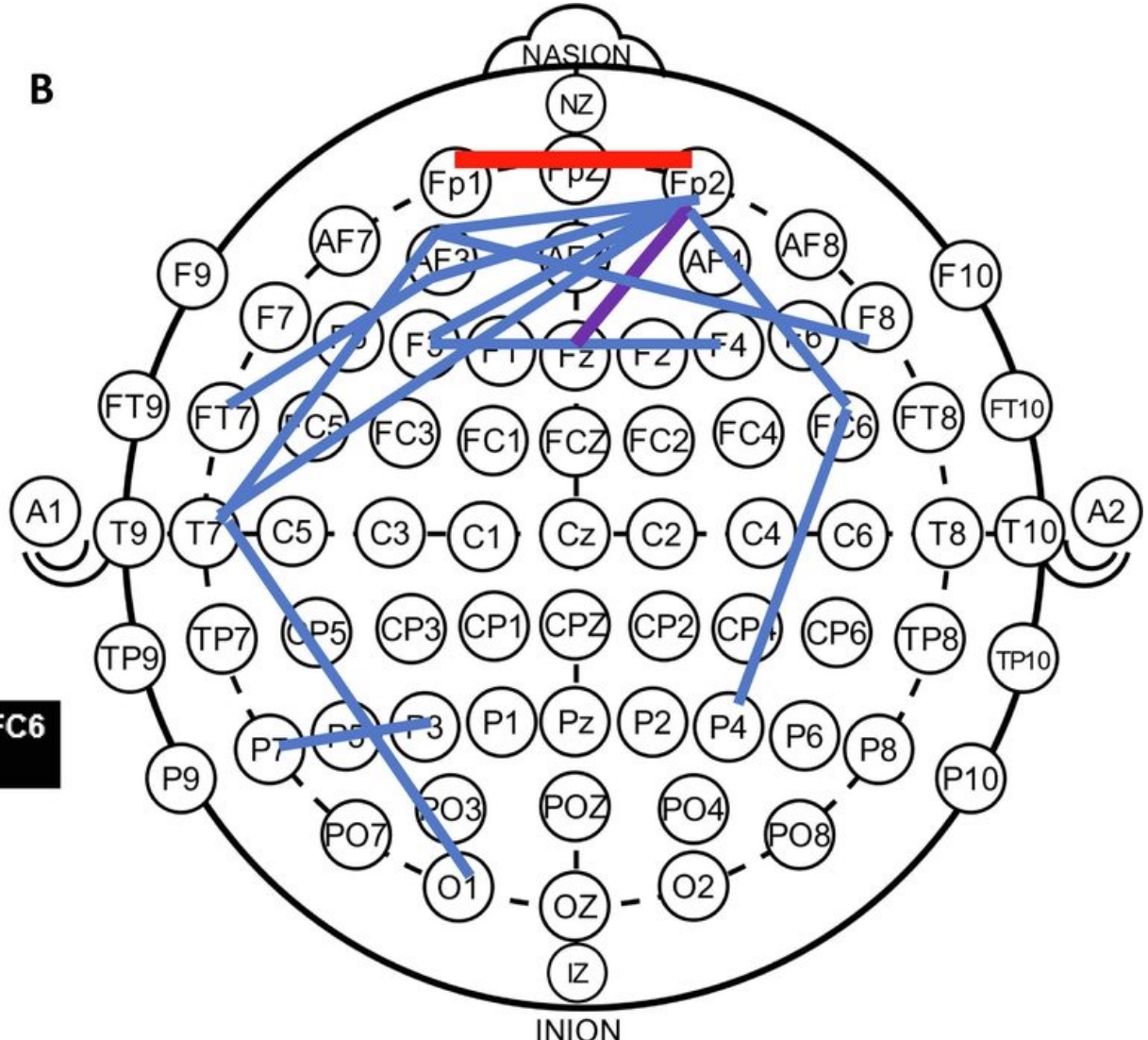
McAleer et al, 2023a

Individualized Electrode Placement

A

	Fp1	AF3	F3	T7	P7	P3	O1	Fp2	F4	P4	Fz	FC6
AF3												
F3												
T7		1										
P7												
P3					1							
O1				1								
Fp2	4	1	1	1								
F4			1									
P4												
Fz								2				
FC6								1		1		
F8		1										

