Role of Spontaneous Conscious Processes in Resting-state fMRI

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University of Cincinnati, BME Seminar Series

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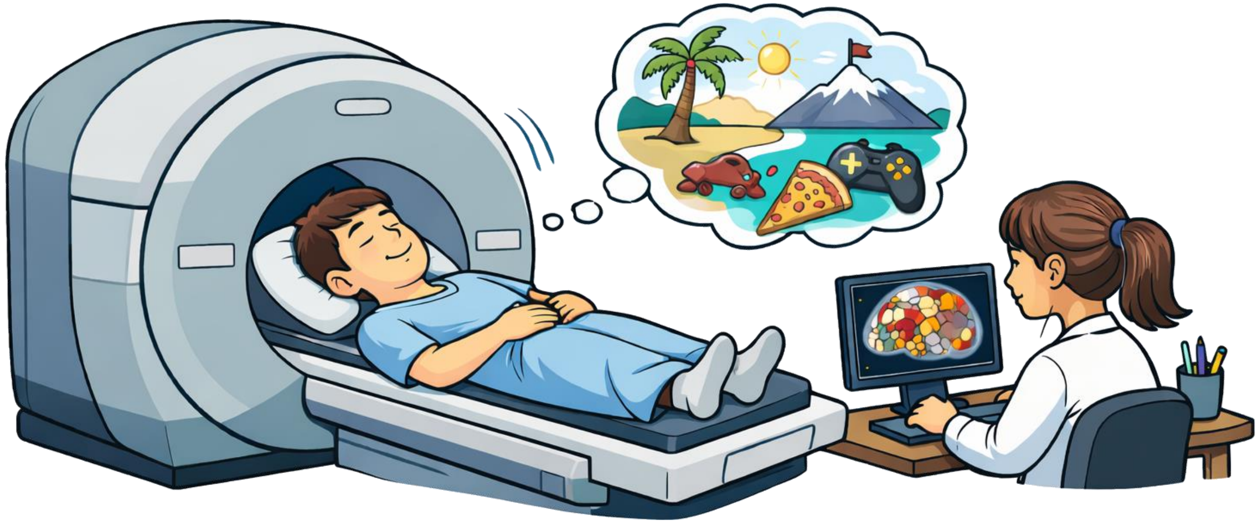
National Institute of Mental Health

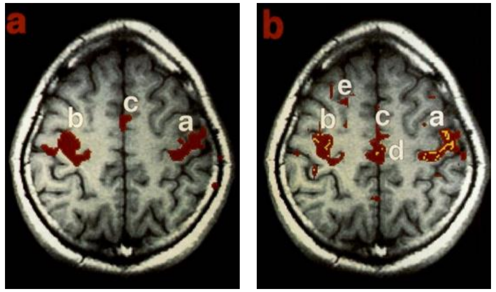
Resting-state fMRI: 30s Primer



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

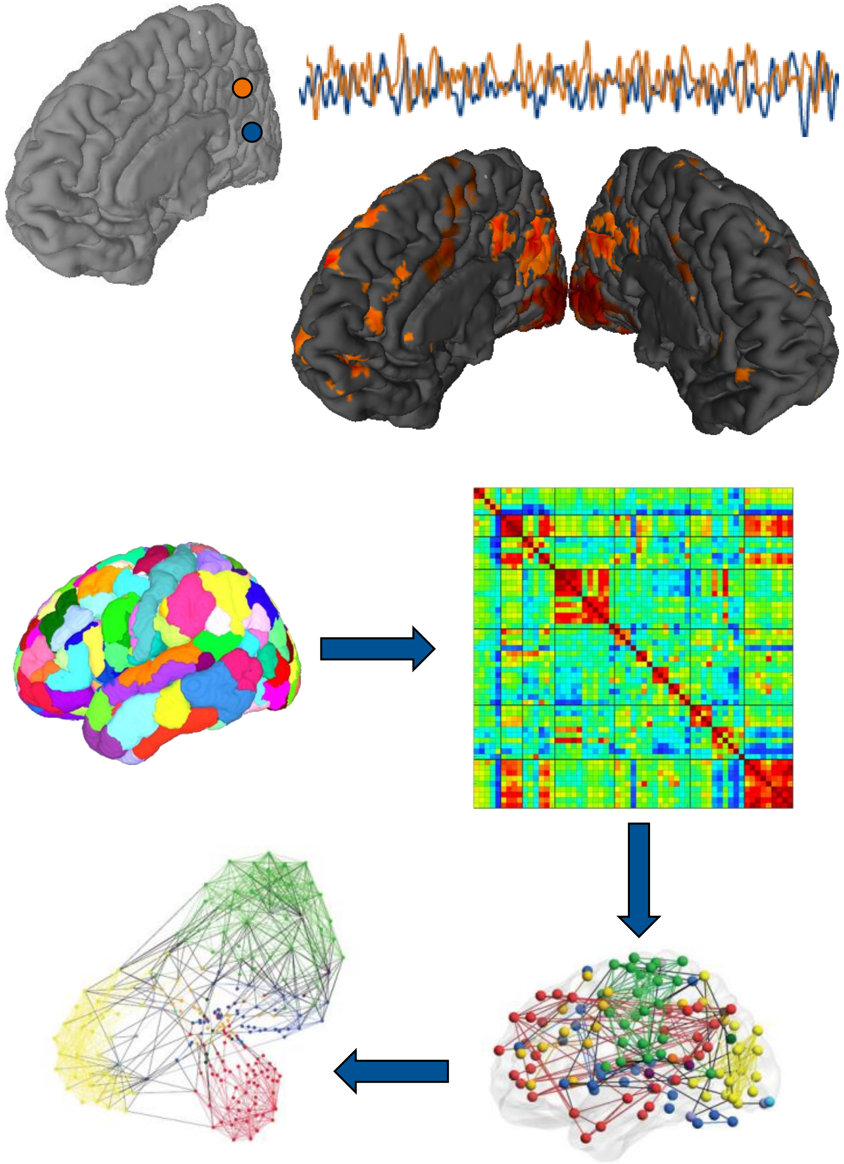
<u>No experimental task demands</u>

- Amenable to all populations
- Easy to acquire and share
- Explore several systems

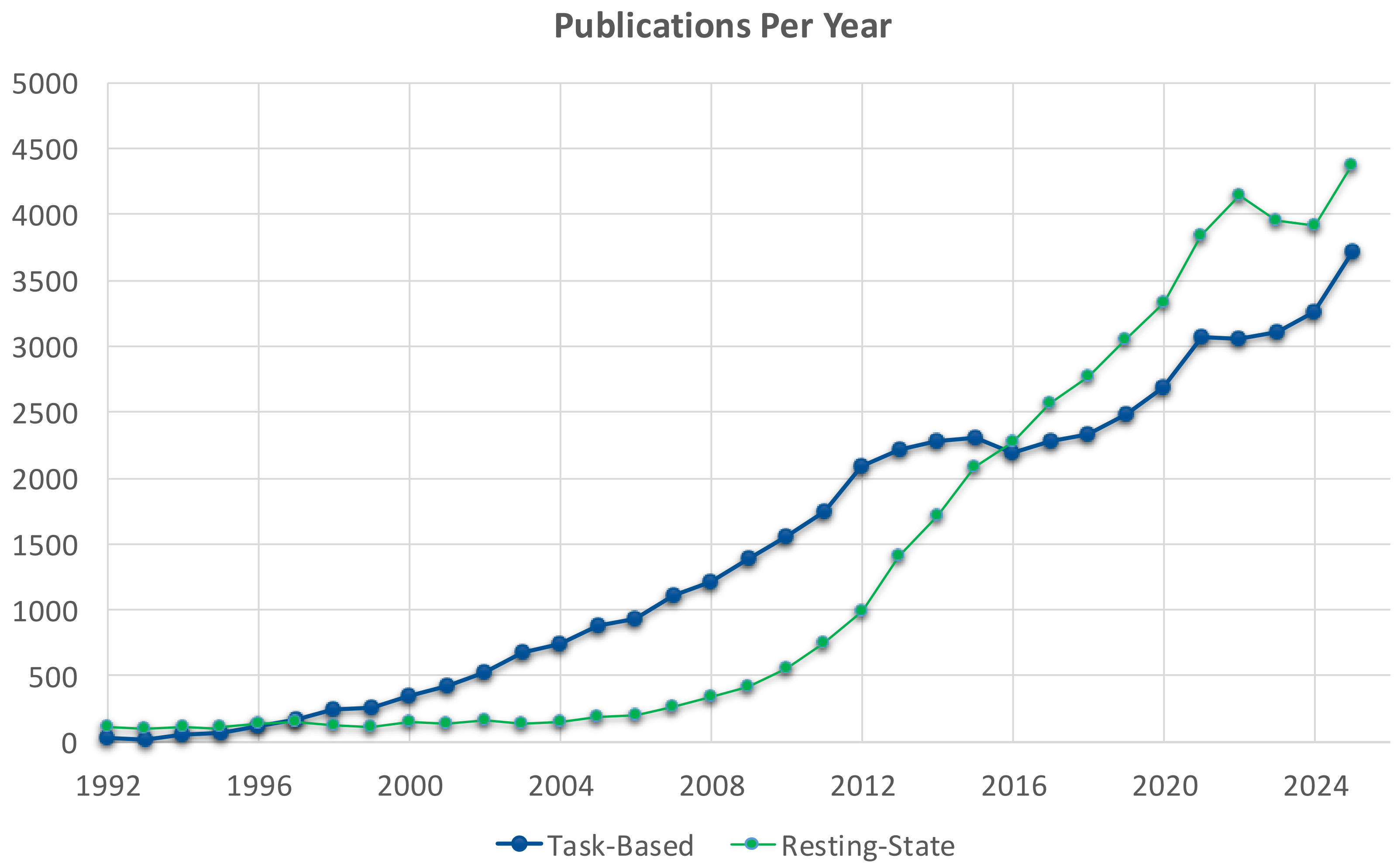


Biswal et al. MRM (1995)

<u>Requires Alternative Analytical Methods</u>



Resting-state fMRI: Relevance | Adoption



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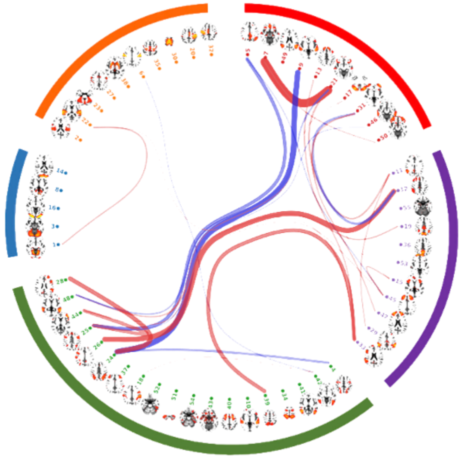
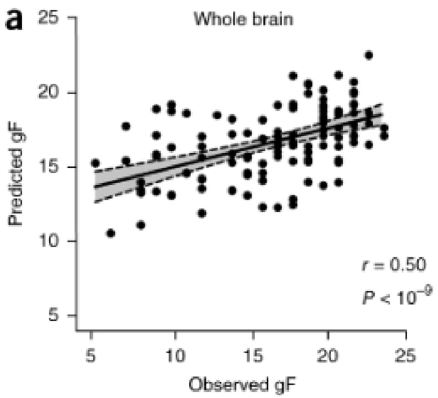
Resting-state: Relevance | Basic & Clinical Value

Cognitive Abilities

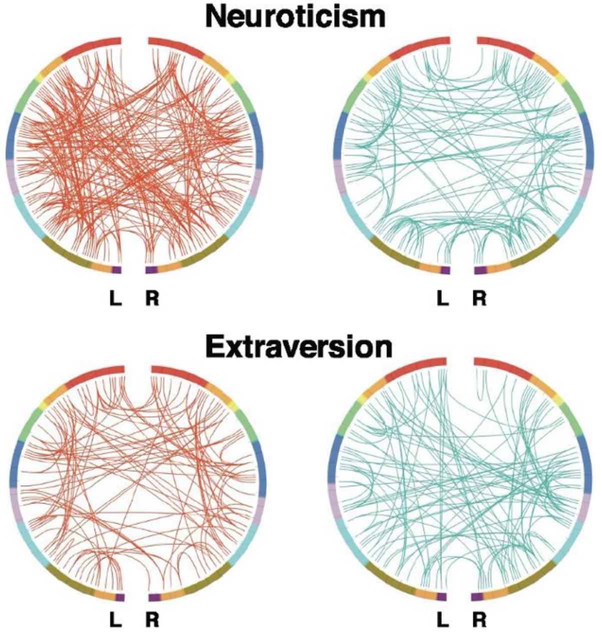


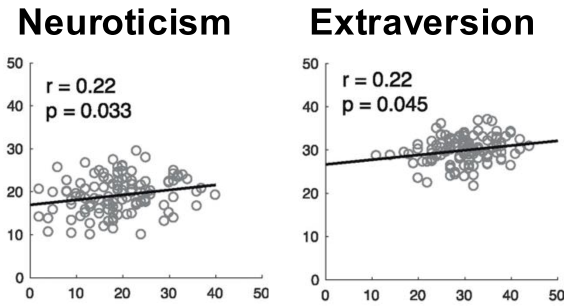
Shen et al. Biol Psychiatry (2018)



Finn et al. Nat Neuro (2015)

