Can we extract individual differences with fMRI? Can we go on to create "biomarkers"?

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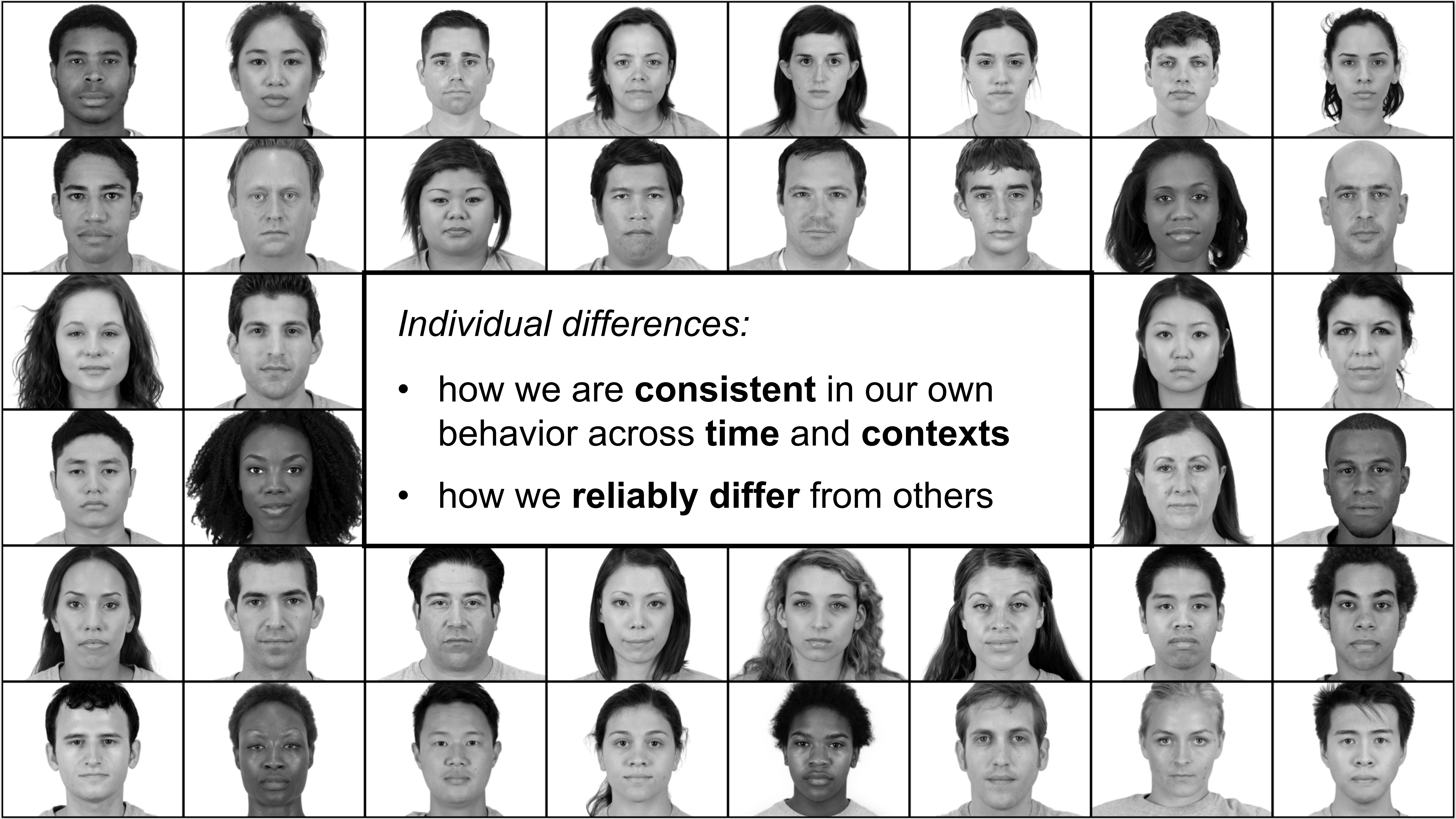
National Institute of Mental Health