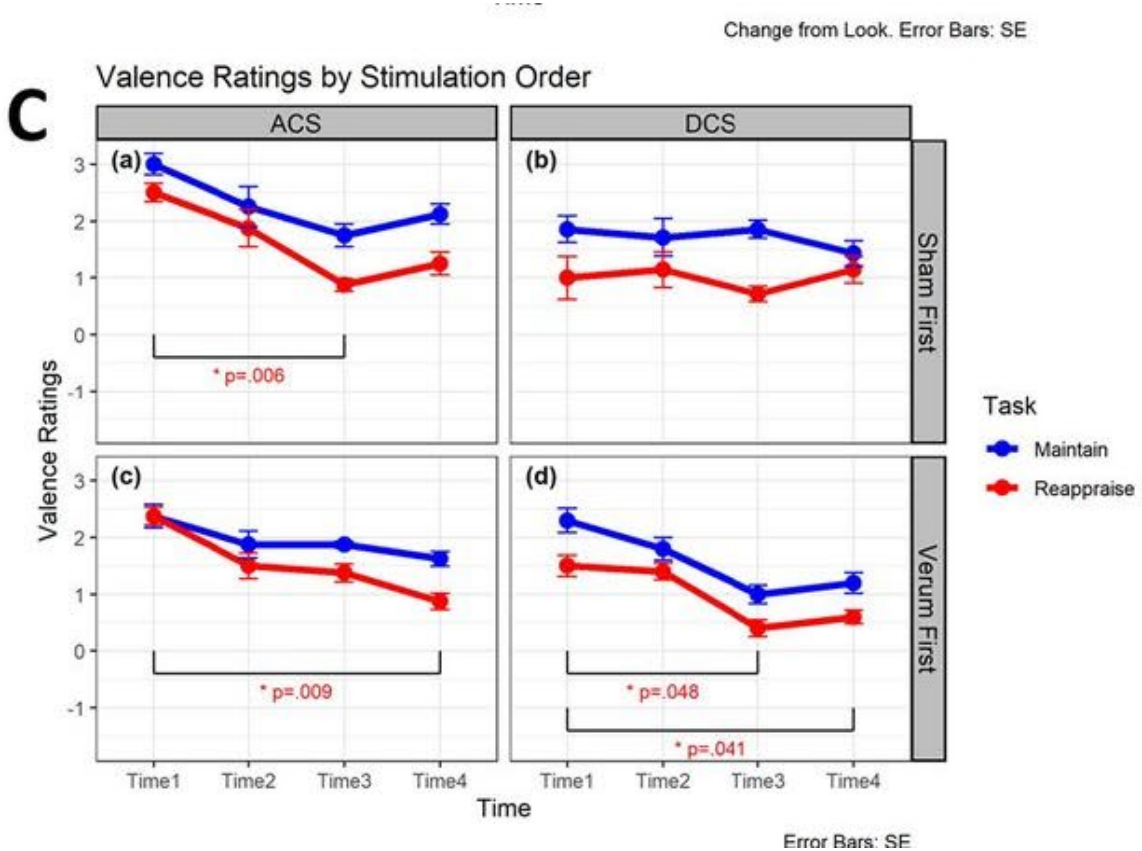
B

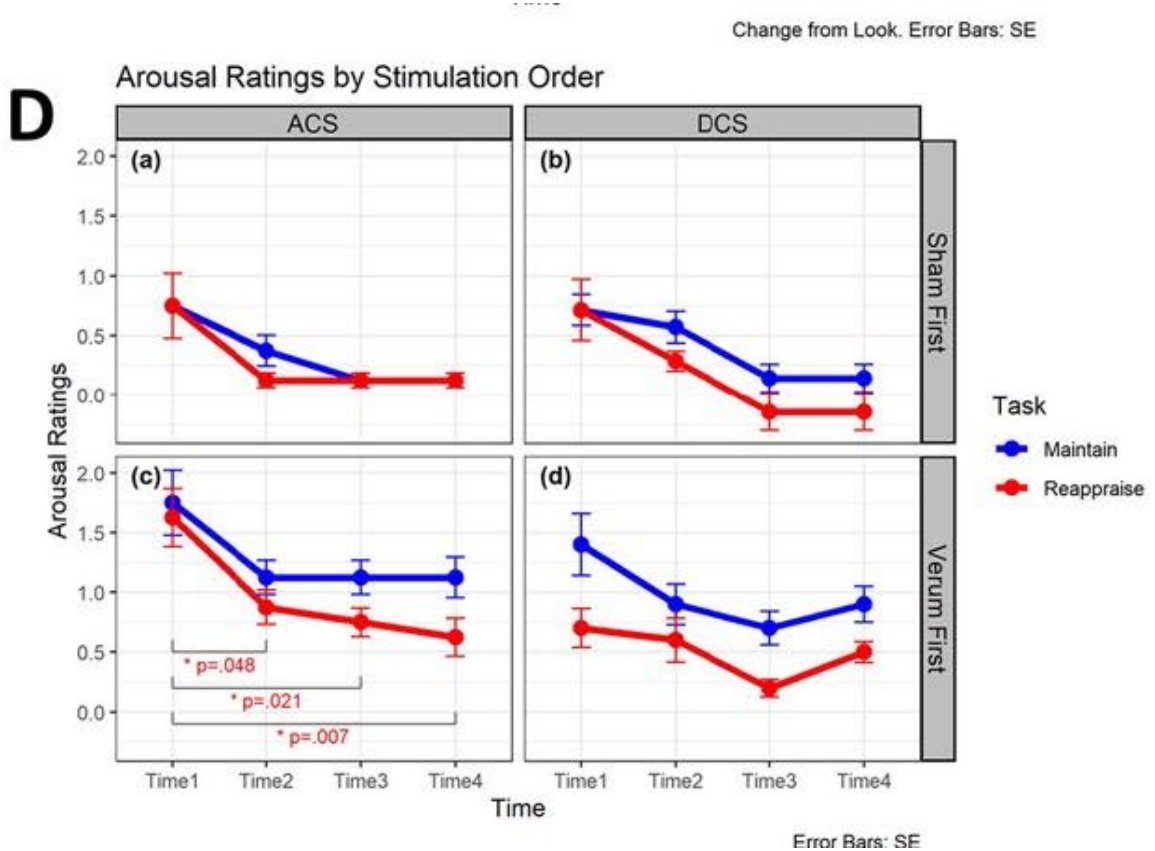


McAleer et al, 2023a

Effect on negative affect ratings



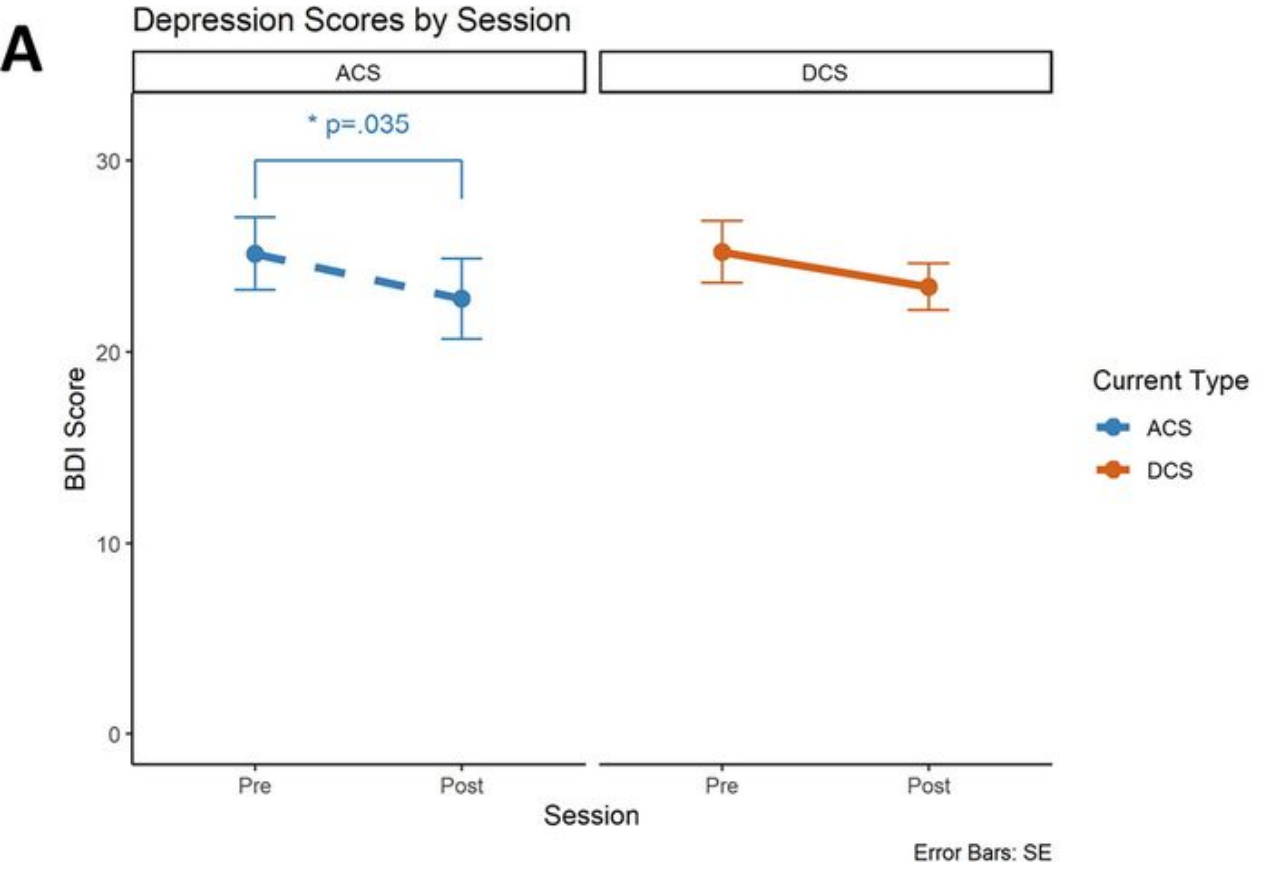


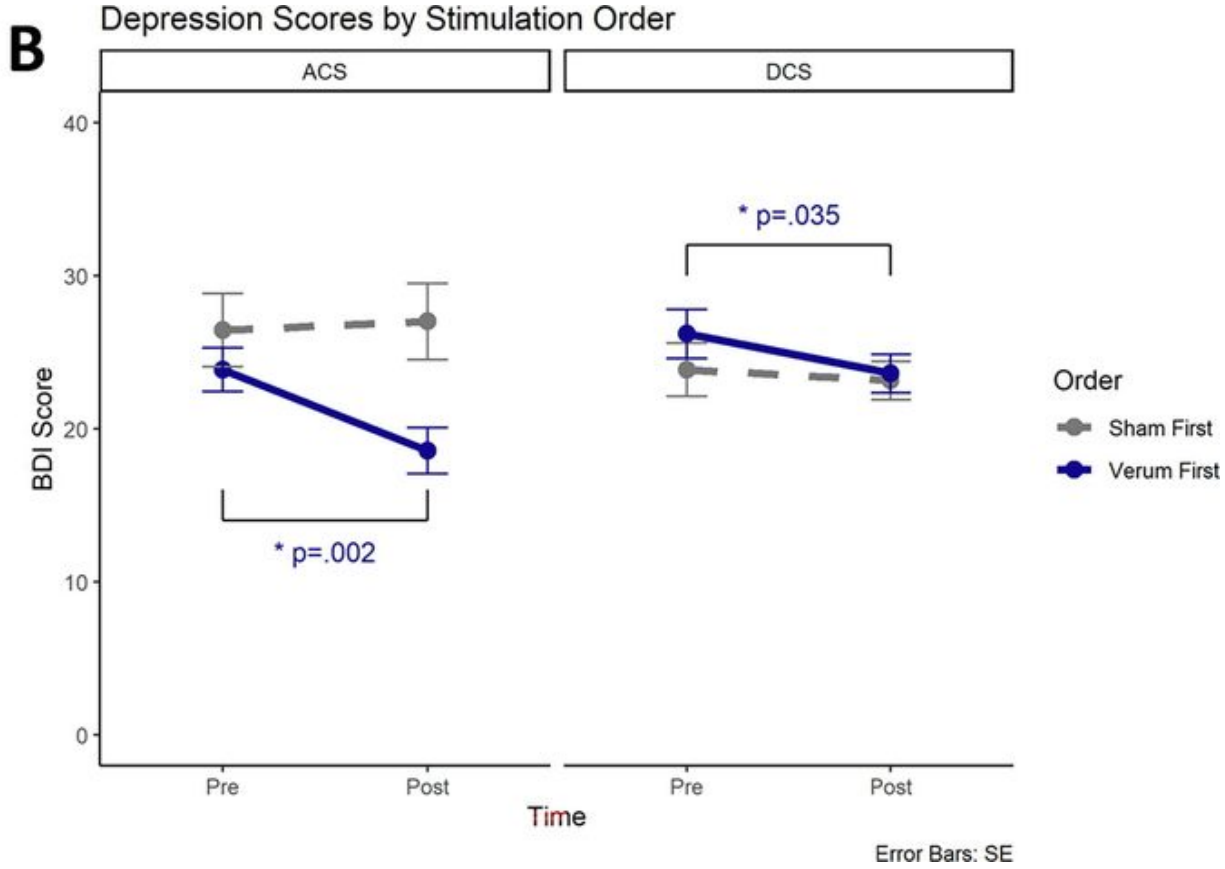


McAleer et al, 2023a

Effect on state depression ratings



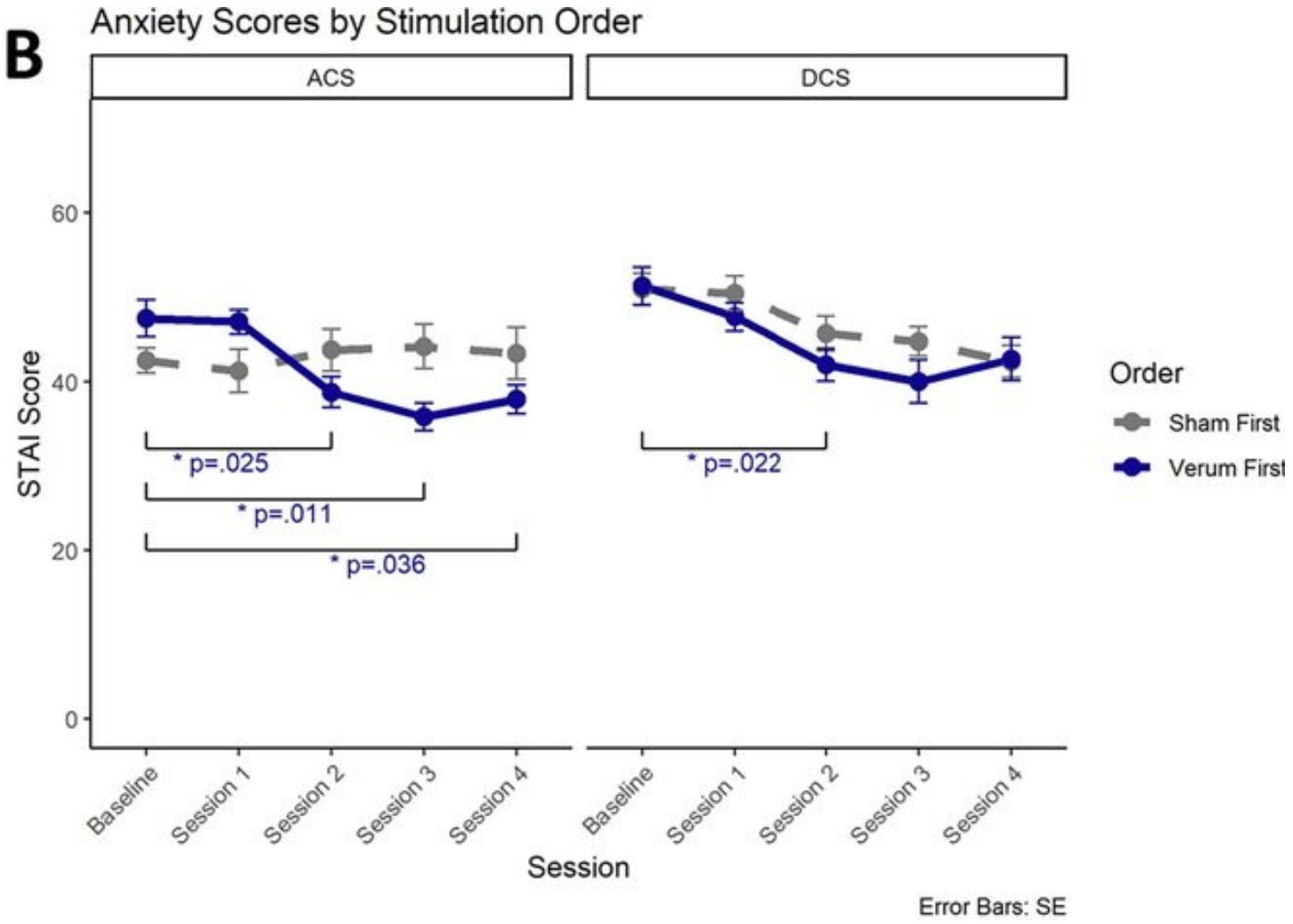




McAleer et al, 2023a



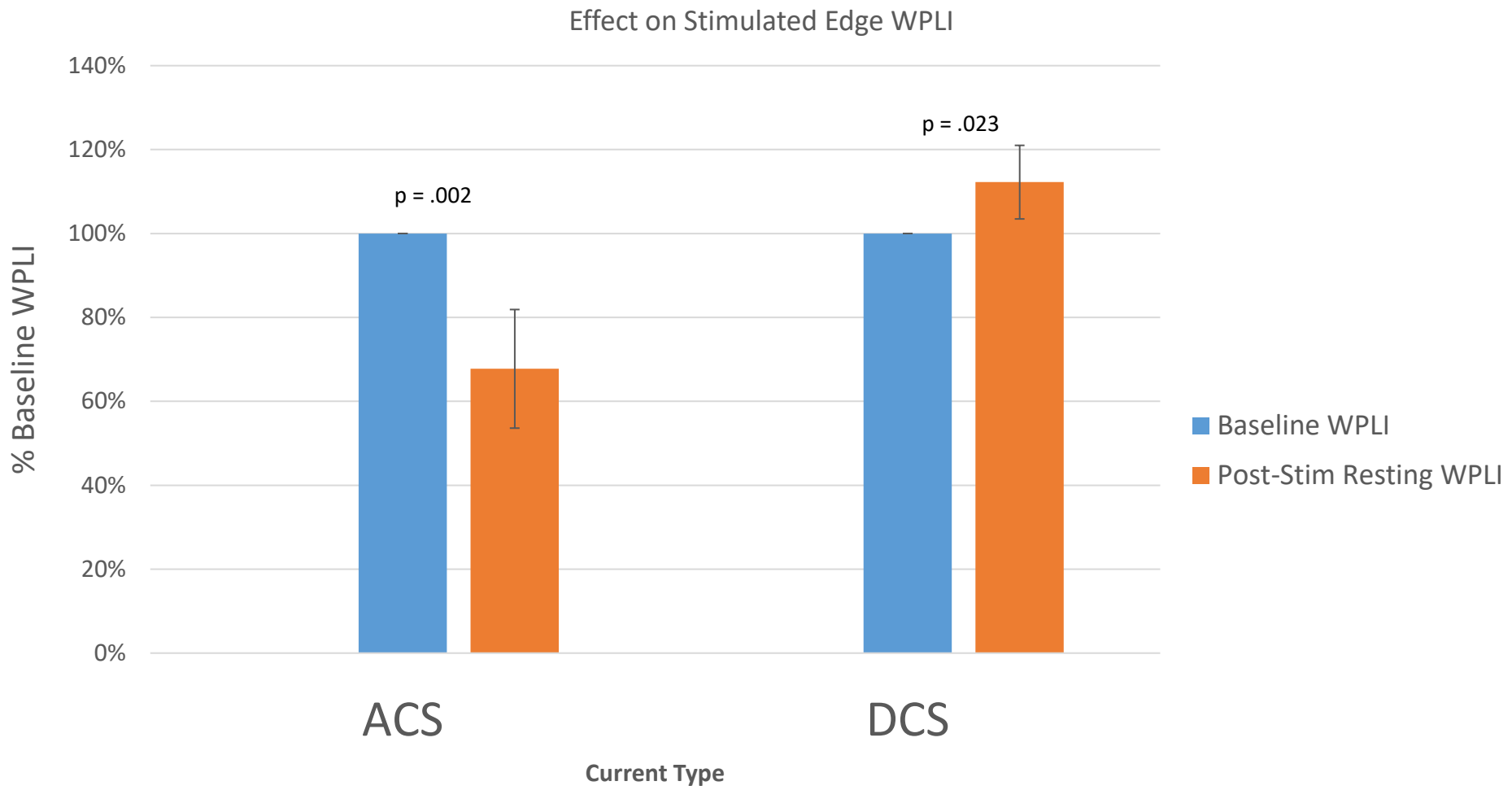
Effect on state anxiety ratings



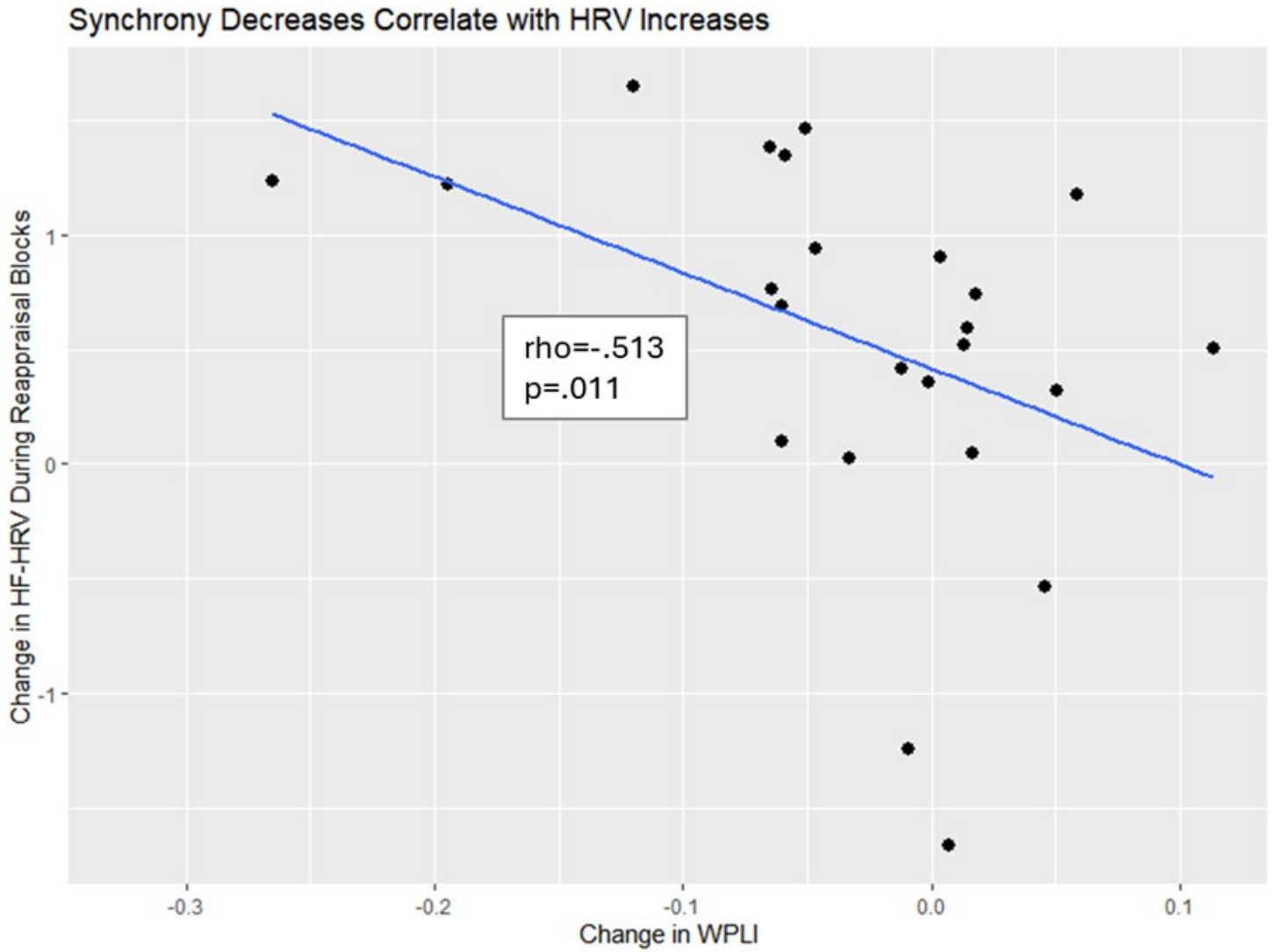
McAleer et al, 2023a

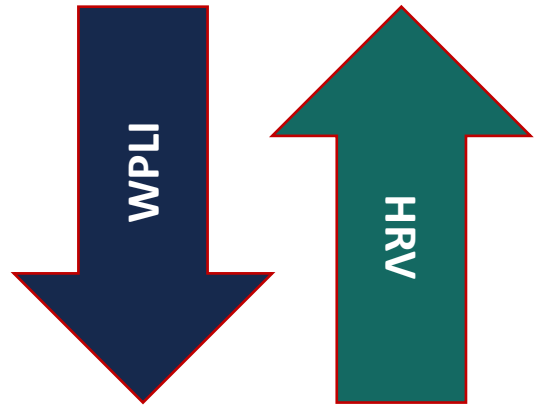
Effects on Resting State Theta Synchrony





McAleer et al, in prep


Synchrony Decreases Correlate with HRV Increases
Change in HF-HRV During Reappraisal Blocks
1
0
-1
rho=-.513
p=.011
-0.3
-0.2
-0.1
0.0
0.1
Change in WPLI


WPLI
HRV

Next Steps

- Altered network dynamics may serve as a target for network-based interventions to enhance emotional regulation in transdiagnostic samples

- Can we replicate these findings in a larger sample?

- Can we improve on this by not only personalizing targeted electrodes but also stimulation frequency (individualized peak theta)?