Personality Traits





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

Clinical Conditions

Disease/condition	References	Findings
Alzheimer's	(Li et al., 2002; Greicius et al., 2004; Wang et al., 2006a,b, 2007; Allen et al., 2007; Supekar et al., 2008)	Decreased correlations within the DMN including hippocampi, decreased anticorrelations with the DMN, and reduced local connectivity as reflected in clustering coefficients
PIB positive	(Hedden et al., 2009; Sheline et al., 2010)	Decreased correlations within the DMN
Mild cognitive impairment	(Li et al., 2002; Sorg et al., 2007)	Decreased correlations within the DMN and decreased anticorrelations with the DMN.
Fronto-temporal dementia	(Seeley et al., 2007a, 2008)	Decreased correlations within the salience network
Healthy aging	(Andrews-Hanna et al., 2007; Damoiseaux et al., 2008)	Decreased correlations within the DMN
Multiple sclerosis	(Lowe et al., 2002; De Luca et al., 2005)	Decreased correlations within the somatomotor network
ALS	(Mohammadi et al., 2009)	Decreased connectivity within the DMN and within the somatomotor network (esp. premotor cortex)
Depression	(Anand et al., 2005a,b, 2009; Greicius et al., 2007; Bluhm et al., 2009a)	Variable: Decreased corticolimbic connectivity (esp. with dorsal anterior cingulate), increased connectivity within the DMN (esp. subgenual prefrontal cortex), decreased connectivity between DMN and caudate
Bipolar	(Anand et al., 2009)	Decreased corticolimbic connectivity
PTSD	(Bluhm et al., 2009c)	Decreased connectivity within the DMN
Schizophrenia	(Liang et al., 2006; Liu et al., 2006, 2008; Bluhm et al., 2007, 2009b; Salvador et al., 2007; Zhou et al., 2007; Jafri et al., 2008; Whitfield-Gabrieli et al., 2009)	Variable: Decreased or increased correlations within the DMN. Decreased, increased or unchanged correlations and anticorrelations between the DMN and other systems.
Schizophrenia 1° relatives	(Whitfield-Gabrieli et al., 2009)	Increased connectivity within the DMN
ADHD	(Zhu et al., 2005, 2008; Cao et al., 2006; Tian et al., 2006; Zang et al., 2007; Castellanos et al., 2008; Wang et al., 2009)	Variable: reduced connectivity within the DMN, reduced anticorrelations with the DMN, increased connectivity in the salience network
Autism	(Cherkassky et al., 2006; Kennedy and Courchesne, 2008; Monk et al., 2009; Weng et al., 2010)	Decreased connectivity within the DMN (although hippocampus is variable and connectivity may be increased in younger patients)
Tourette syndrome	(Church et al., 2009)	Delayed maturation of task-control and cingulo-opercular networks
Epilepsy	(Waites et al., 2006; Lui et al., 2008; Bettus et al., 2009; Zhang et al., 2009b,c)	Variable: decreased connectivity in multiple networks including the medial temporal lobe, decreased connectivity within the DMN (esp. in patients with generalized seizures)
Blindness	(Liu et al., 2007; Yu et al., 2008)	Decreased connectivity within the visual cortices and between visual cortices and other sensory and multimodal regions
Chronic pain	(Greicius et al., 2008a; Cauda et al., 2009a,c,d)	Variable: Increased/decreased connectivity within the salience network, decreased connectivity in attention networks
Neglect	(He et al., 2007)	Decreased connectivity within the dorsal and ventral attention networks
Coma/vegetative state	(Boly et al., 2009; Cauda et al., 2009b; Vanhaudenhuyse et al., 2010)	Progressively decreased DMN connectivity with progressive states of impaired consciousness
Generalized anxiety disorder	(Etkin et al., 2009)	increased connectivity between amygdala and frontoparietal control network and decreased connectivity between amygdala and salience network

*DMN = default mode network including regions in the posterior cingulate/precuneus, lateral parietal cortex, medial temporal lobes, and medial prefrontal cortex (**see Figure 1**). Salience network: includes regions in the dorsal anterior cingulate and bilateral fronto/insular cortices; dACC = dorsal anterior cingulated cortex; PIB = Pittsburg compound B, a marker of amyloid plaque accumulation in the brain. PTSD = post-traumatic stress disorder; ALS = amyotrophic lateral sclerosis; ADHD = attention deficit hyperactivity disorder. Note: some references (Greicius et al., 2004; He et al., 2007) reflect "near-rest" conditions in which task-related variance has been minimized and other references (Zhu et al., 2005, 2008; Cao et al., 2006; Zang et al., 2007) reflect local changes in spontaneous BOLD fluctuations as opposed to correlations in these fluctuations between separate regions.*

Fox & Greicius Font. Sys, Neuro (2010)

Resting-state: What is it? What processes drive these observations?

Mostly 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

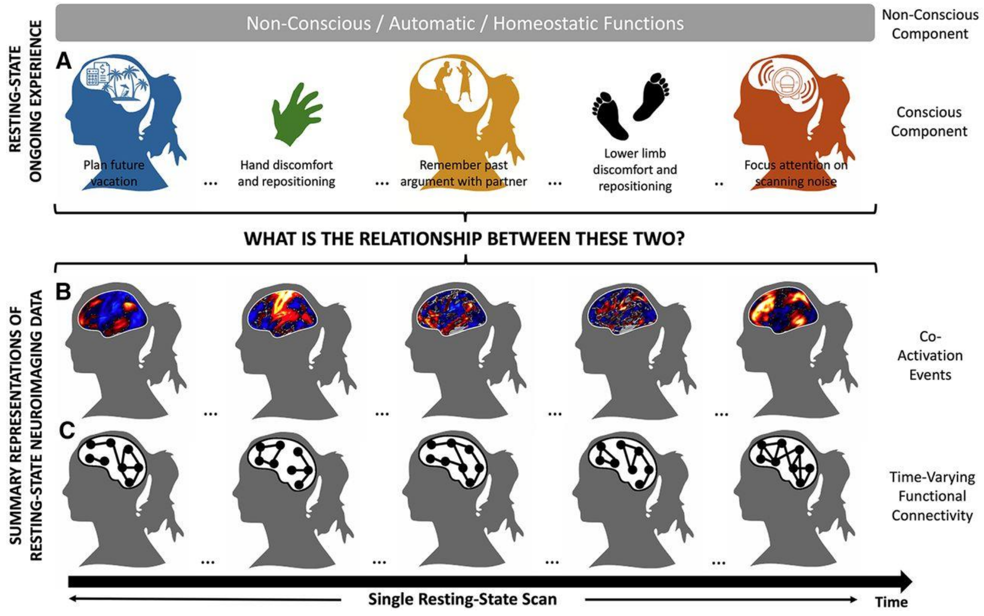
Sampling Variability

Laumann & Snyder (2021) Cur Op Bio Sci

~~OR~~

AND

Conscious Processes / Experience

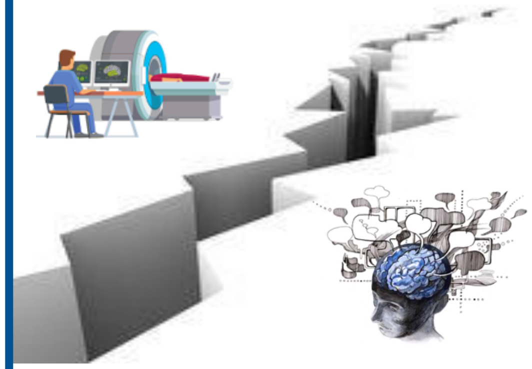


Gonzalez-Castillo et al, J of Neuroscience (2021)

Incremental Approach to elucidate the role of in-scanner experience in resting-state fMRI

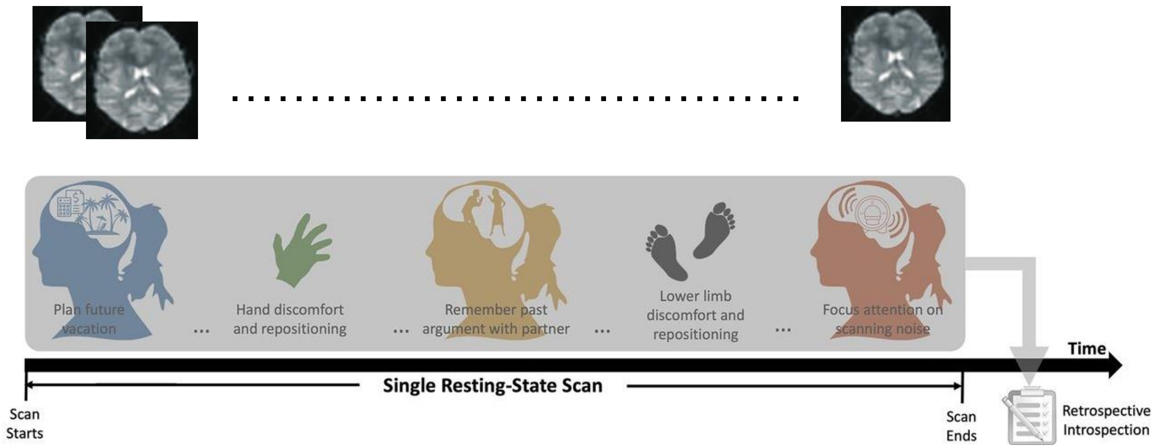
STEP 1

Separate fMRI & Self-Reports Data



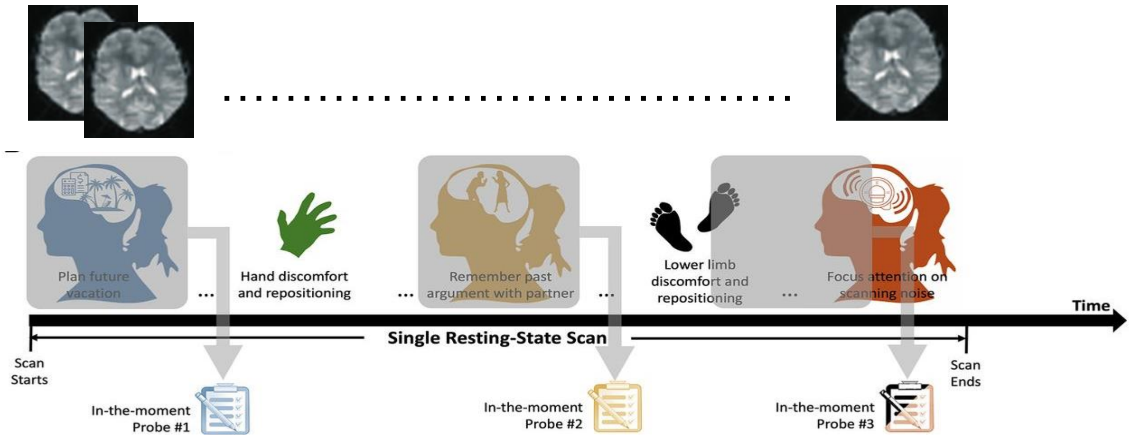
STEP 2

RS-fMRI with retrospective self reports



STEP 3

RS-fMRI with in-the-moment self reports



What are common activities during rest?

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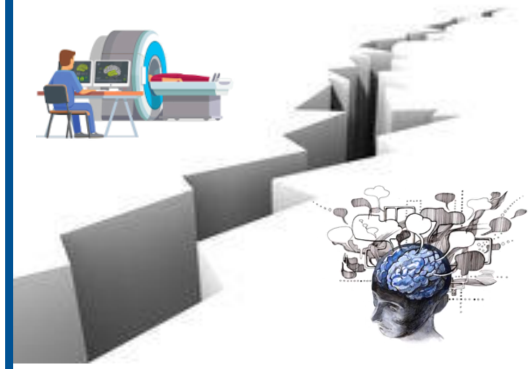

Heavy & Hurlburt, Consc. & Cogn. (2008)

Hurlburt et al., Front. Psychol. (2015)

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What are common activities during rest?

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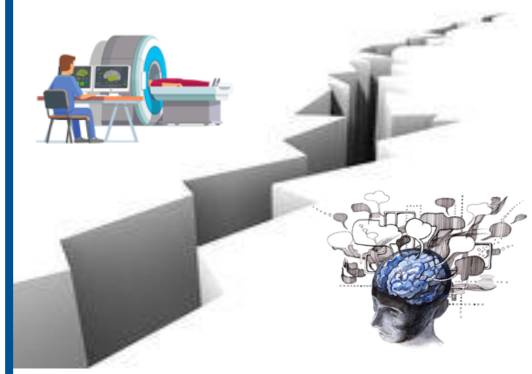
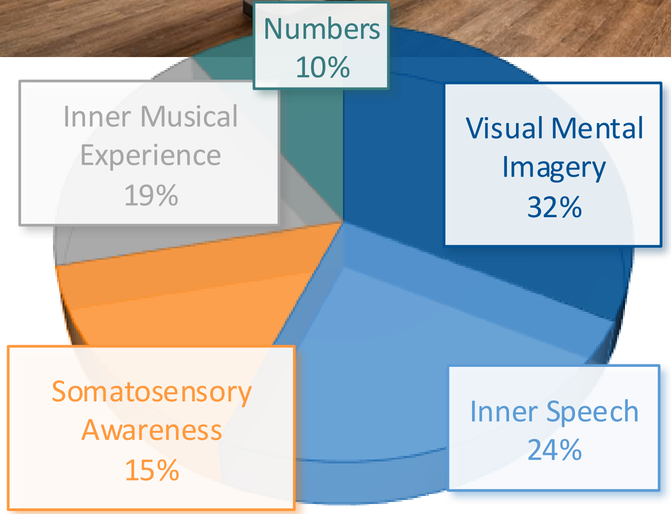




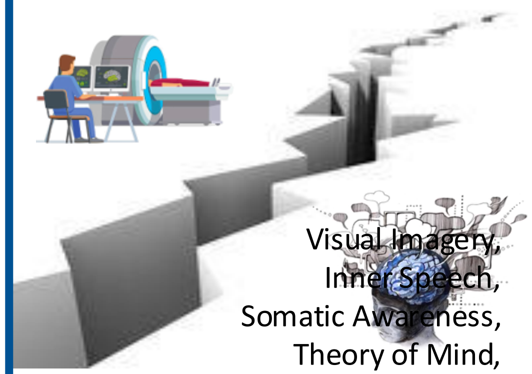
Dellamillieure et al., Brain Res. Bull. (2010)

Diaz et al., Front. Hum. Neurosci. (2013)

Do mental states inferred directly from rs-fMRI data agree with these?

STEP 1

Separate fMRI & Self-Reports Data



Visual Imagery,
Inner Speech,
Somatic Awareness,
Theory of Mind,
Planning,
Inner Musical Experience,
Numerical Computations,
Self,
...

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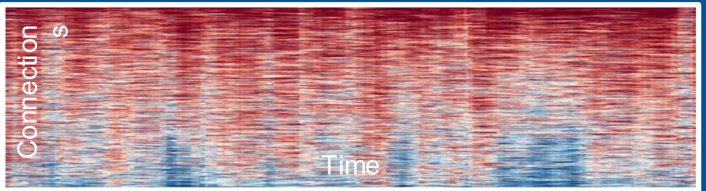
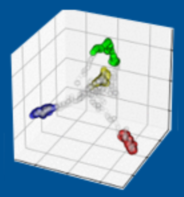
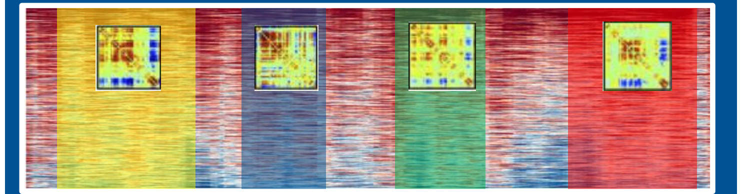
Sliding Window Correlation

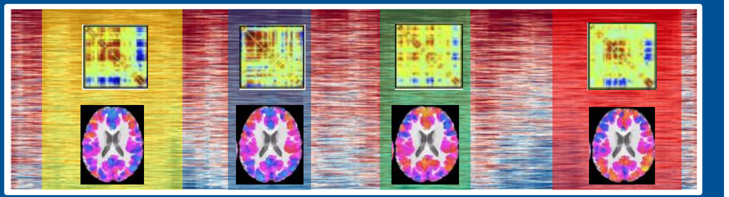




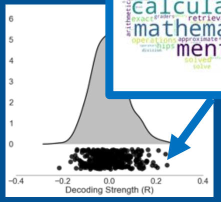
3D Trajectory of time-varying FC

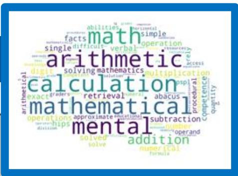


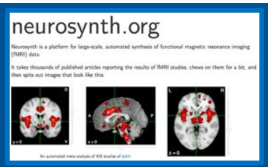
Identify Scan Segments with Distinct, stable FC



Hemodynamic Deconvolution







Reverse Inference with NeuroSynth

Gonzalez-Castillo et al., NeuroImage (2019)

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Do mental states inferred directly from rs-fMRI data agree with these?

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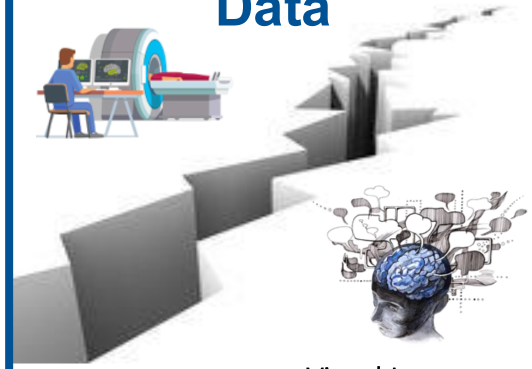

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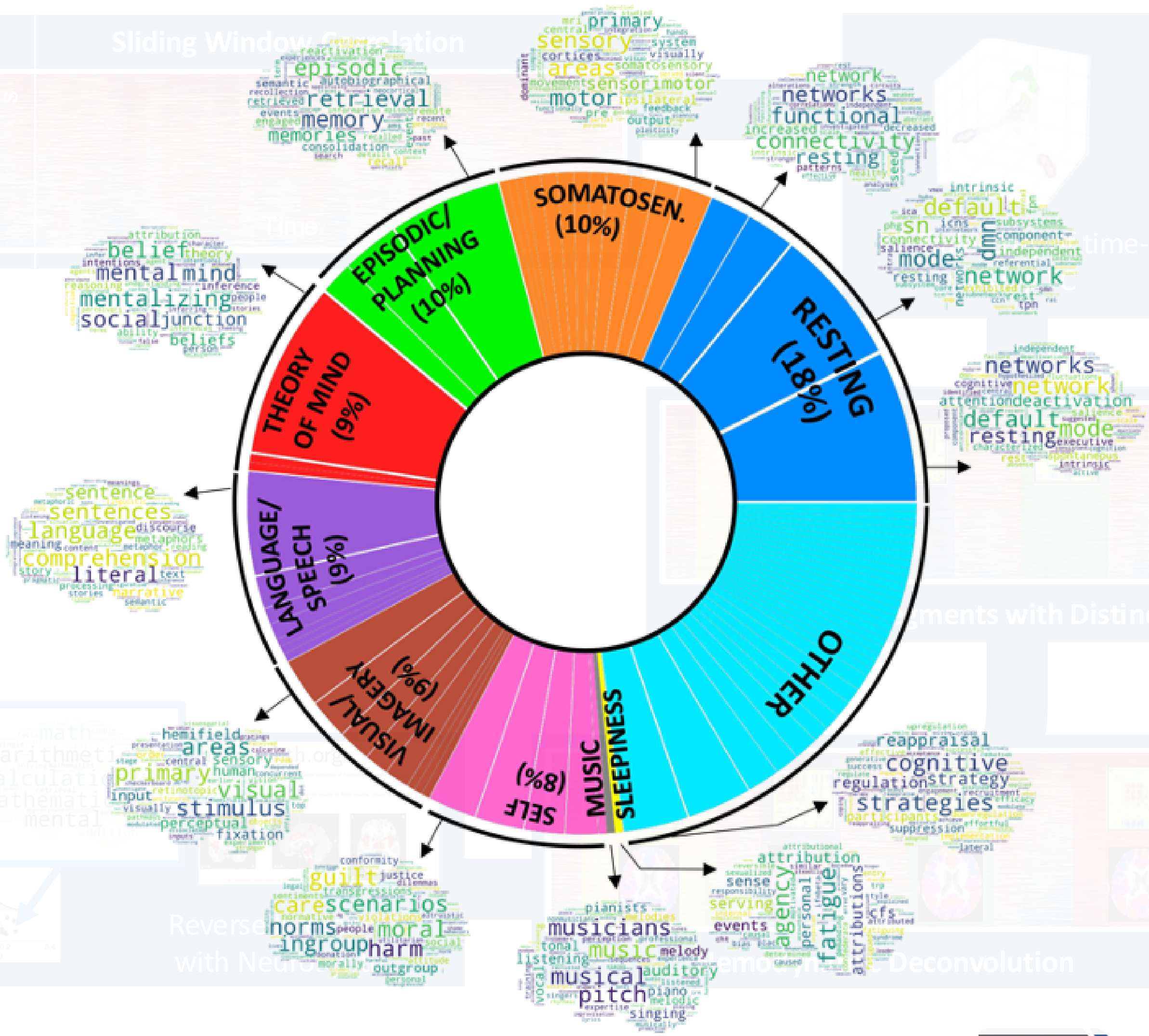
HUMAN CONNECTOME PROJECT



Gonzalez-Castillo et al., NeuroImage (2019)

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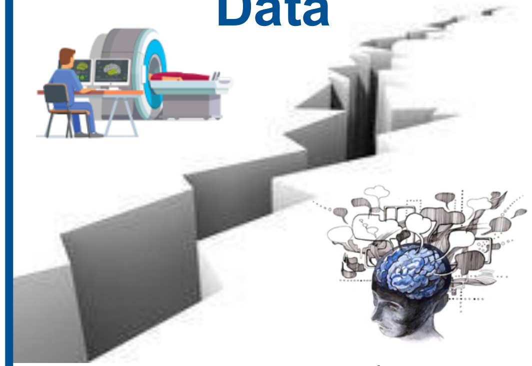
Study I - Conclusions

STEP 1

Separate fMRI & Self-Reports Data



Visual Imagery,
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Self,
...

- Data-driven estimates of covert cognition agree with previous reports of what are the most common mental activities subjects perform during rest.
  - *"dFC + Deconvolution + Neurosynth"* can help us uncover the cognitive correlates of distinct *dFC* patterns during task and rest.
- Preliminary evidence in support of the idea that FC is substantially contributed by covert on-going cognition happening during rest.

We cannot evaluate the accuracy of individual decoding instances

Validation / Decoding through the lens of task results

Gonzalez-Castillo et al., NeuroImage (2019)

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Incremental Approach to elucidate the role of in-scanner experience in resting-state fMRI

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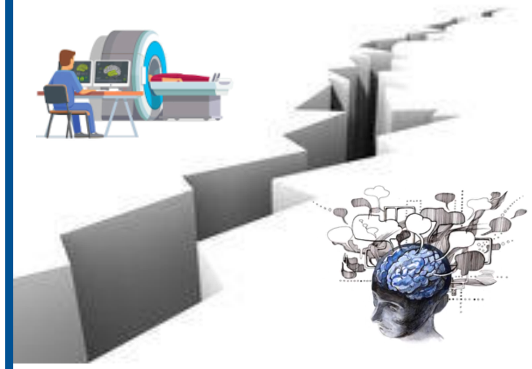
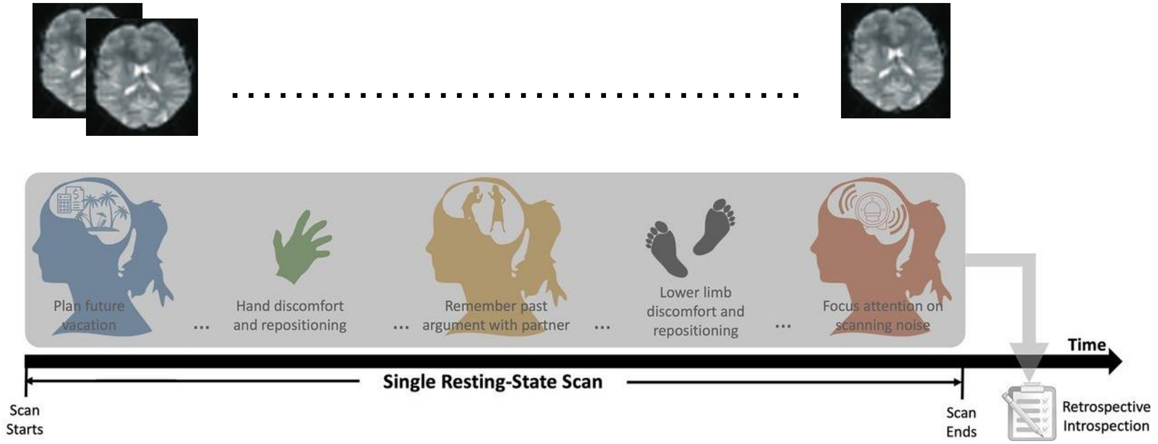


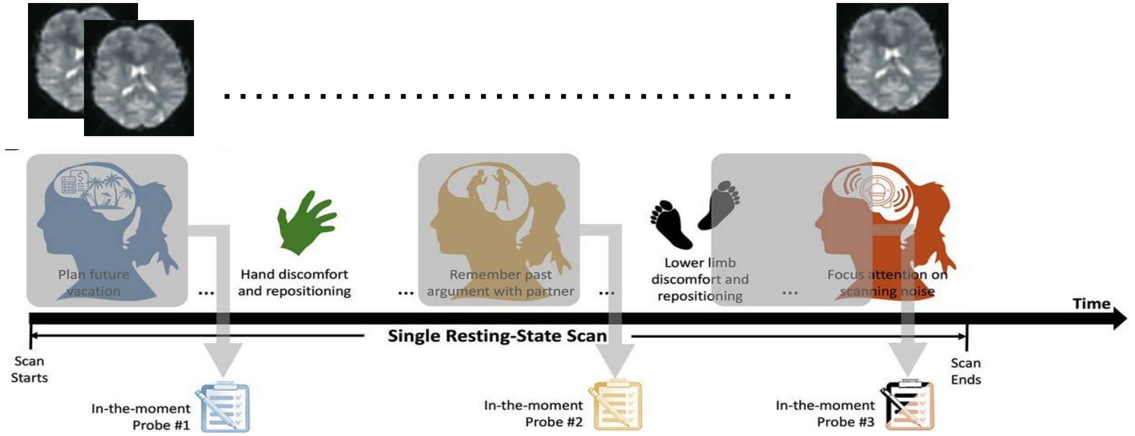
STEP 2

RS-fMRI with retrospective self reports

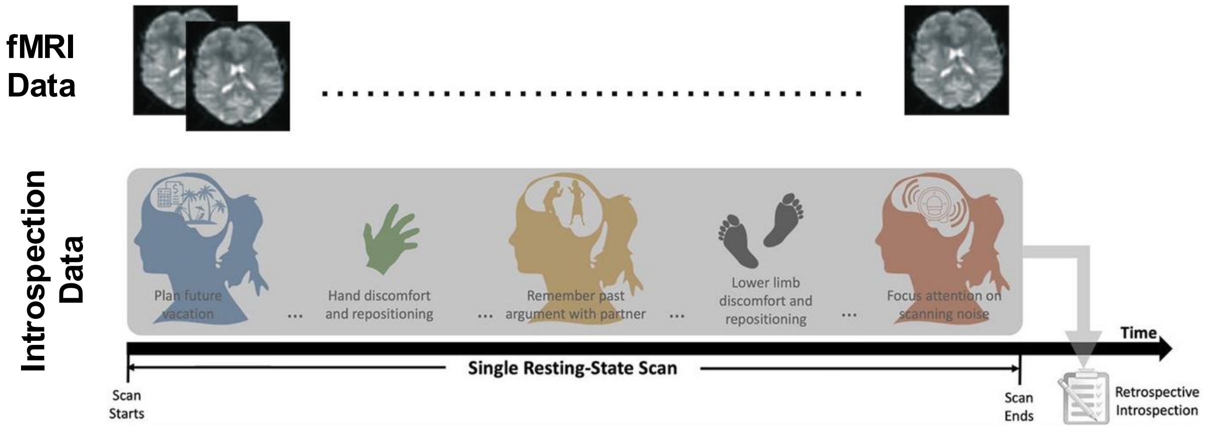


STEP 3

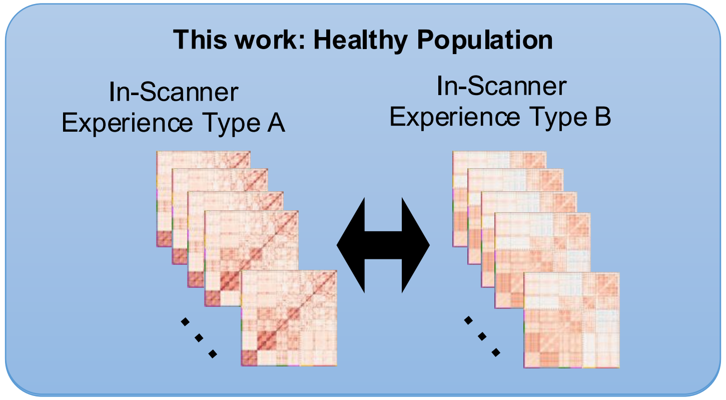
RS-fMRI with in-the-moment self reports



STEP 2: Experimental Questions



Population Differences 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?