Summary

- Brain network (“connectome”) properties can
  - identify targets for existing treatments like CBT (*What is the right treatment?)*
  - identify personalized targets for transcranial stimulation
    (personalization in intervention delivery)
- Precision in intervention development not only informs where treatments work but also *for whom (Who is the right person?)*
- *When is the right time?*

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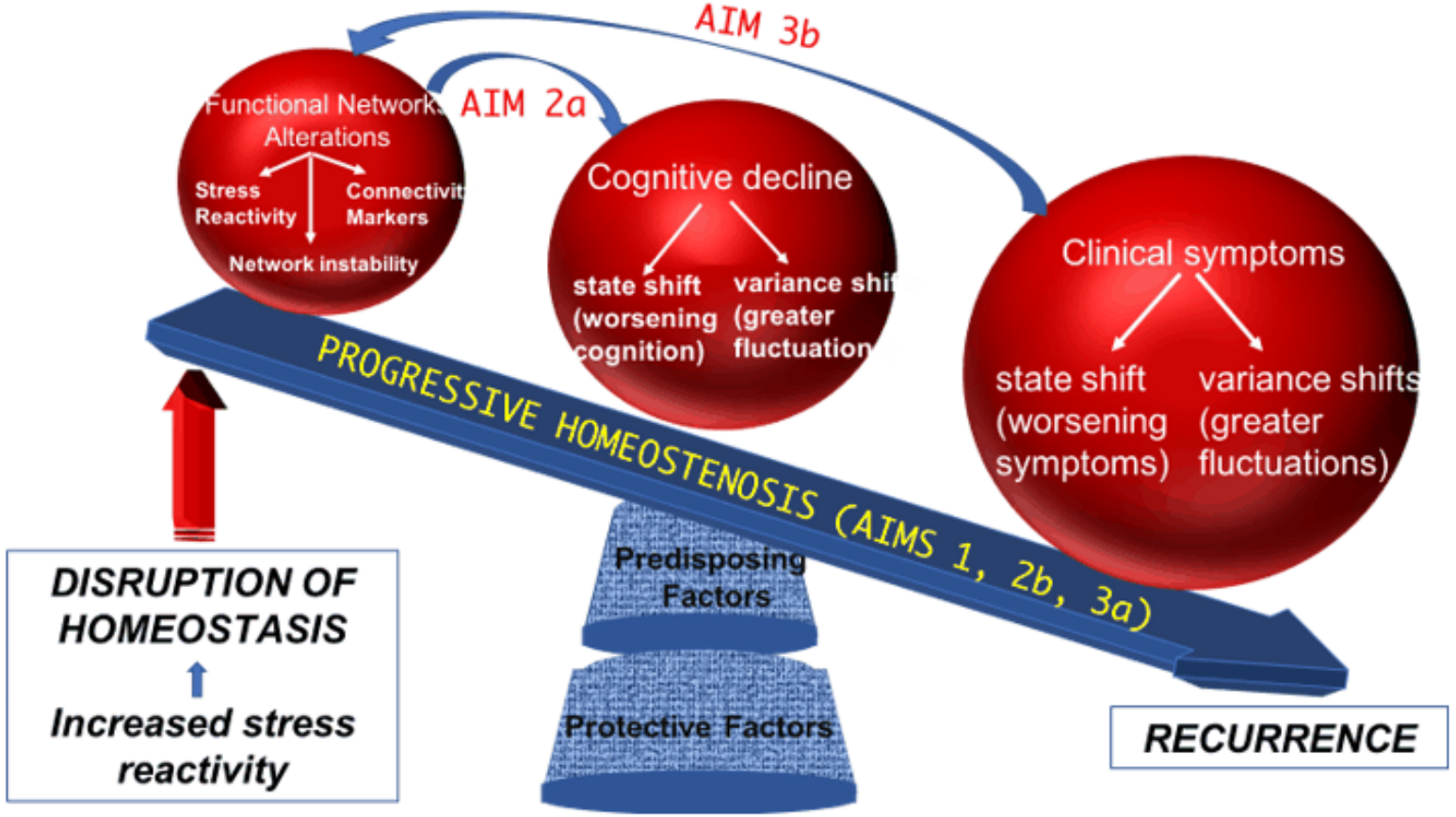
UIC

Can we better understand mechanisms underlying risk of recurrence in LLD?

REMBRANDT:

Recurrence markers, cognitive burden and neurobiological homeostasis in late-life depression

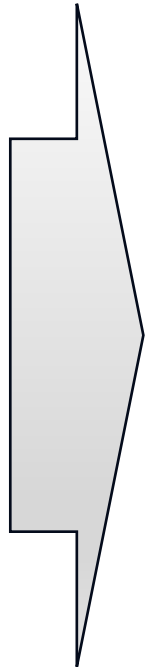
Model: Recurrence as a result of disrupted neural homeostasis