Gonzalez-Castillo et al. (under review Nature Comms)

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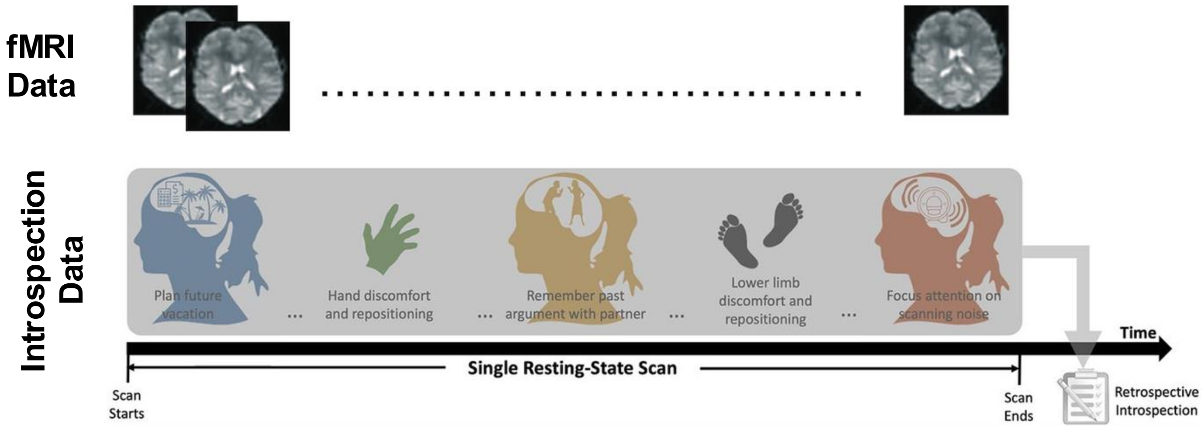
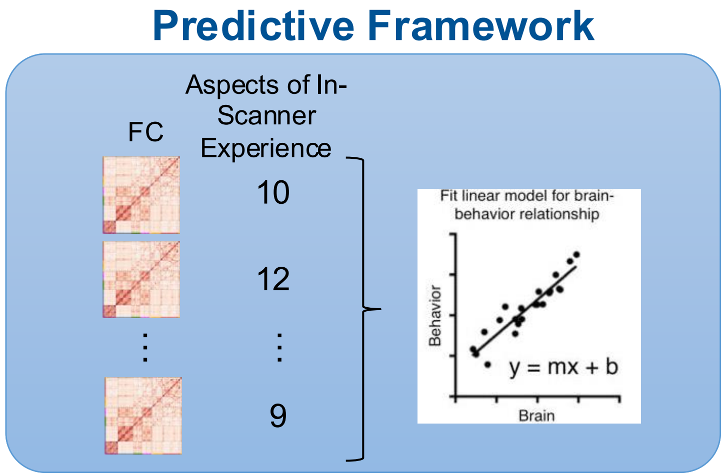
STEP 2: Experimental Questions





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 | TBD

Gonzalez-Castillo et al. (under review Nature Comms)

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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

Demographics Data

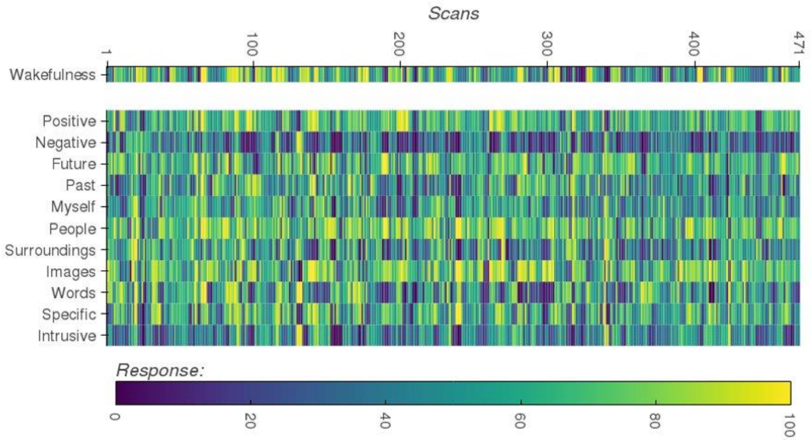
Age Range (5 year intervals) & Gender

Experience Reports

FORM	My thoughts were intrusive	0 … 100
	My thoughts were more specific than vague	0 … 100
	My thoughts were in the form of words	0 … 100
	My thoughts were in the form of images	0 … 100
CONTENT	I thought about my environment / surrounding	0 … 100
	I thought about other people	0 … 100
	I thought about myself	0 … 100
	I thought about past events	0 … 100
	I thought about future events	0 … 100
	I thought about something negative	0 … 100
	I thought about something positive	0 … 100
	I was completely awake	0 … 100

Mendes et al. Scientific Reports (2019)

Introspective Data



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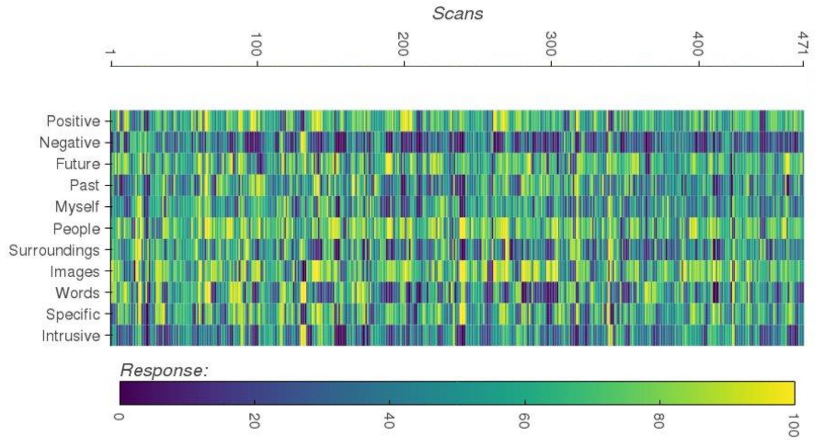

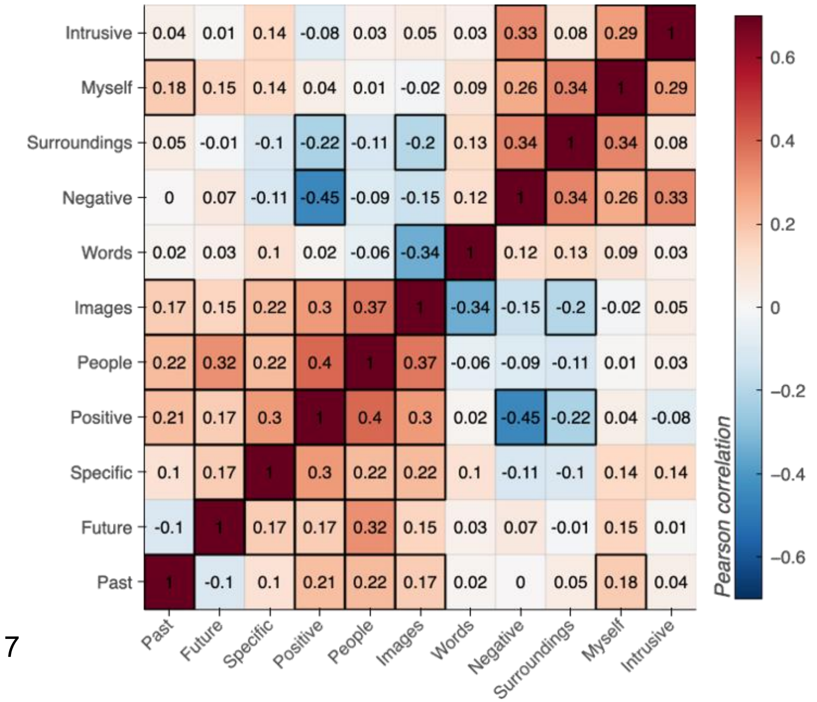

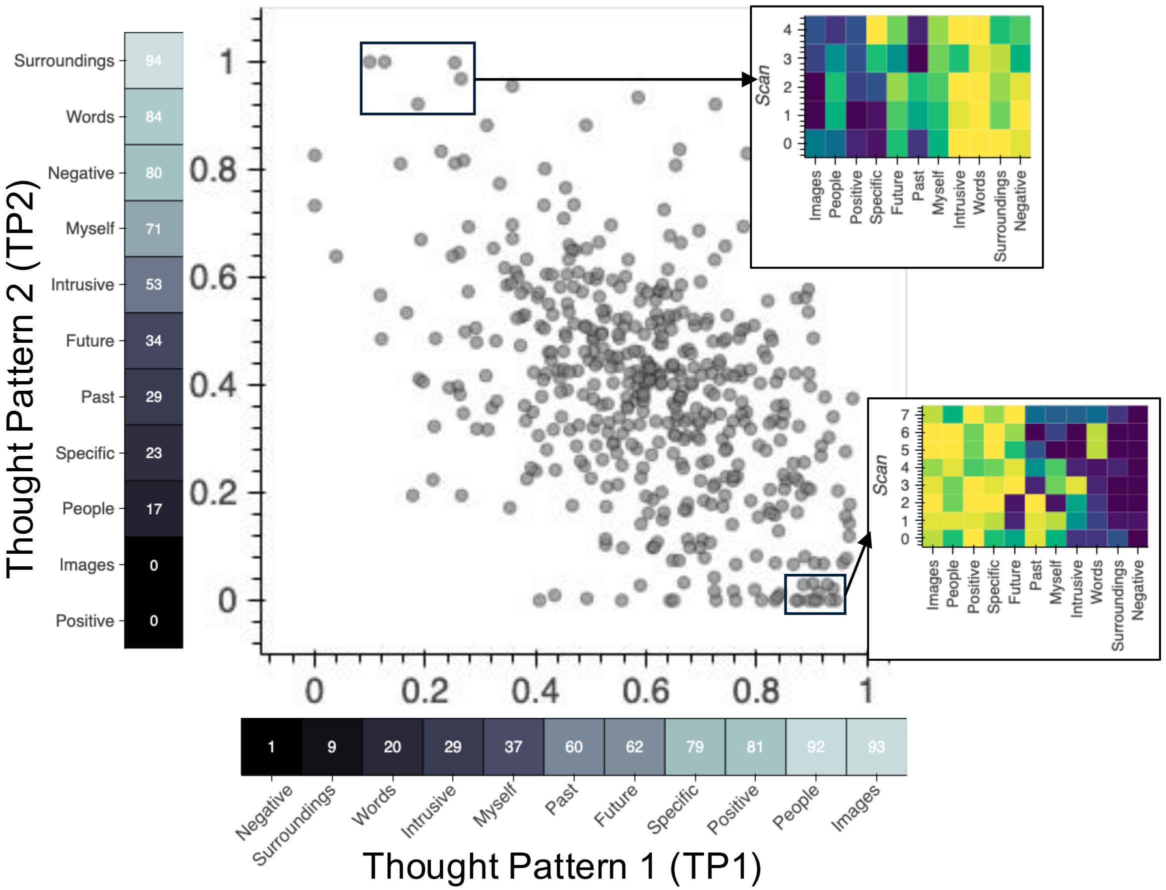

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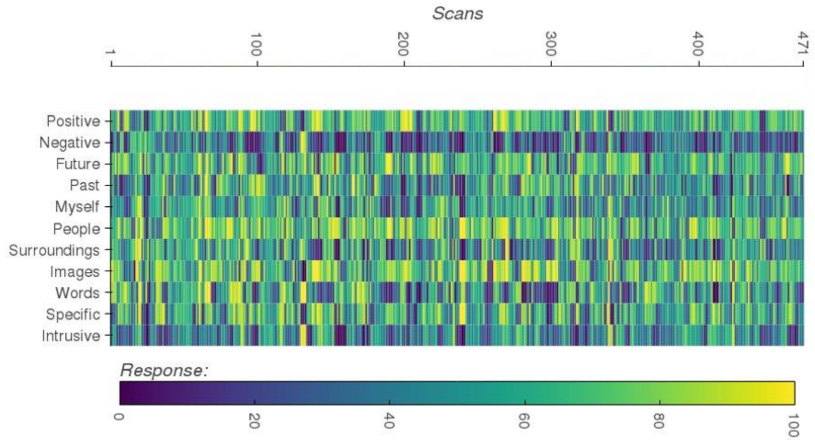
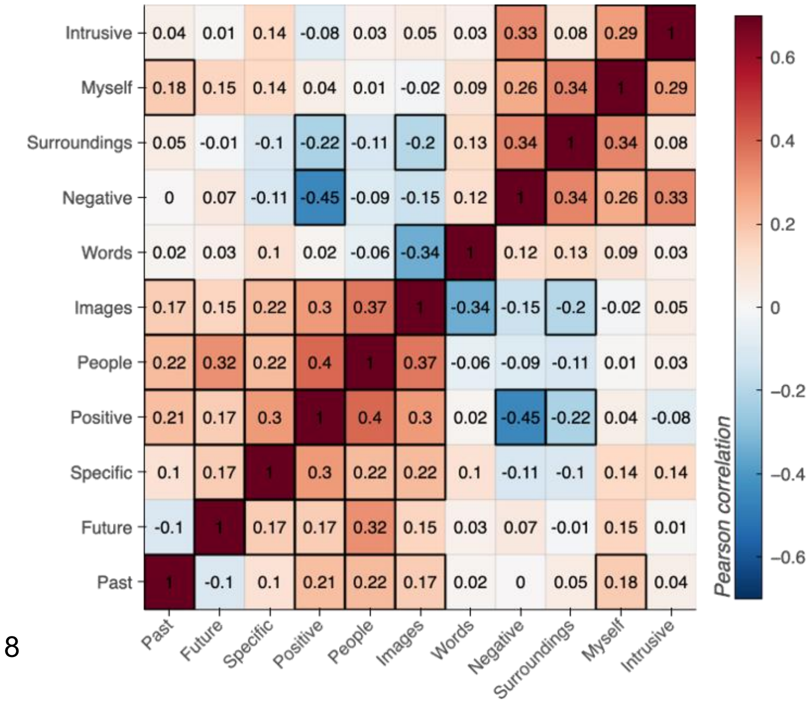
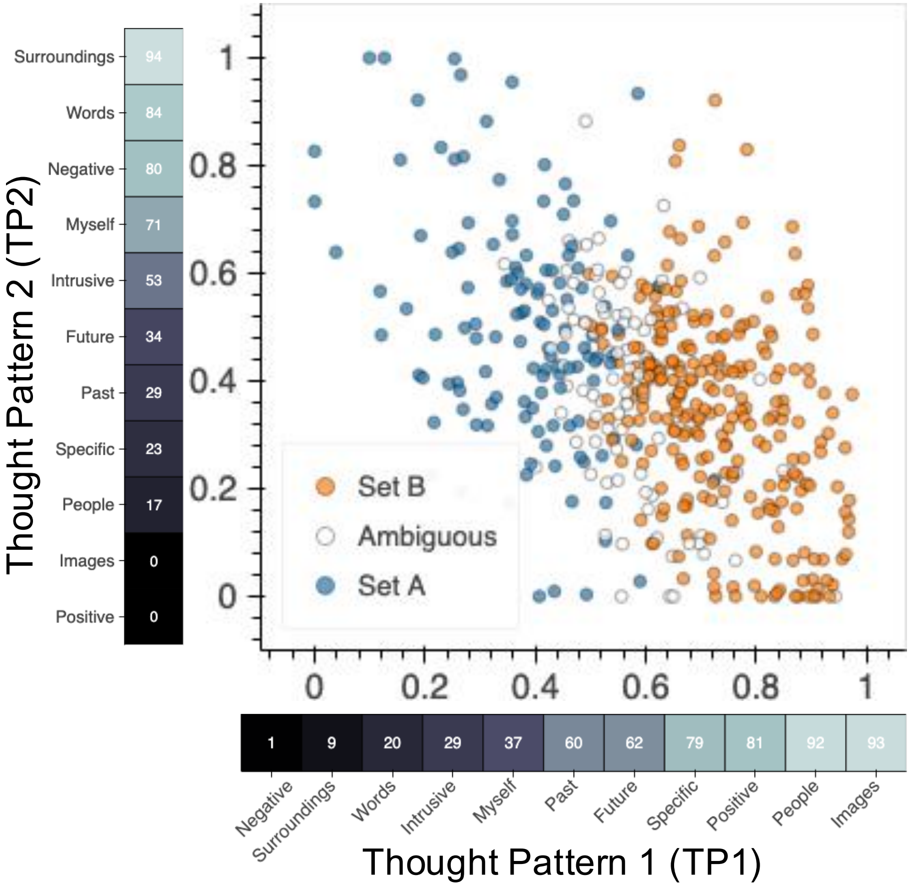
Introspective Data







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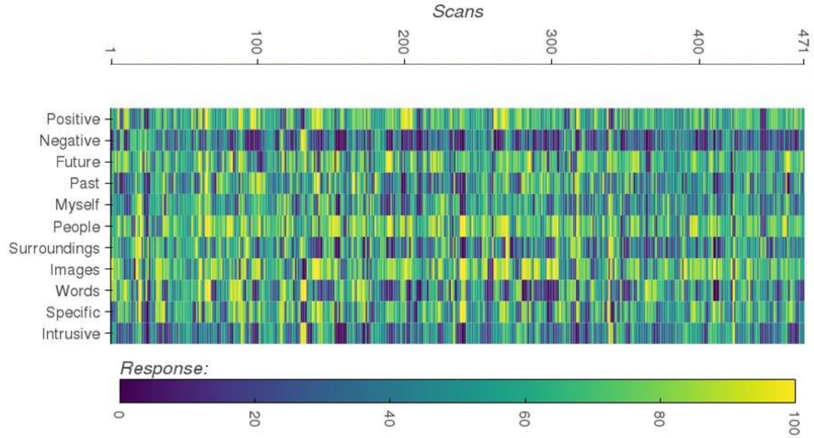
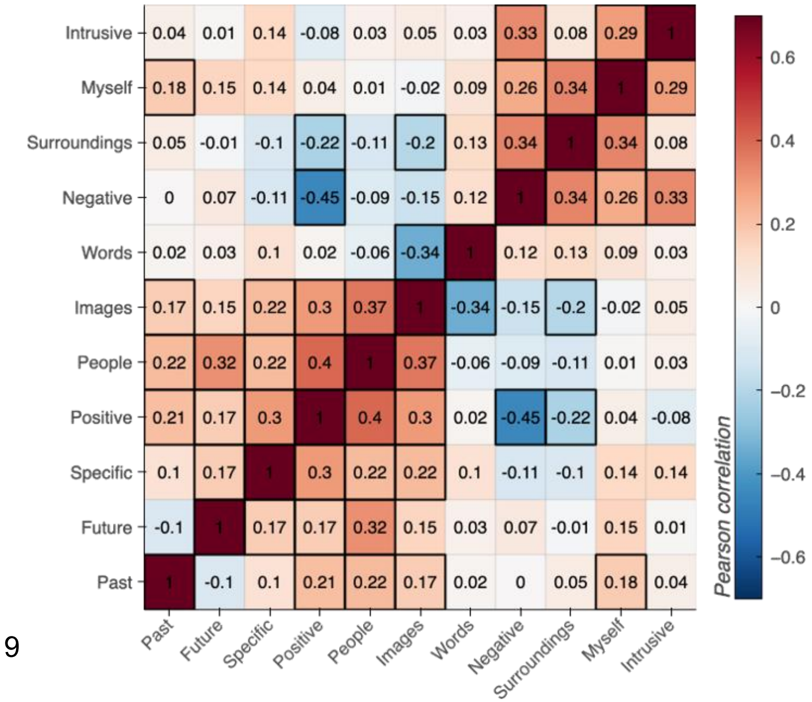
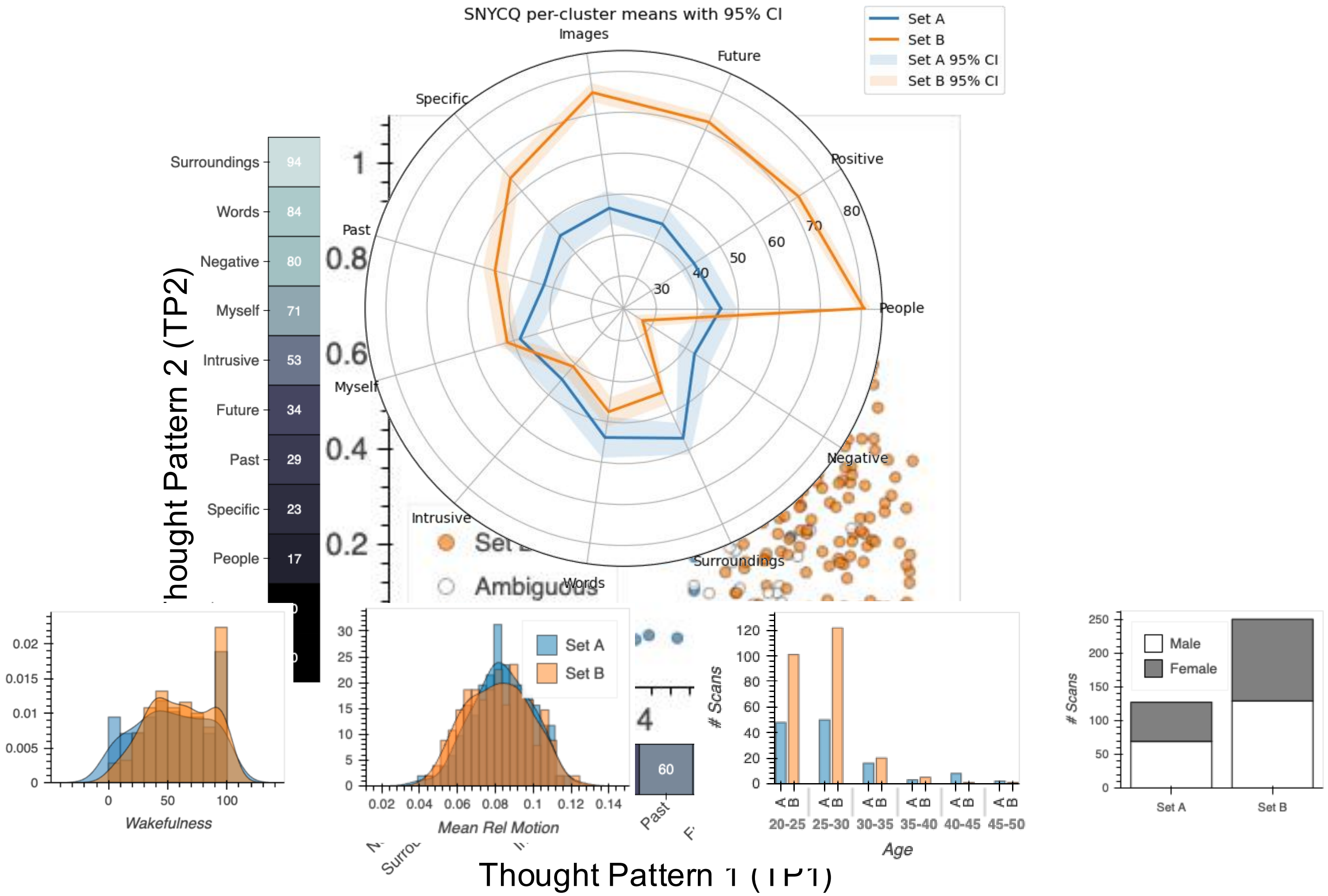
Introspective Data





	Past	Future	Specific	Positive	People	Images	Words	Negative	Surroundings	Myself	Intrusive
Intrusive	0.04	0.01	0.14	-0.08	0.03	0.05	0.03	0.33	0.08	0.29	1
Myself	0.18	0.15	0.14	0.04	0.01	-0.02	0.09	0.26	0.34	1	0.29
Surroundings	0.05	-0.01	-0.1	-0.22	-0.11	-0.2	0.13	0.34	1	0.34	0.08
Negative	0	0.07	-0.11	-0.45	-0.09	-0.15	0.12	1	0.34	0.26	0.33
Words	0.02	0.03	0.1	0.02	-0.06	-0.34	1	0.12	0.13	0.09	0.03
Images	0.17	0.15	0.22	0.3	0.37	1	-0.34	-0.15	-0.2	-0.02	0.05
People	0.22	0.32	0.22	0.4	1	0.37	-0.06	-0.09	-0.11	0.01	0.03
Positive	0.21	0.17	0.3	1	0.4	0.3	0.02	-0.45	-0.22	0.04	-0.08
Specific	0.1	0.17	1	0.3	0.22	0.22	0.1	-0.11	-0.1	0.14	0.14
Future	-0.1	1	0.17	0.17	0.32	0.15	0.03	0.07	-0.01	0.15	0.01
Past	1	-0.1	0.1	0.21	0.22	0.17	0.02	0	0.05	0.18	0.04



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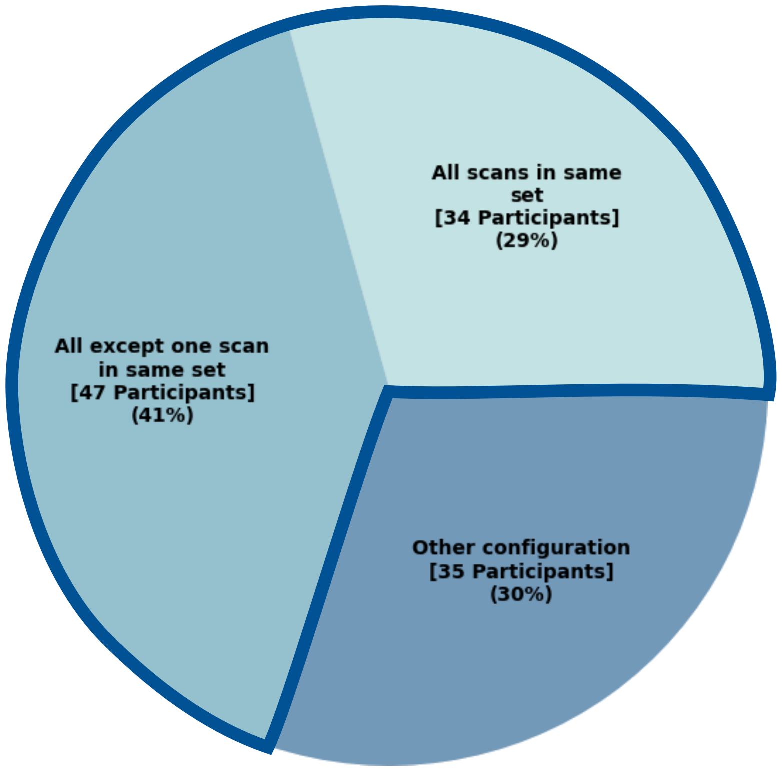
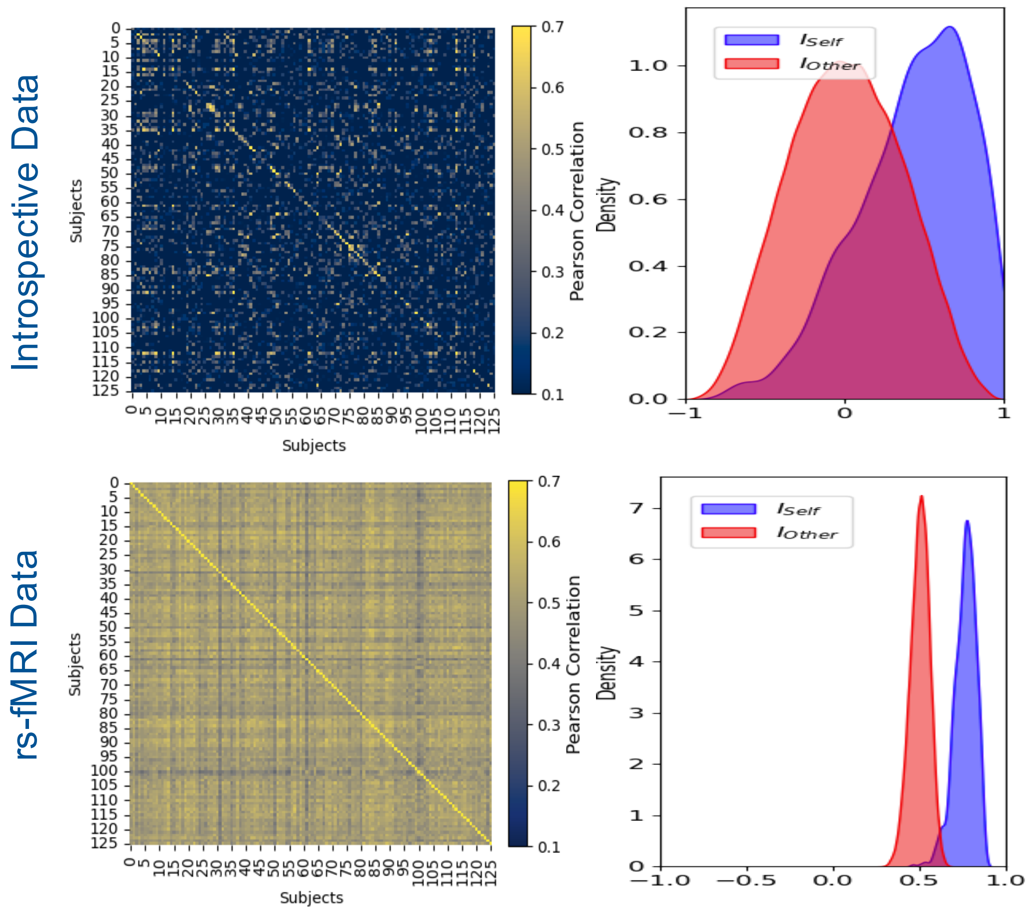
Q1 | Do subjects tend to be in the same mental state when asked to rest?