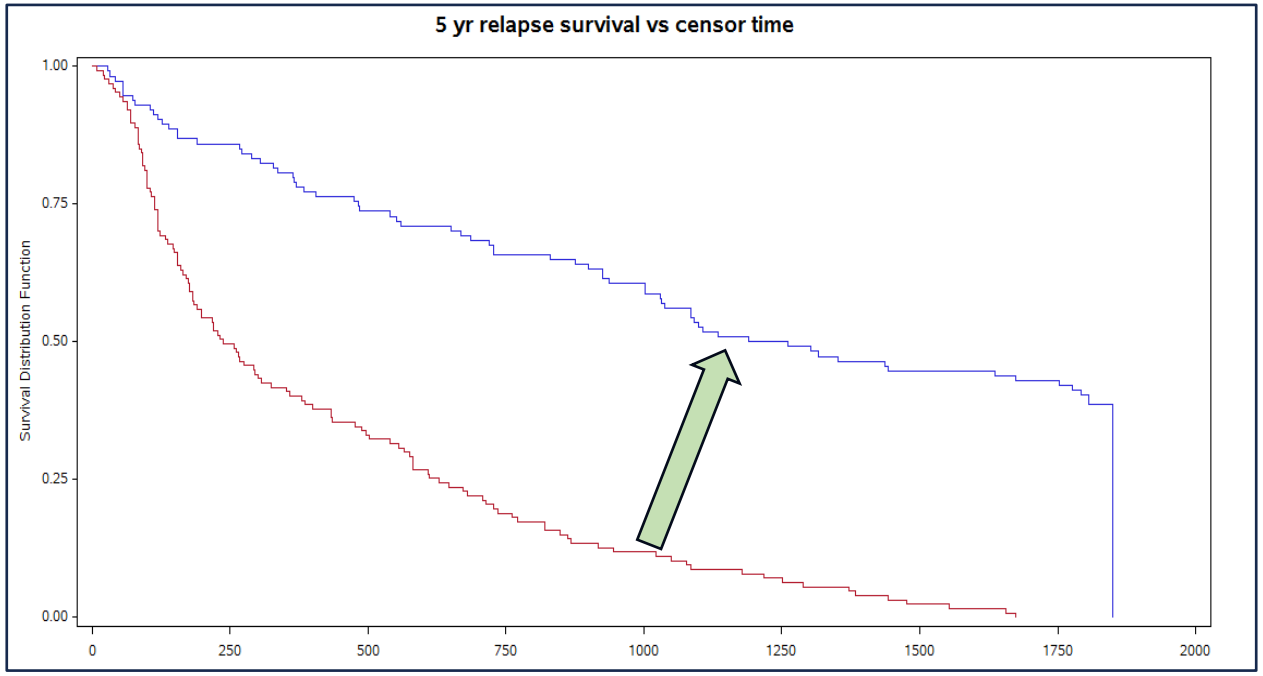


Andreescu CA….Taylor WD. Am J Geriatr Psychiatry 2019

Design:
REMBRANDT Study



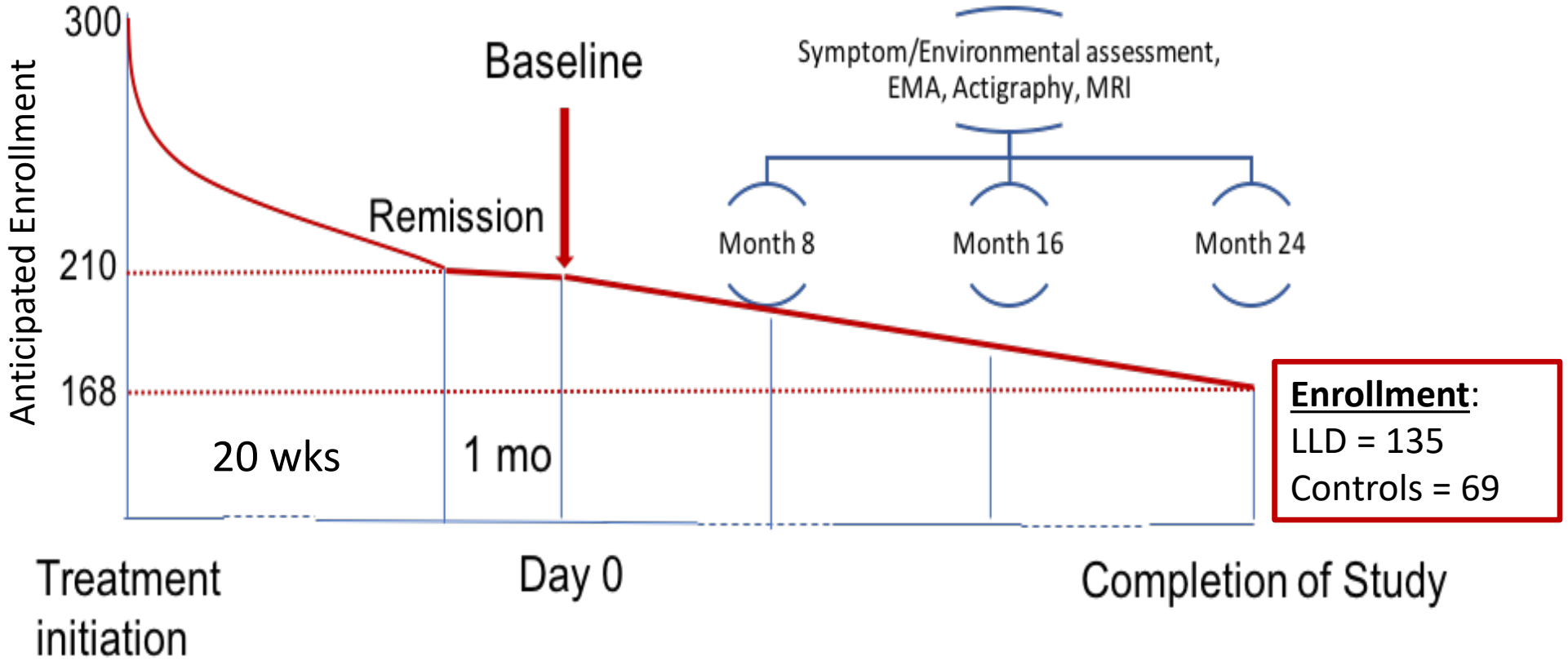




Andreescu CA. Am J Geriatr Psych, 2019. Taylor WD et al, JMAD, 2024

Design: REMBRANDT Study

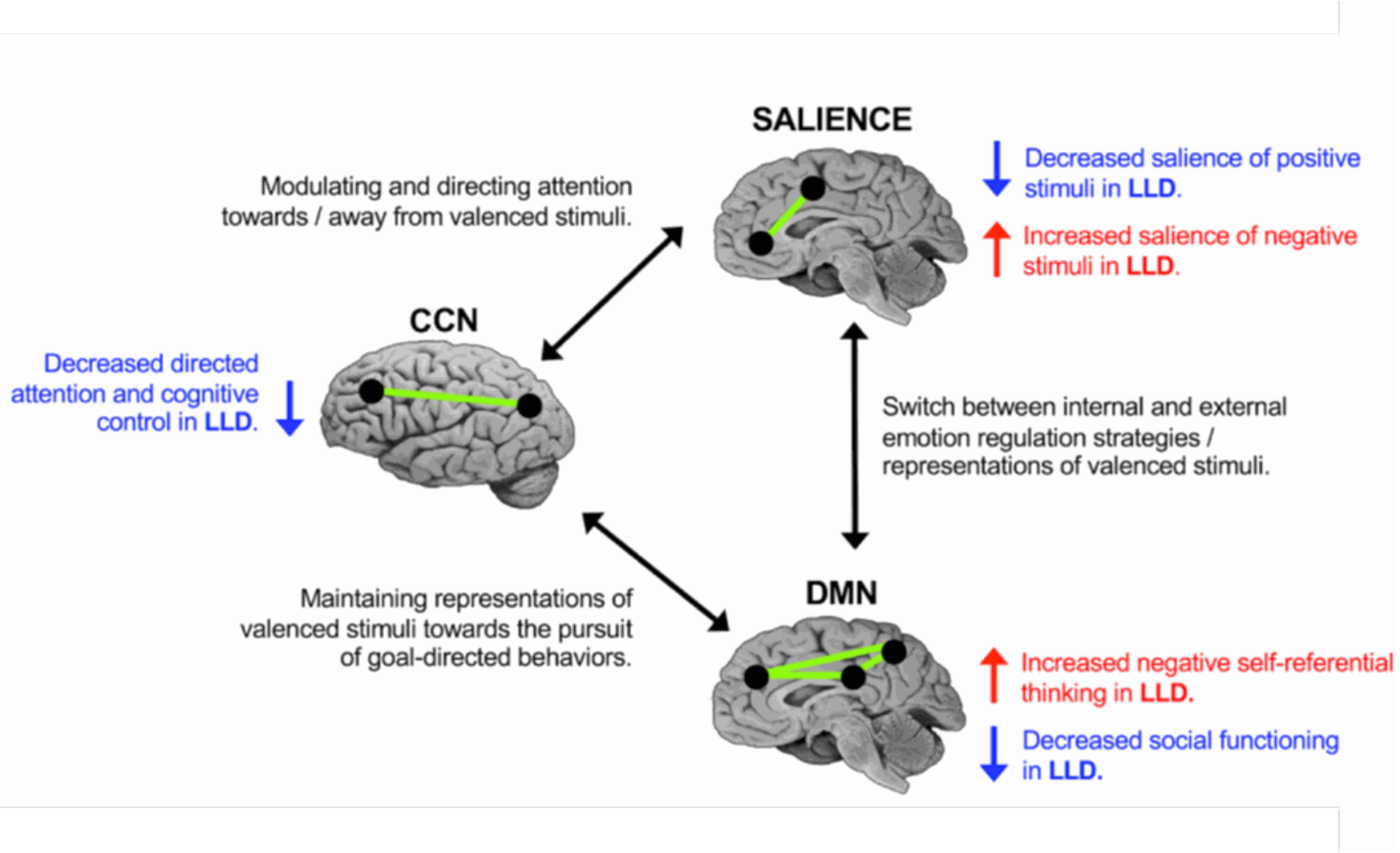
LLD Sample Characteristics:
- Age 60y or older
- **Recurrent** MDD
- MADRS ≤ 10 at two timepoints, 1 month apart
- Enrolled Within 4 months of remission

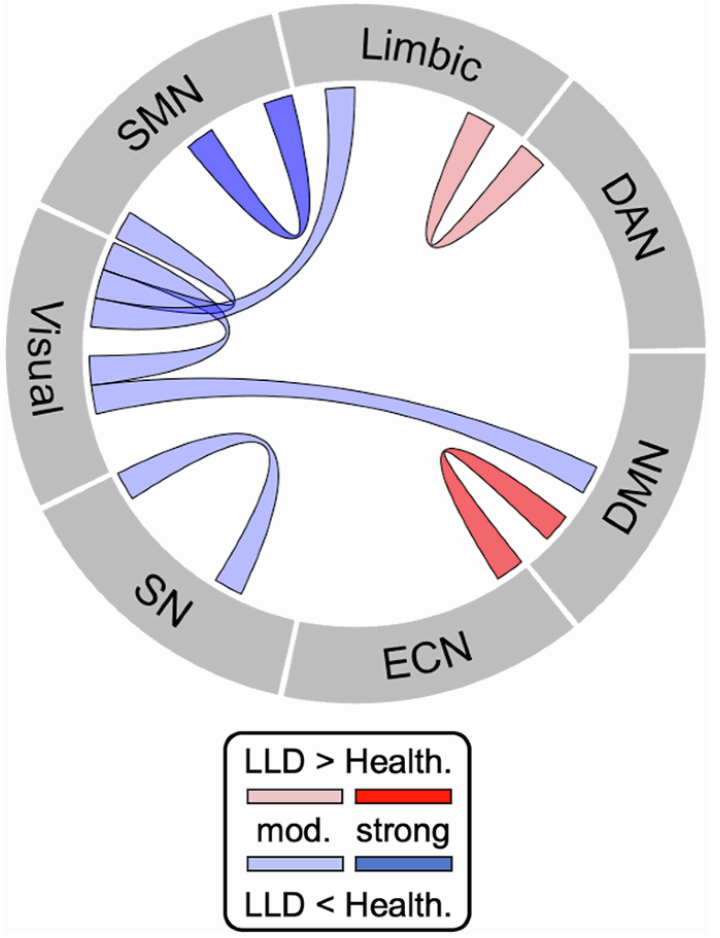


Enrollment:
LLD = 135
Controls = 69

Andreescu CA. Am J Geriatr Psych, 2019. Taylor WD et al, JMAD, 2024

fMRI: Intrinsic Functional Network Connectivity: Beyond the Triple Network Model

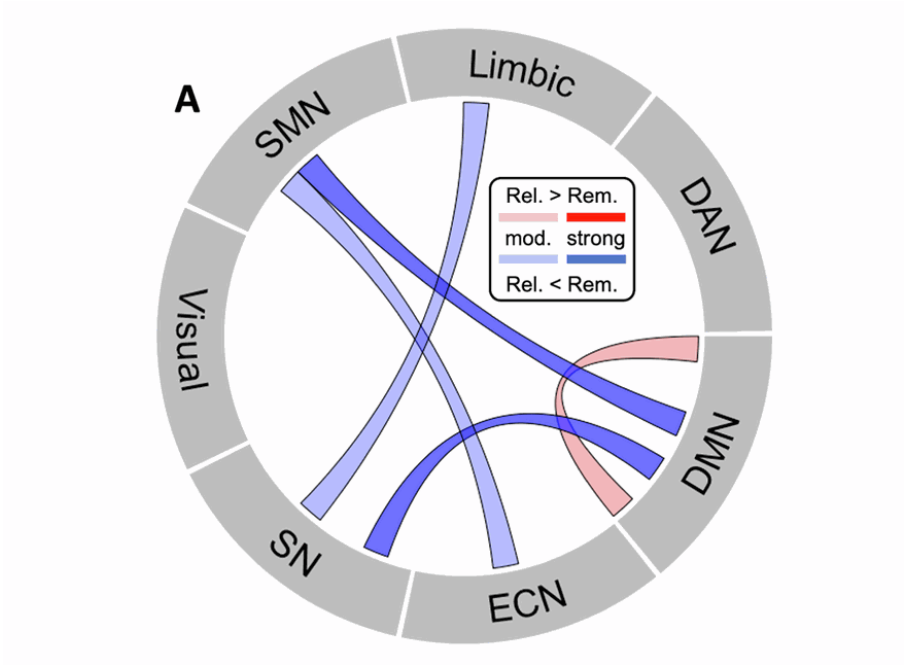




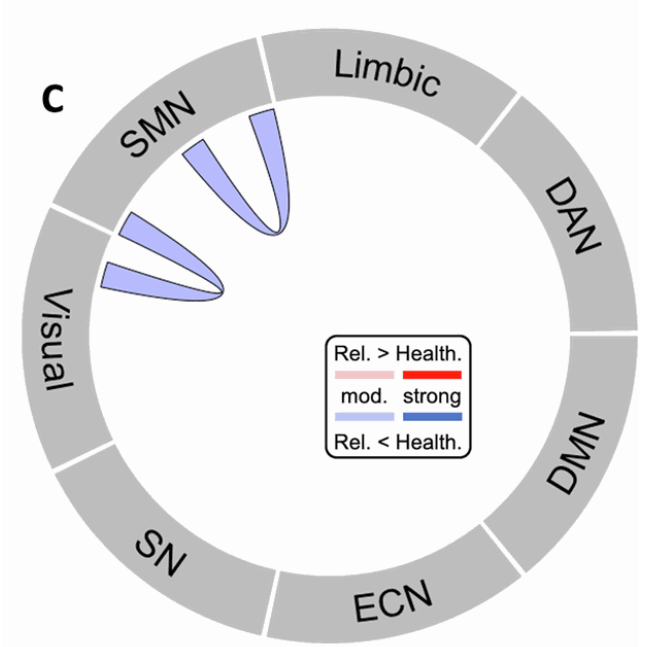
Szymkowicz, Gerlach, Homiak, Taylor. Transl Psych 2023
Gerlach et al. Neuropsychopharmacology. 2025

fMRI: Intrinsic Functional Network Connectivity
Is a ‘new normal’ pattern needed for stability?

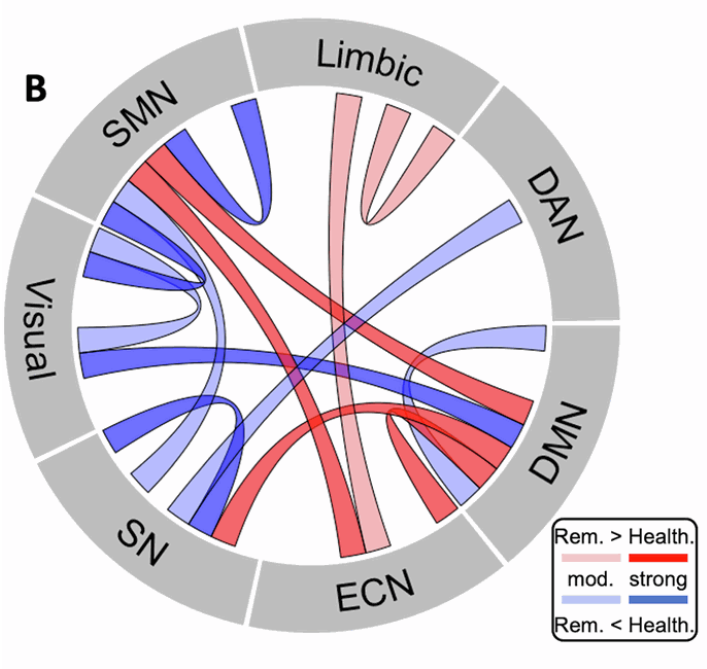
Stable Remitted vs. Relapse



Relapse vs. Healthy Comparison



Stable Remitted vs. Healthy Comparison



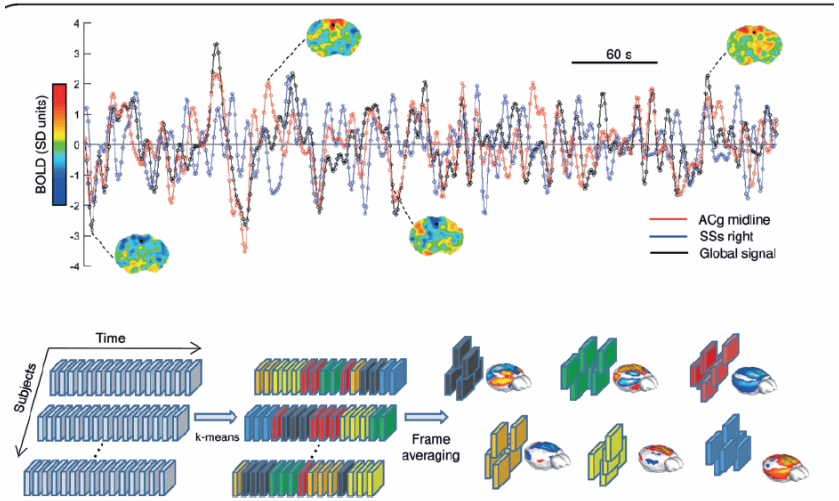
Gerlach et al. Neuropsychopharmacology. 2025

fMRI: Network Dynamics

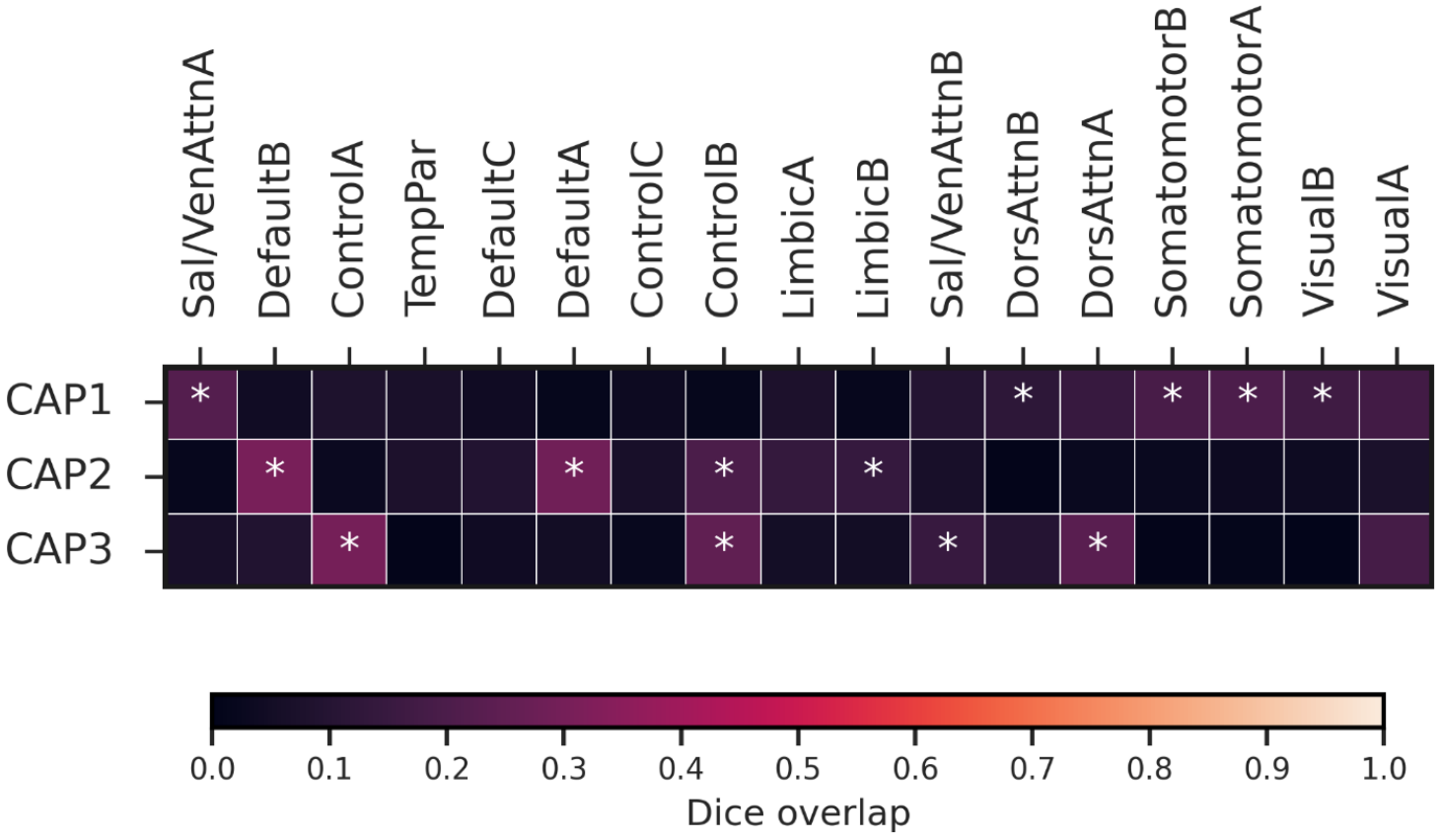
Coactivation Patterns

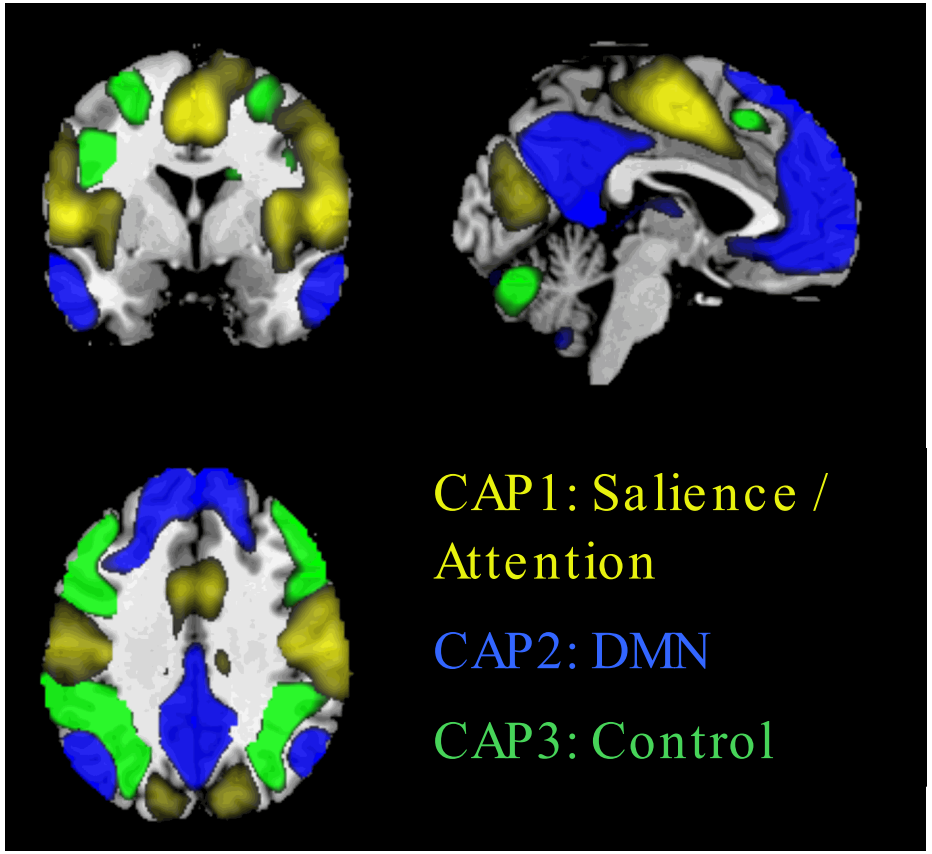
- Utilized the TbCAPS Toolbox from Thomas Bolton to examine dynamic functional connectivity differences between Never Depressed, Remitters, Relapsers