Repeated Set Membership



Identifiability Matrix

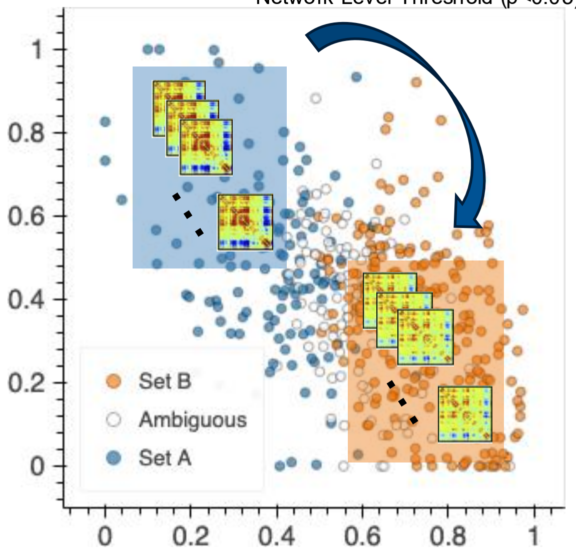


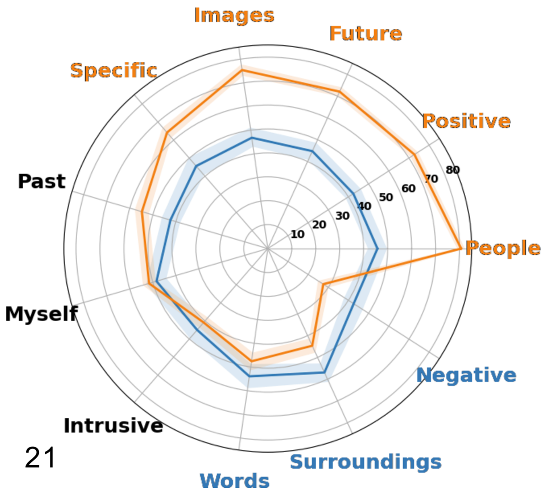
Gonzalez-Castillo et al. (under review Nature Comms)

National Institute of Mental Health

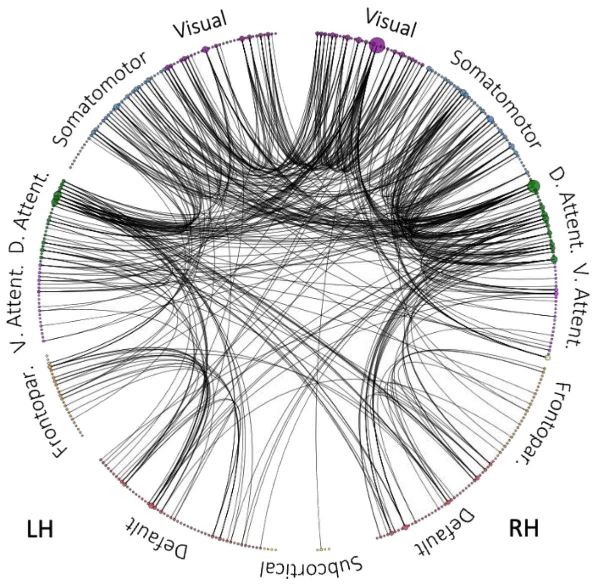
Q2 | Can we detect differences in FC if we group scans according to thought pattern?

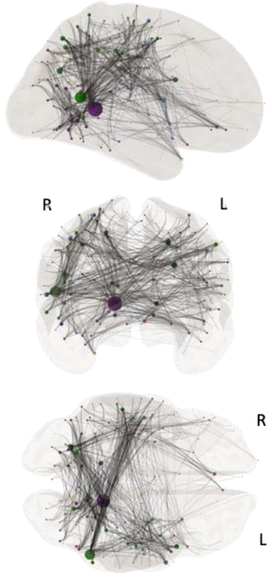
NBS | 5000 Permutations
Edge-Level Threshold (T=3.1; p < 0.001)
Network-Level Threshold (p<0.05)

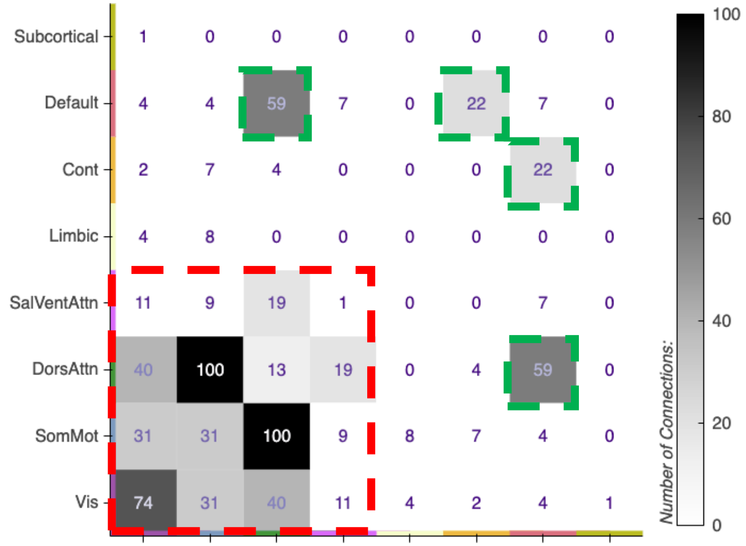




Set A > Set B

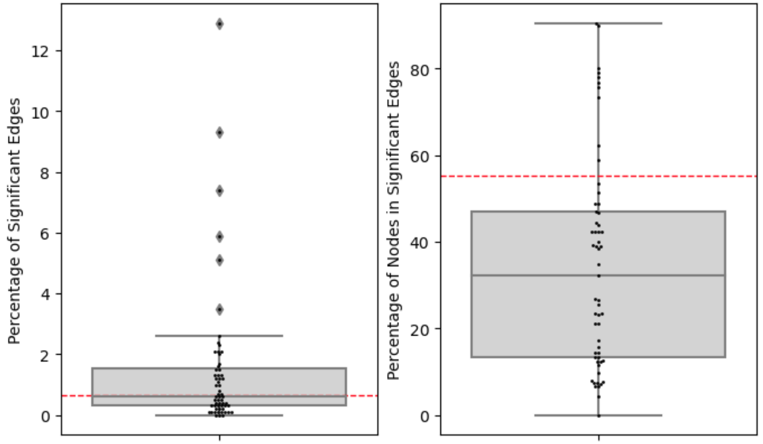






Laterality Index = -0.32 (right)
Number of Nodes = 210 (out of 380) → 55%
Number of Connections = 458 → 0.7%

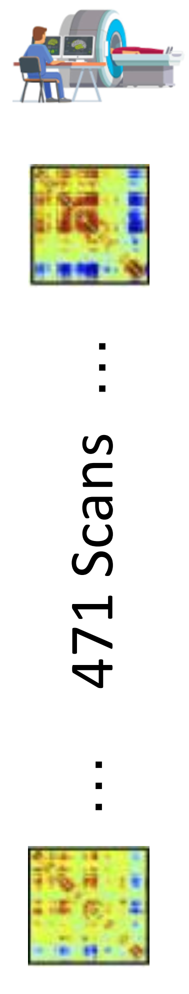
Comparison to Prior Literature



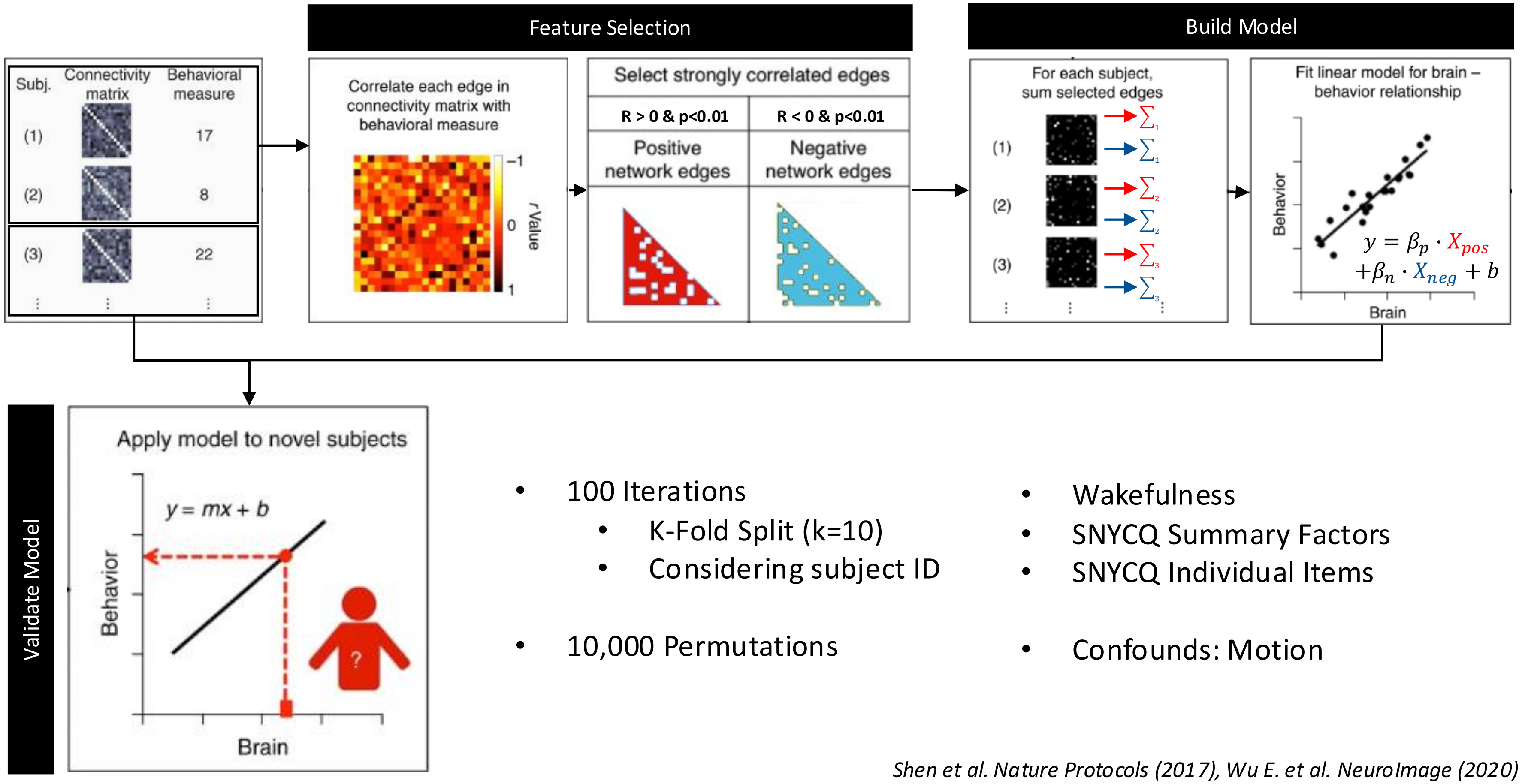
Gonzalez-Castillo et al.
(under review Nature Comms)

NIH National Institute of Mental Health

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



Connectome Predictive Modeling (CPM)



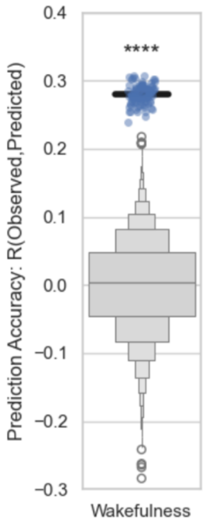
- 100 Iterations
  - K-Fold Split (k=10)
  - Considering subject ID
- 10,000 Permutations

- Wakefulness
- SNYCQ Summary Factors
- SNYCQ Individual Items
- Confounds: Motion

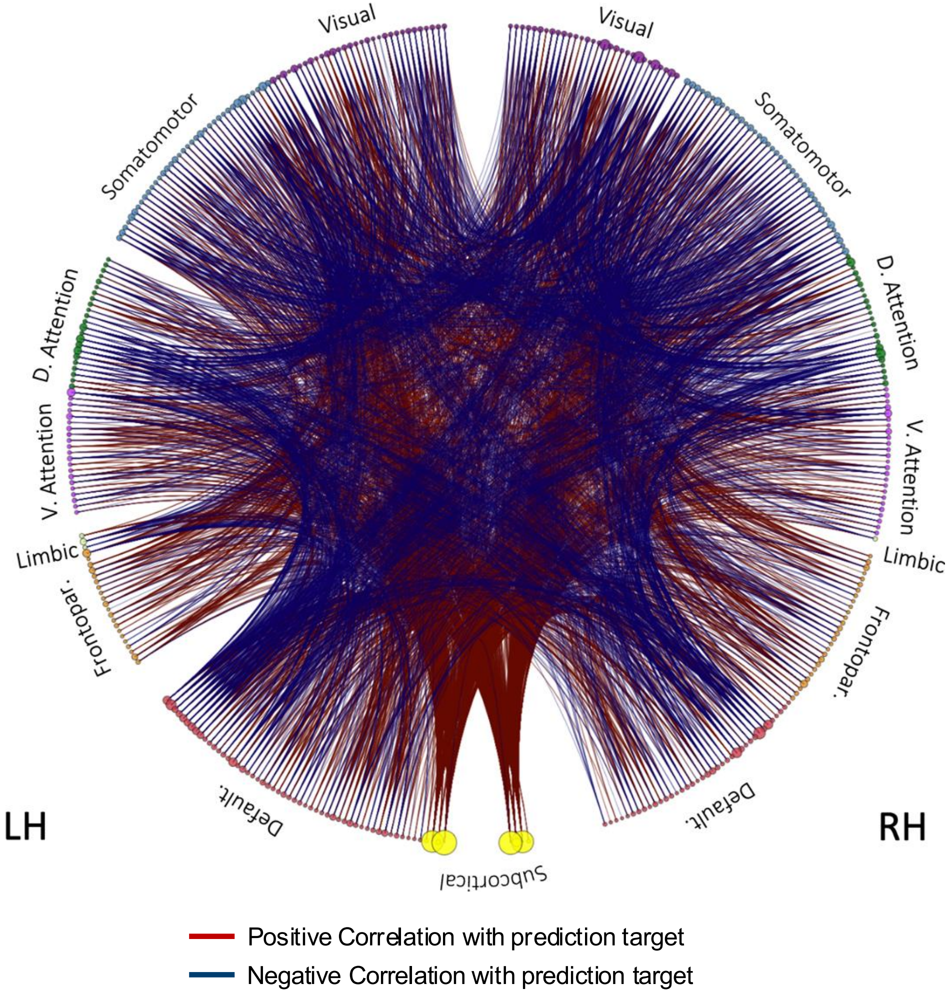
Shen et al. Nature Protocols (2017), Wu E. et al. NeuroImage (2020)

National Institute of Mental Health

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

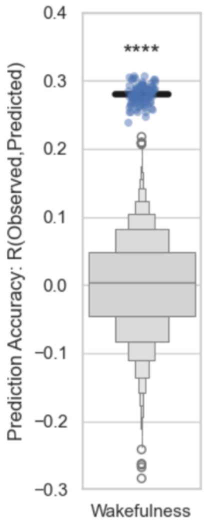


* p<0.05 | ** p<0.01 | *** p< $1e^{-3}$ | **** p < $1e^{-4}$



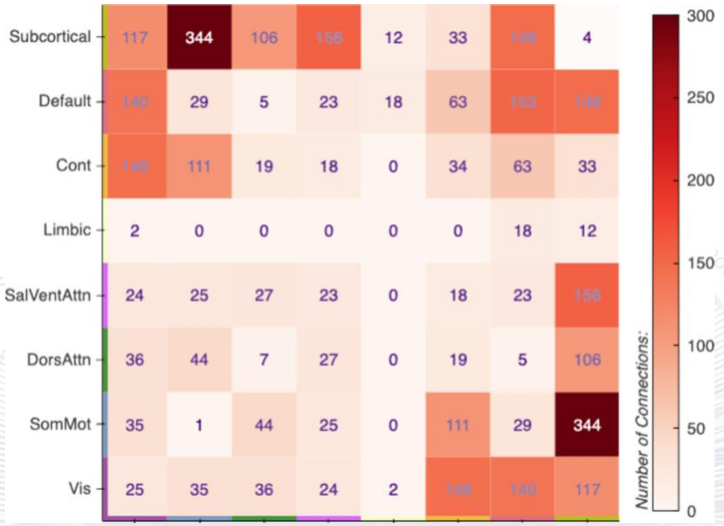
Gonzalez-Castillo et al. (under review Nature Comms)

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

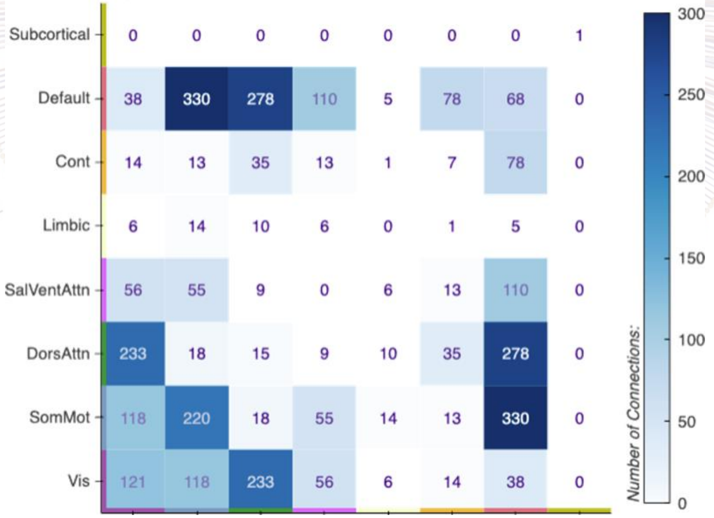


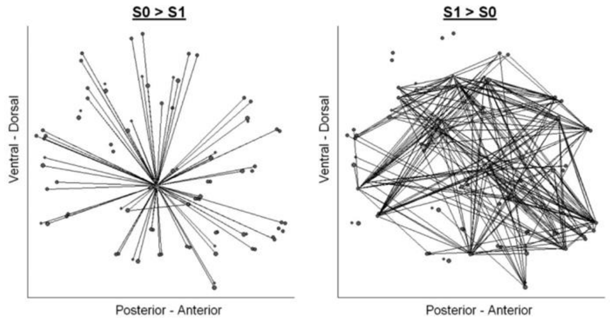
* p<0.05 | ** p<0.01 | *** p< 1e-3 | **** p < 1e-4

Positively Correlated Edges

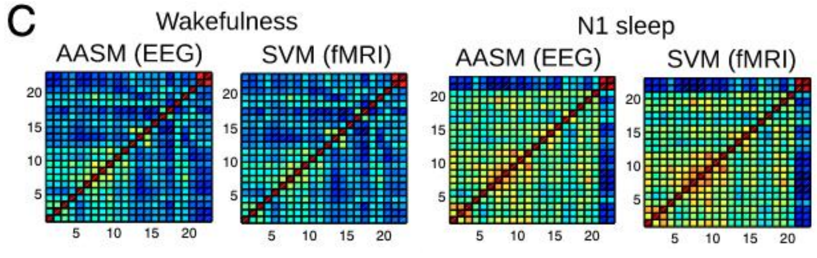


Negatively Correlated Edges

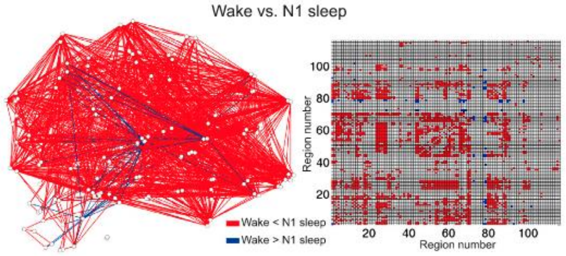




Spoormaker et al. J. of Neuroscience (2010)



Tagliazucchi et al. NeuroImage (2012)



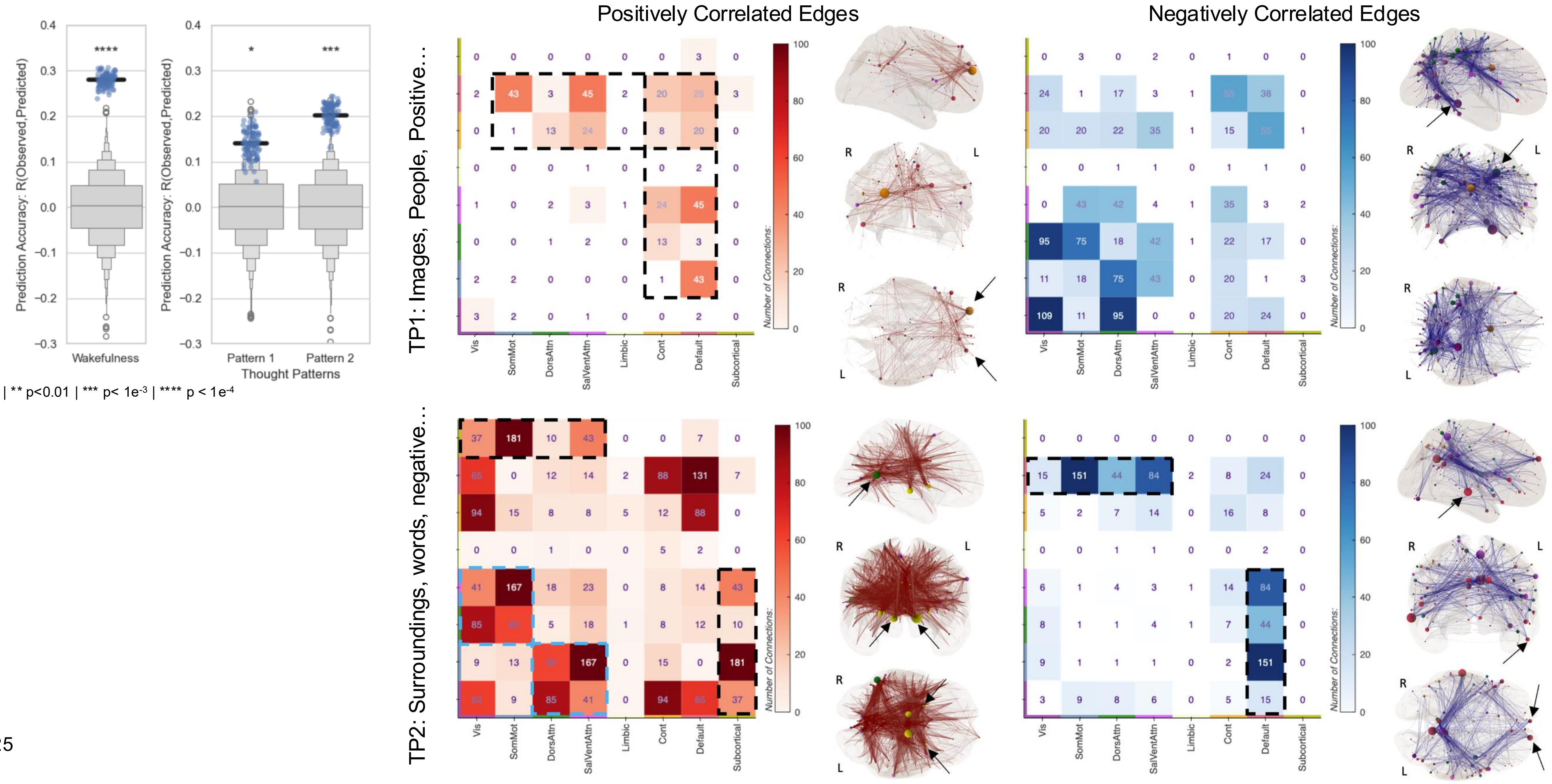
Tagliazucchi & Laufs, Neuron (2014)

As wakefulness decreases into light sleep:

- Thalamocortical connectivity sharply reduced
- Cortico-cortico connectivity increases

Gonzalez-Castillo et al. (under review Nature Comms)

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



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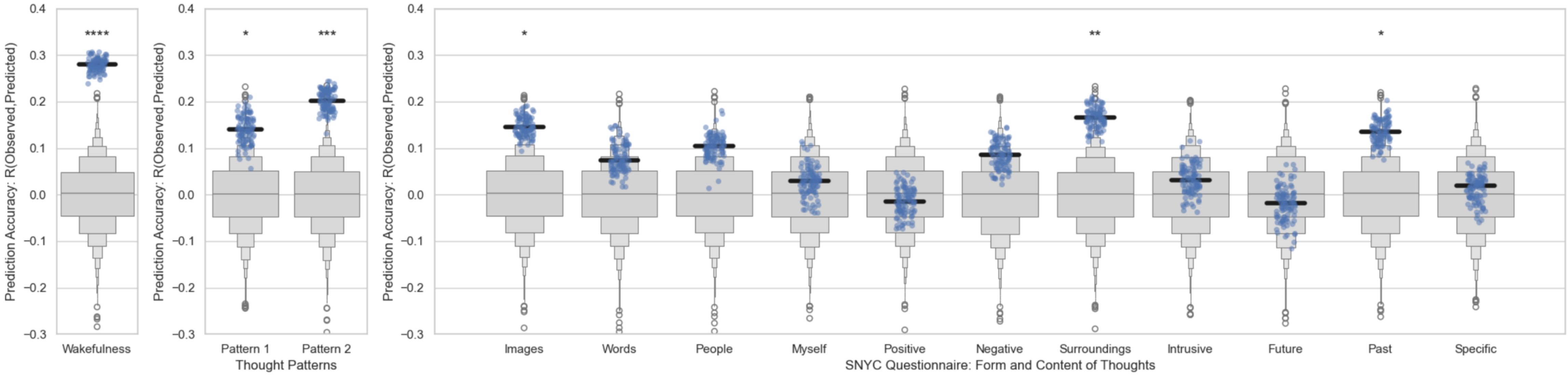
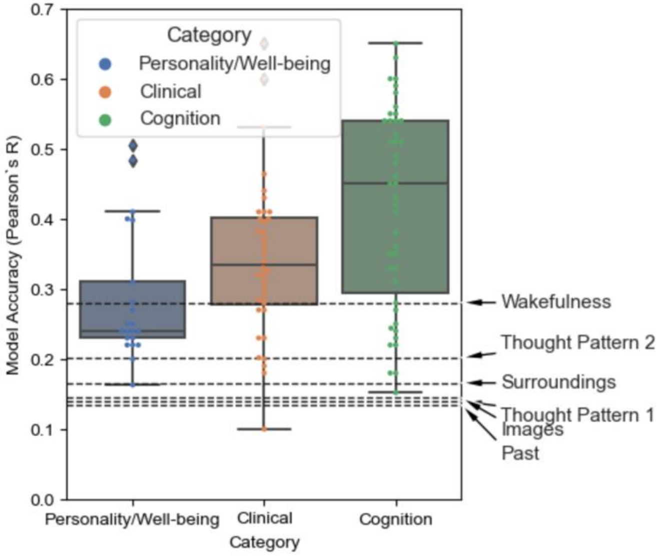
Q3 | Can we predict characteristics of ongoing thought based on FC measures?



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

Comparison to Prior Literature



Gonzalez-Castillo et al.
(under review Nature Comms)

NIH National Institute of Mental Health

Interim Summary

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 | TBD

Gonzalez-Castillo et al. (under review Nature Comms)

Interim Summary

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 | Could these observations be driven by correlations of in-scanner experience to other subclinical or phenotypic traits?

Gonzalez-Castillo et al. (under review Nature Comms)

Dataset: additional behavioral data

SCIENTIFIC DATA

OPEN **Data Descriptor: A functional connectome phenotyping dataset including cognitive state and personality measures**

Received: 27 October 2017
Accepted: 5 November 2018
Published: 12 February 2019

Natacha Mendes[1], Sabine Oligschläger[1,2,3], Mark E. Lauckner[1], Johannes Golchert[1], Julia M. Huntenburg[1,4], Marcel Falkiewicz[1], Melissa Ellamil[1], Sarah Krause[1], Blazej M. Baczkowski[1,2,3], Roberto Cozatl[5], Anastasia Osoianu[1,6], Deniz Kumral[7,8], Jared Pool[1], Laura Golz[9,10], Maria Dreyer[7], Philipp Haueis[1,8], Rebecca Jost[1], Yelyzaveta Kramarenko[1], Haakon Engen[11,12], Katharina Ohrnberger[1,8], Krzysztof J. Gorgolewski[13], Nicolas Farrugia[14], Anahit Babayan[7], Andrea Reiter[7,15], H. Lina Schaare[2,7], Janis Reinelt[7], Josefin Röbbig[7], Marie Uhlig[2,7], Miray Erbey[7], Michael Gaebler[7,8], Jonathan Smallwood[16], Arno Villringer[7,8] & Daniel S. Margulies[1]

Neuroimaging Data

Demographic Data

Introspective Data

Abbreviation	Behavioral Measure	N
Personality and Habitual Behaviors		
AMAS	Abbreviated Math Anxiety Scale[9]	145
ASR	Adult Self Report adapted from[13]	213
BDI	Beck Depression Inventar-II[14–16]	210
BIS/BAS	Behavioral Inhibition and Approach System[17–20]	288
BCQ	Body Consciousness Questionnaire[21]	79
BP	Boredom Proneness Scale[22]	209
SCS	Brief Self-Control Scale[23,24]	214
ESS	Epworth Sleepiness Scale[25,26]	210
FBI	Facebook Intensity Scal	
Gold-MSI	Goldsmiths Musical So	
HADS	Hospital Anxiety and I	
IAT	Internet Addiction Test	
IMIS	Involuntary Musical In	
MPU	Mobile Phone Usage	
MGIQ	Multi-Gender Identity	
MMI	Multimedia Multitaskin	
NEO PI-R	NEO Personality Inven	
PSSI	Personality Style and D	
SE	Self-Esteem Scale[38]	
SD3	Short Dark Triad[39]	
SDS	Social Desirability Scale	
TPS	Tuckman Procrastinati	
UPPS-P	UPPS-P Impulsive Beh	

31 Behavioral Surveys

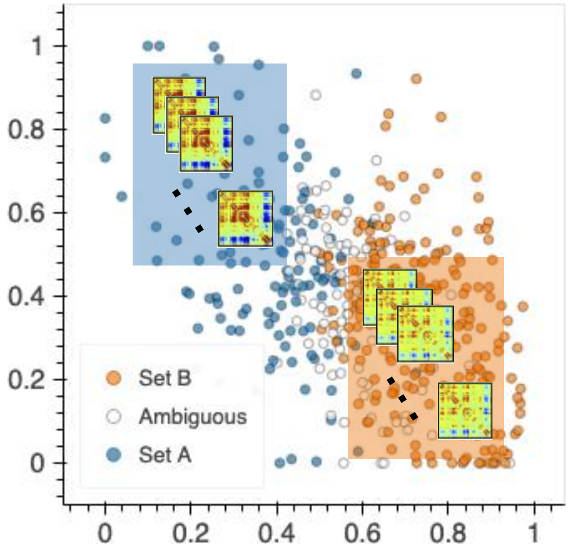
- Personality / Habitation Behaviors (21)
- Mind Wandering / Mindfulness (4)
- Synesthesia (1)
- Cognitive Controls / Sustained Att. (1)
- Creativity (4)