- Uses a K-means consensus clustering technique to examine patterns of co-activated voxels in functional imaging



fMRI: Network Dynamics
Coactivation Patterns



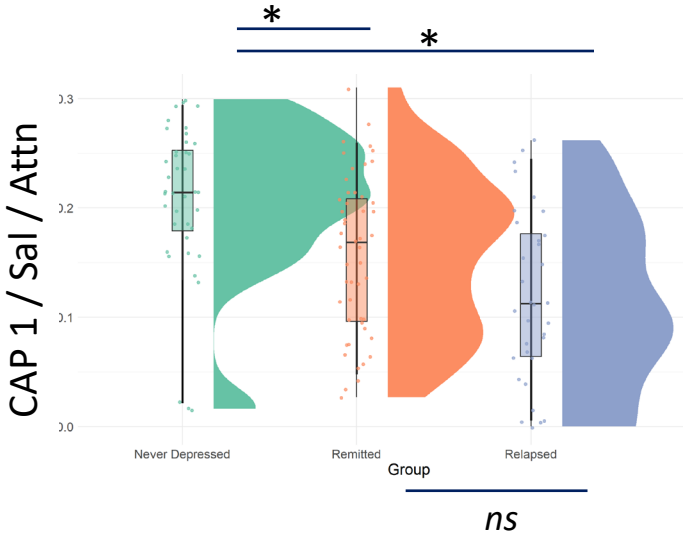


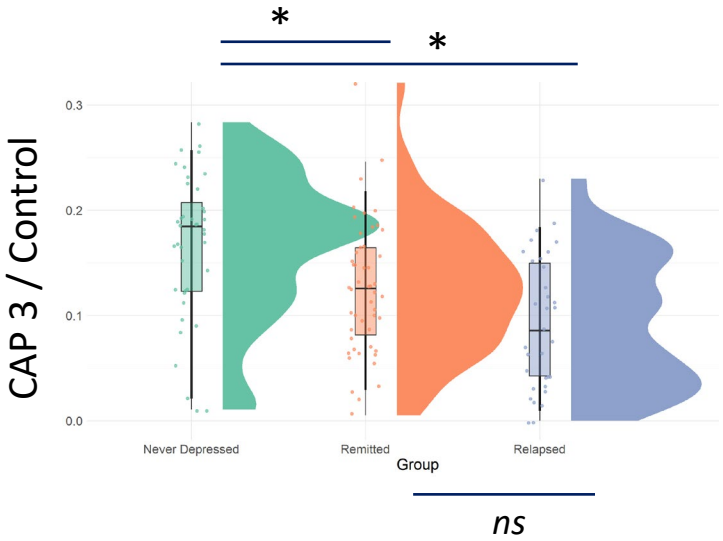
Method: Bolton TAW et al. TbCAPs toolbox. NeuroImage, 2020

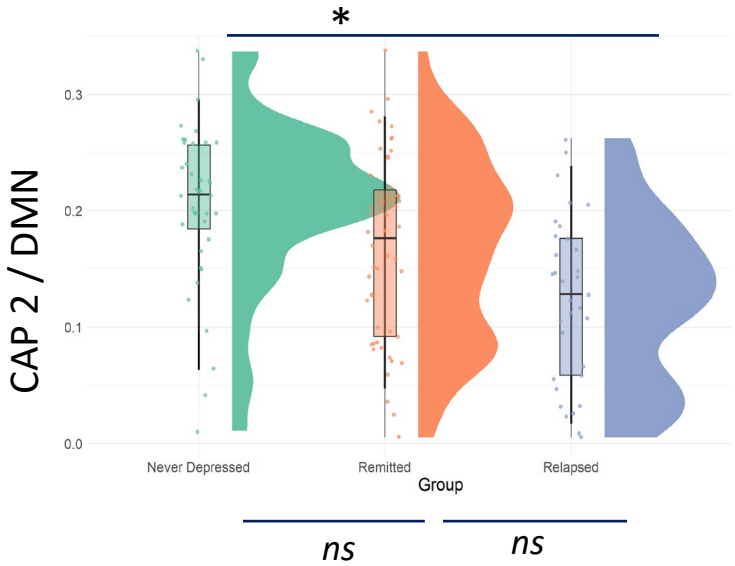
Homiack et al. Biol Psychiatry CNNI. 2025

fMRI: Network Dynamics

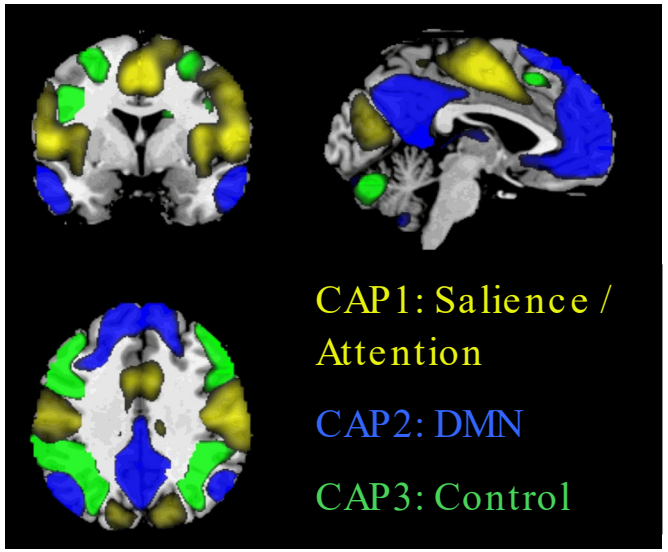
Coactivation Patterns: *Resilience*

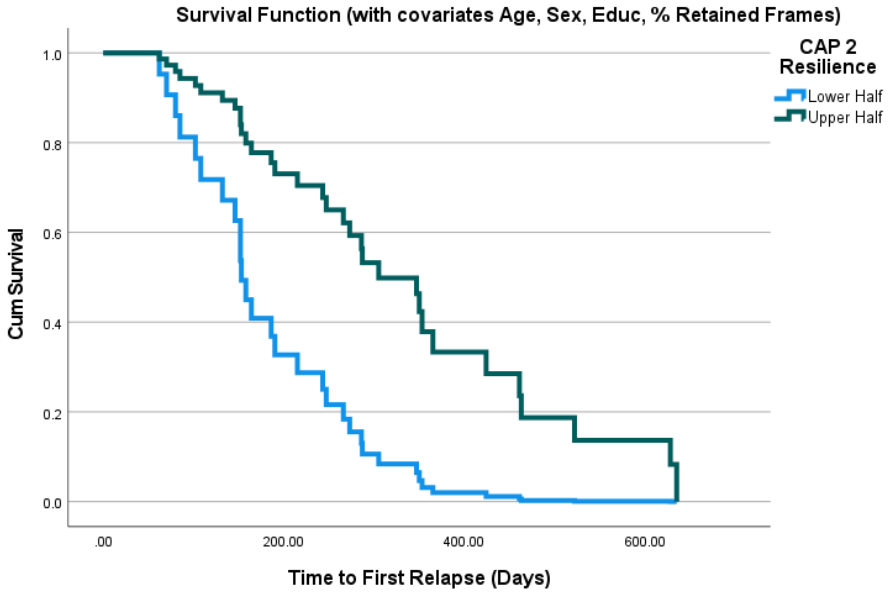






**Individual group differences in posthoc analyses, $p < 0.05$*

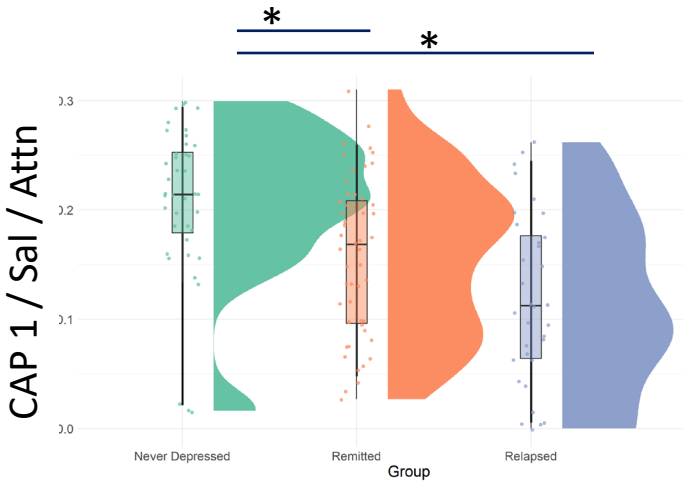




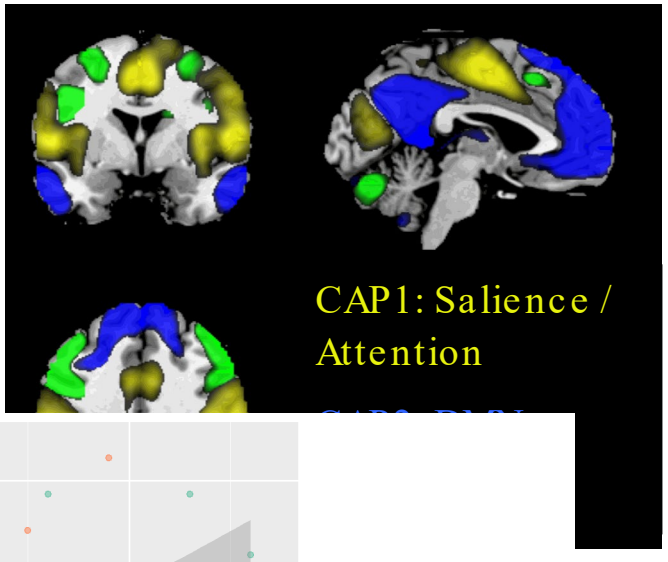
Homiack et al. Biol Psychiatry CNNI. 2025

fMRI: Network Dynamics

Coactivation Patterns: *Resilience*



Group	Correlation	p value
All Subjects	$\rho_{(114)}$= 0.258	p= 0.006
Control	$\rho_{(37)}$= 0.225	p = 0.180
Sustained Remitted	$\rho_{(40)}$= 0.297	p = 0.045
Relapsed	$\rho_{(31)}$= 0.095	p = 0.61