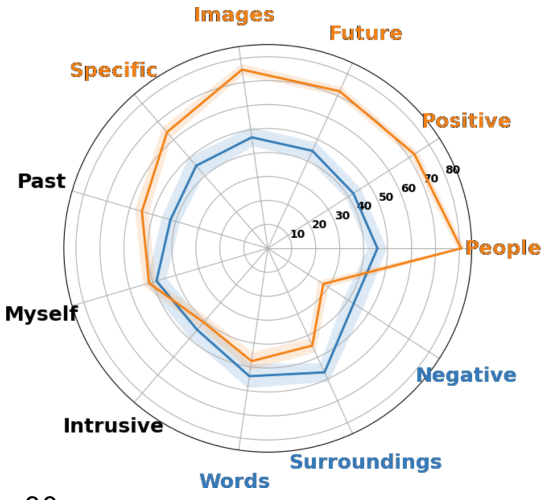
51 Behavioral Metrics

- Available in at least 70%

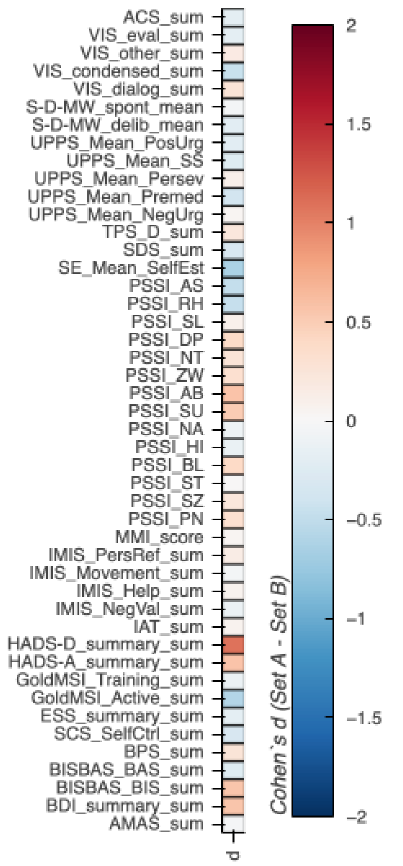
CATEGORY	SURVEY	# METRICS	SURVEY NAME
PERSONALITY / HABITUATION BEHAVIORS	AMAS	1	Abbreviated Math Anxiety Scale
	BDI	1	Beck Depression Inventory II
	BISBAS	2	Behavioral Inhibition and Approach System
	BPS	1	Boredom Proneness Scale
	SCS	1	Brief Self-Control Scale
	ESS	1	Epworth Sleepiness Scale
	GoldMSI	2	Goldsmiths Musical Sophistication Index
	HADS	2	Hospital Anxiety and Depression Scale
	IAT	1	Internet Addition Test
	IMIS	4	Involuntary Musical Imagery Scale
	MPU	19	Mobile Phone Usage
	MNI	1	Multimedia Multitasking Index
	NEO	5	NEO Personality Inventory (Revised)
	PSSI	14	Personality Style and Disorder Inventory
	SE	1	Self-Esteem Scale
	SDS	1	Social Desirability Scale
	TPS	1	Tuckman Procrastination Scale
	UPPS	5	Impulsive Behavior Scale
MINDFULNESS	SDMW	5	Spontaneous and Deliberate Mind-Wandering
	VISQ	4	Varieties of Inner Speech Questionnaire
COGNITIVE CONTROL	ACS	1	Attention Control Scale

Influence of trait-level phenotypes in group differences

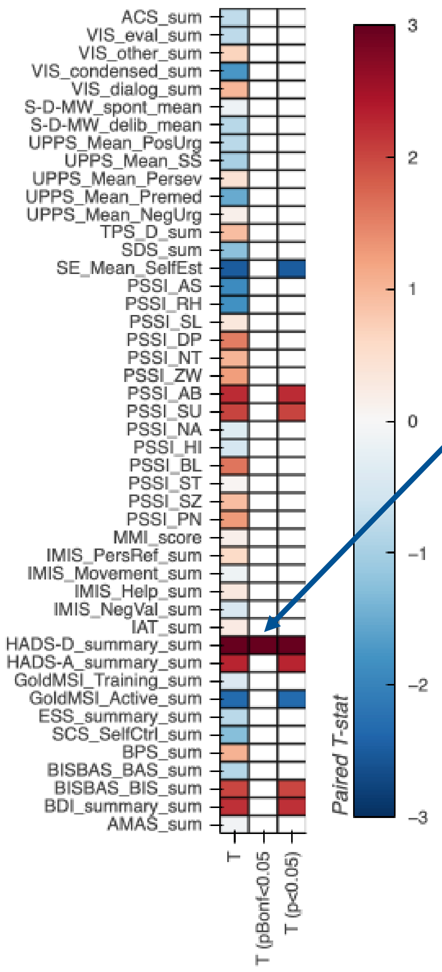




Cohen's d (A – B)



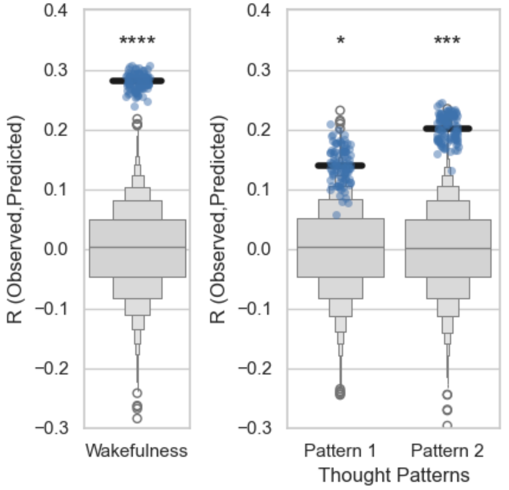
T-test

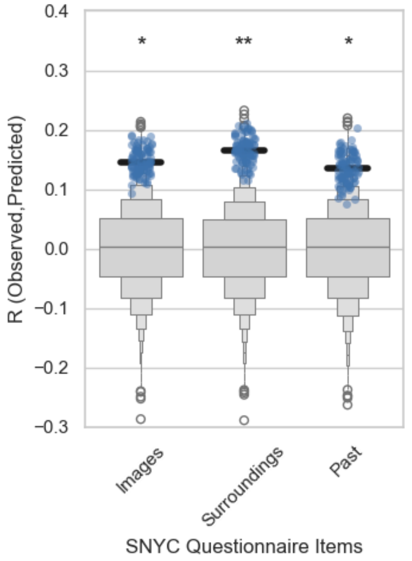


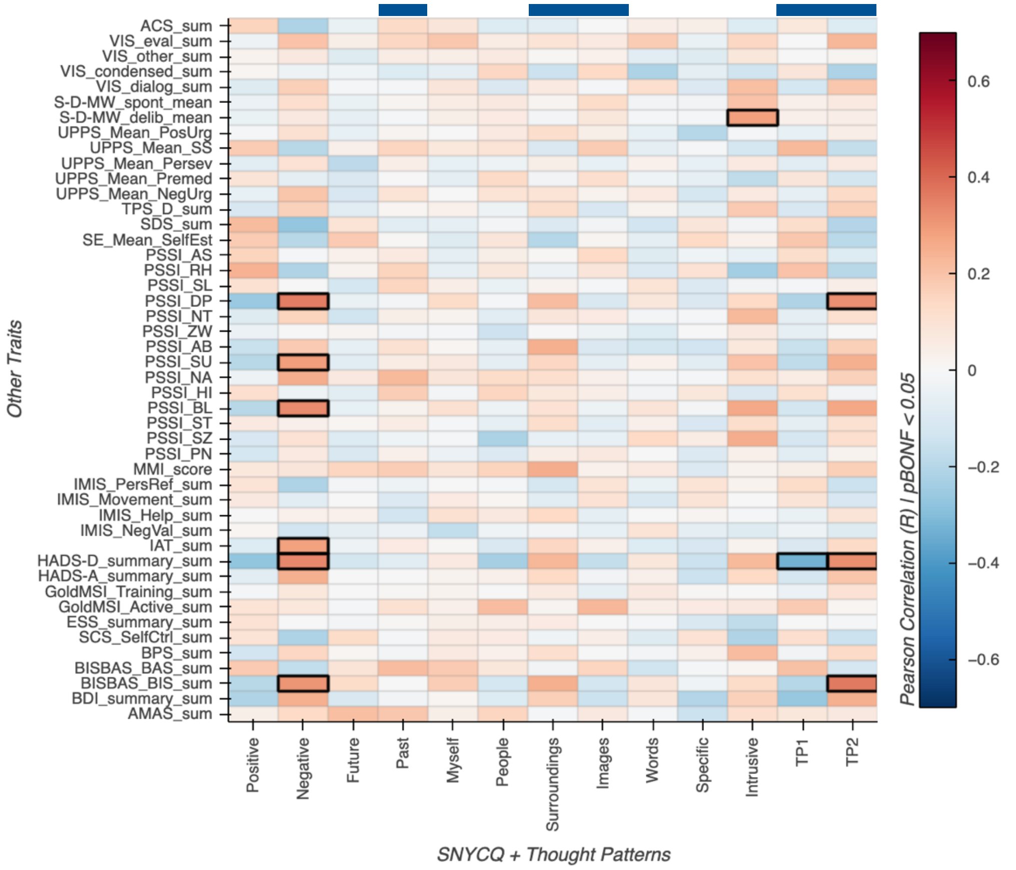
Hospital Anxiety and Depression Scale (HADS)

"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."

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

Conclusions

In-scanner subjective experience meaningfully shapes resting-state functional connectivity

- **Systematic differences in thought content produced widespread FC differences,** even when healthy groups were similar in motion, wakefulness, age, and gender.
- **FC could significantly predict several experiential measures** beyond wakefulness, including both latent thought-pattern dimensions, and specific items such as images and surroundings.
- **Observations could not be explained by correlations to other trait-level phenotypes**.

Practical implication: rs-fMRI studies should collect brief post-scan experiential reports

- Modeling in-scanner experience may reduce unexplained variance and improve biomarker interpretation.
- Small cost compared to that of an *rs-fMRI* scan.
- Increases the research value of *rs-fMRI* scans → study other aspects of spontaneous thought

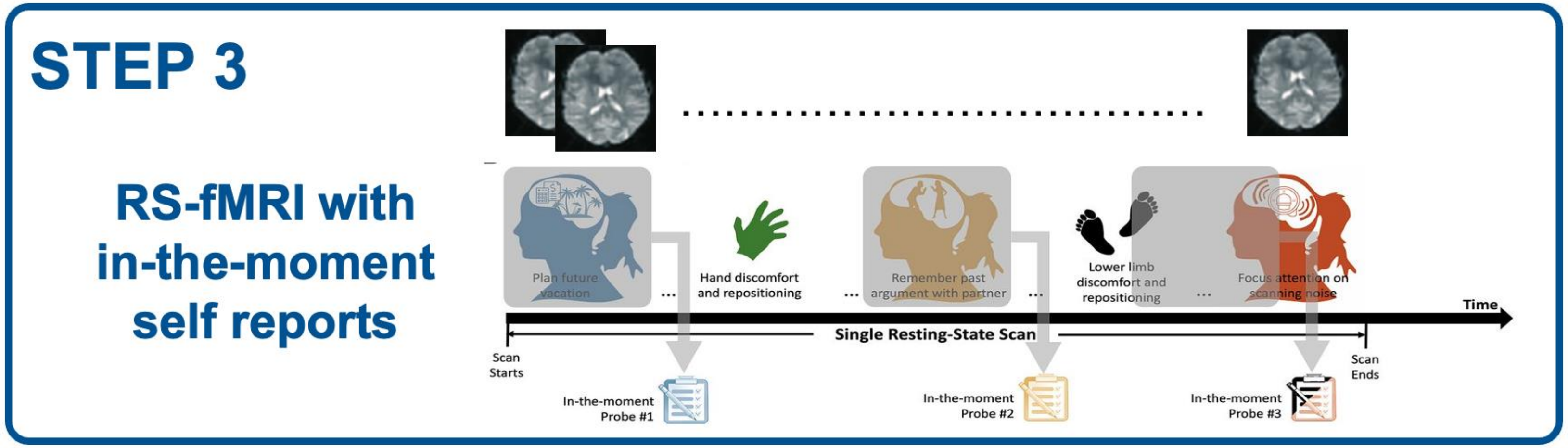
Future work / Open Questions

Brain – Mind relationships as a function of spatio-temporal scales

Activity vs. Connectivity

Dynamic vs. Static

In the moment vs. Retrospective



Future work / Open Questions

Brain – Mind relationships as a function of spatio-temporal scales

Activity vs. Connectivity

Dynamic vs. Static

In the moment vs. Retrospective

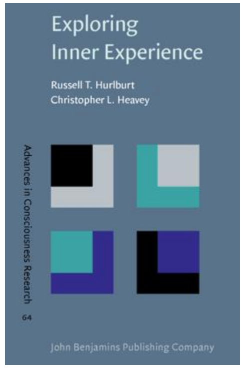
Reliability, Precision, etc. of Introspective Data

MDES vs. Open Ended

Training

What aspects matter most

Covert Measures

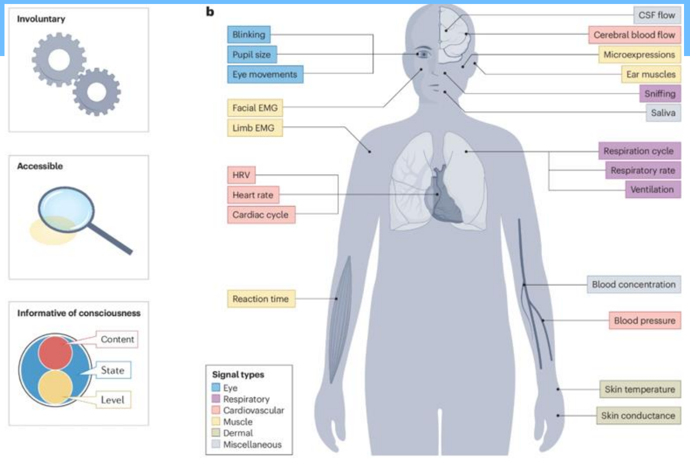


Resting-State Q	Amsterdam Resting-State Q	NYC-Q
62 Items	50 Items	31 Items
5 Mental Activities + Content	Thoughts + Feelings	Content and Form of Thoughts

Delamillieure et al. (2009) Brain Research Bulletin

Diaz et al. (2013) Frontiers in Human Neuroscience

Gorgolewski et al. PLoS ONE (2014)



Kronemer, Bandettini & Gonzalez-Castillo, 2025 Nat Rev Neuroscience

Future work / Open Questions

Brain – Mind relationships as a function of spatio-temporal scales

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What aspects matter most

Covert Measures

Reciprocal Causation Problem

Thank you…

NIMH

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