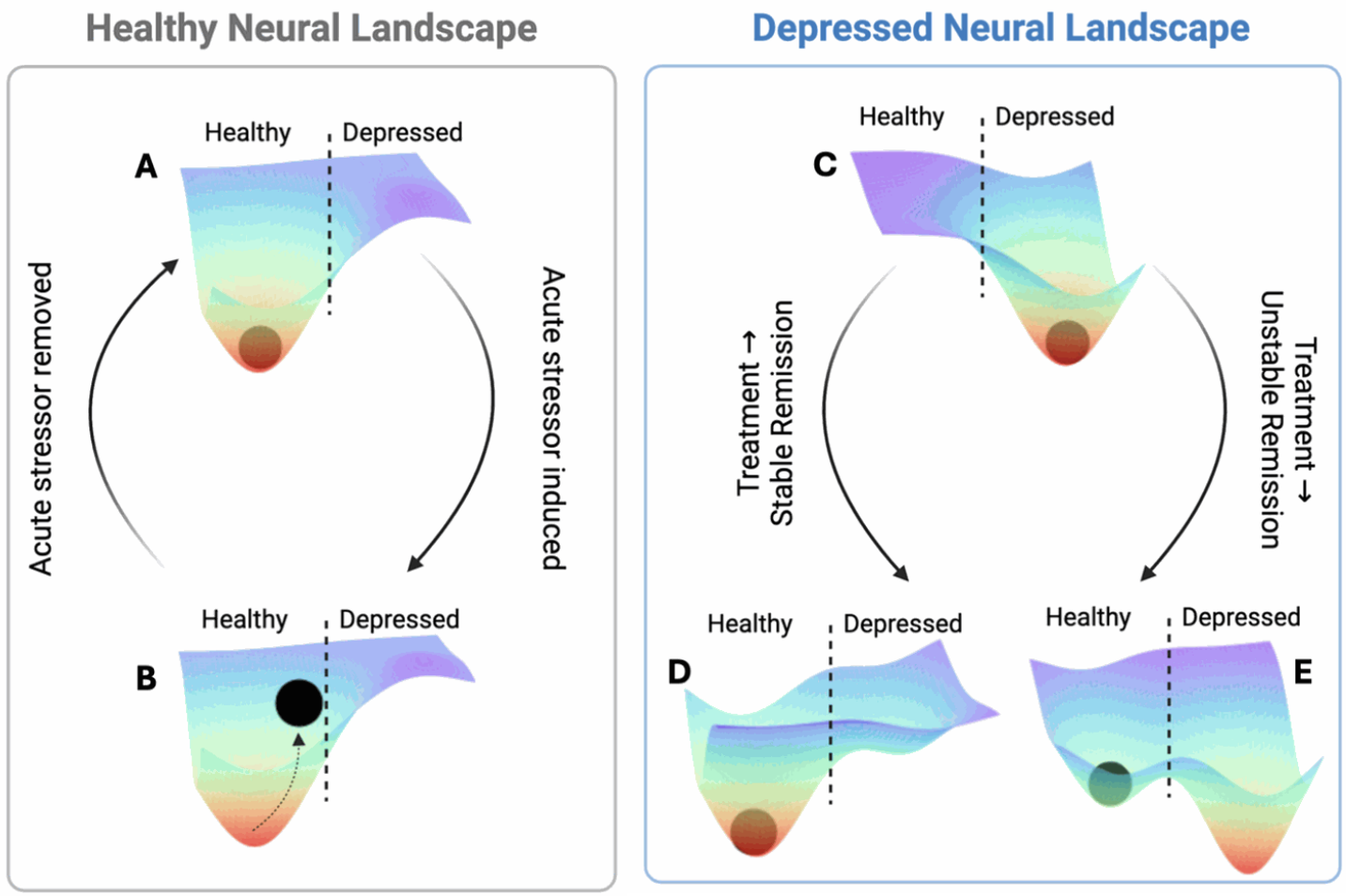
Homiack et al. Biol Psychiatry CNNI. 2025

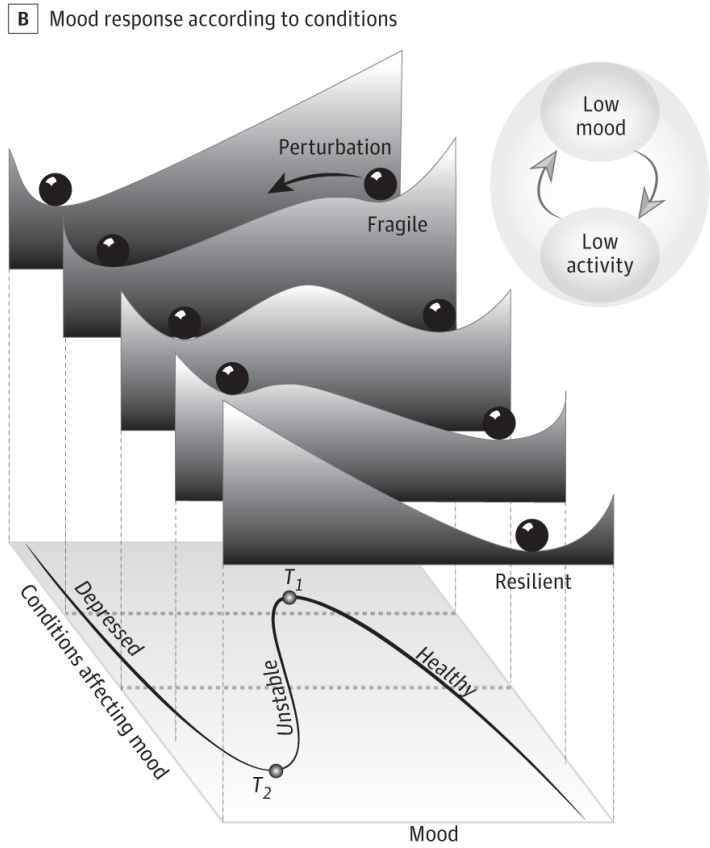
Dynamical Systems Model of Recurrence

Concepts:

Attractor State

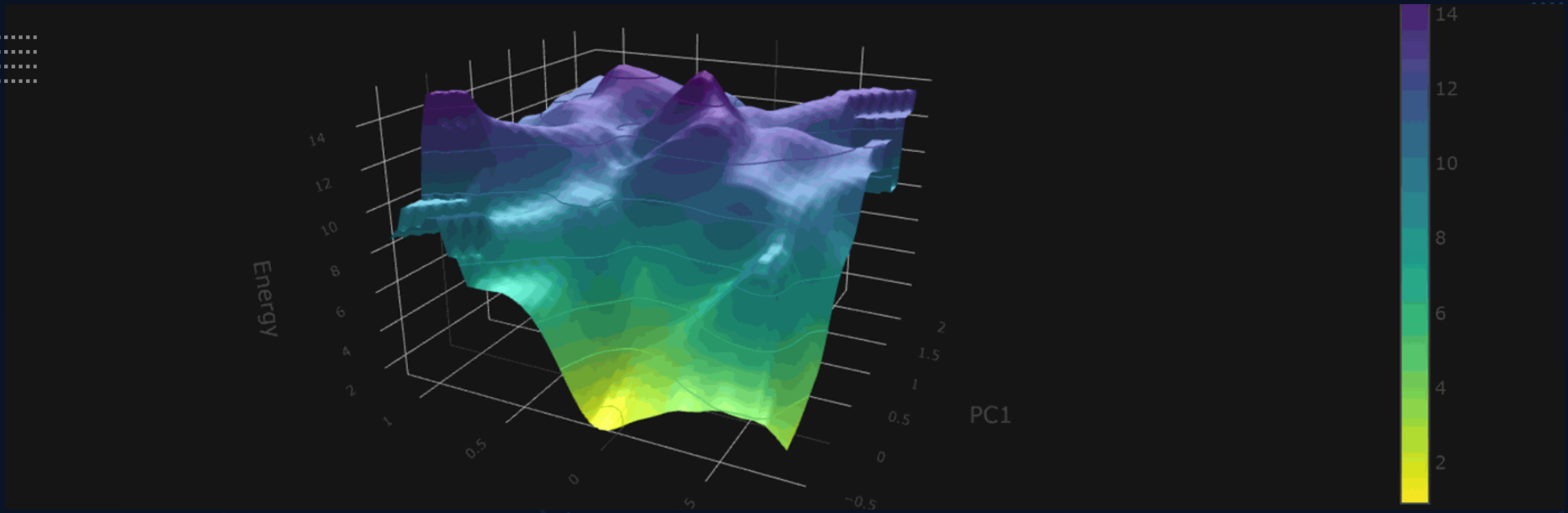
Resilience





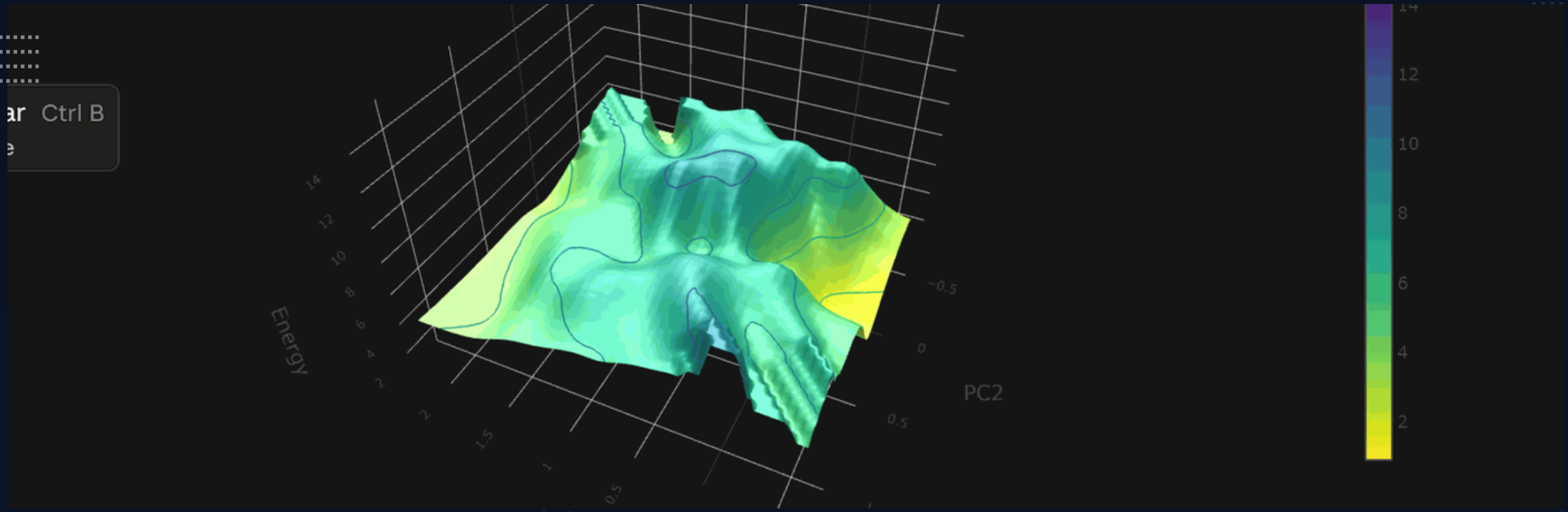
Scheffer M, Bockting CL, et al. JAMA Psychiatry 2024

Color Figure: Gerlach et al. Neuropsychopharmacology 2025



MADRS never > 15 – stable remitters landscape

- N = 107



MADRS ever ≥15 – relapsers landscape

- N = 62
- Bistable landscape
  - 59% state-space in healthy basin
  - 41% state-space in illness basin

- Illness basin active symptoms (Reported sadness, Inner tension, Reduced sleep, Concentration difficulties, Lassitude, Pessimistic thoughts)

Dynamical Systems Model of Recurrence

- Are there static or dynamic connectome correlates of how a patient traverses the symptoms landscape (from remission to depression)?

- Given all participants started in remission, state transitions were typically healthy basins → illness basins; what about transitions from illness to healthy?

- Can we use baseline connectome patterns to identify person-specific points of intervention to prevent relapse?

Acknowledgements

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  - Pares Chowdhury
  - Camryn Gill
- Research Volunteers
- NIMH 5R01MH121384










THE ARCHITECTS' CHOICE