NIH Summer Neuroimaging Course
August 6, 2019

@esfinn

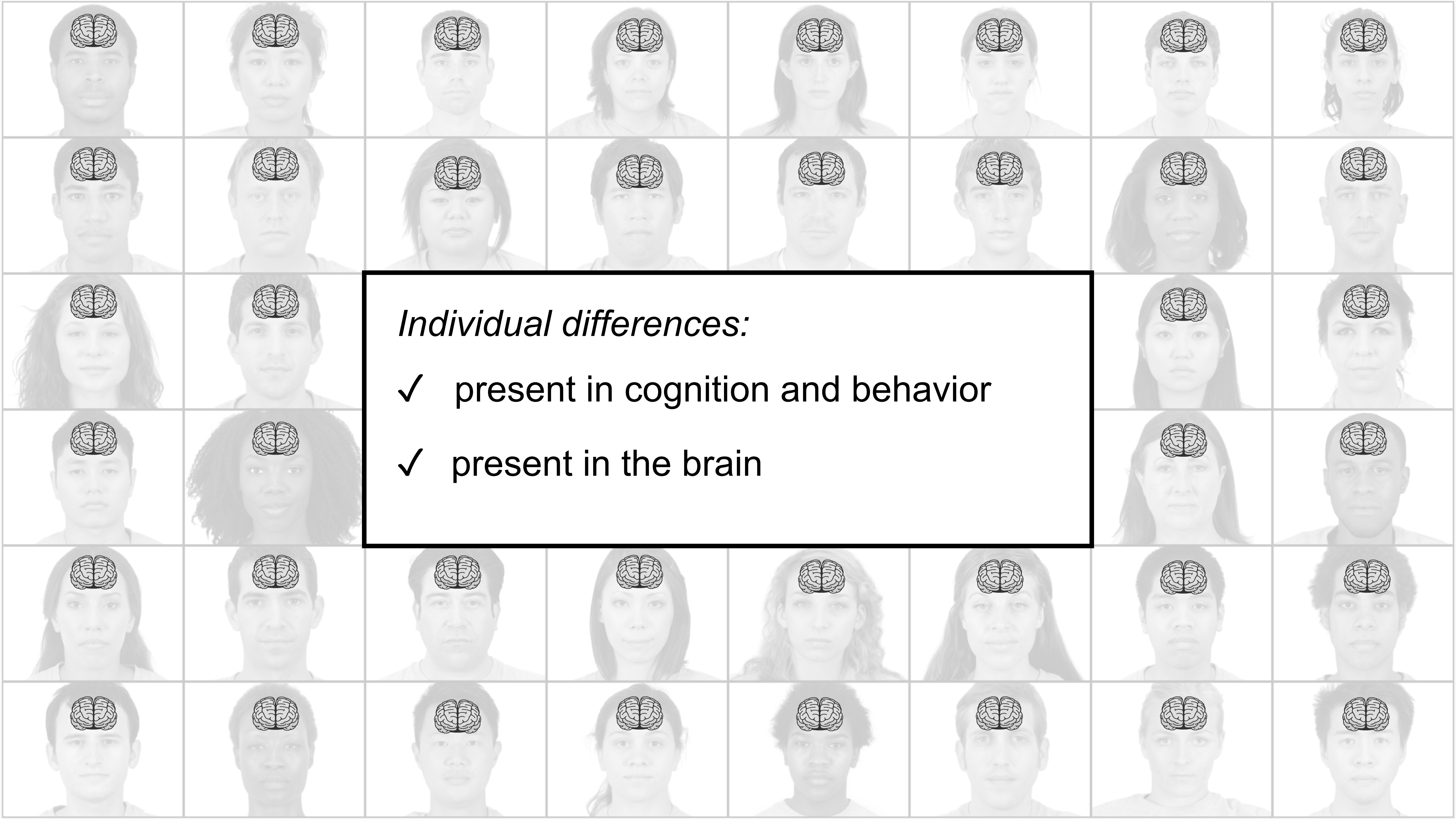


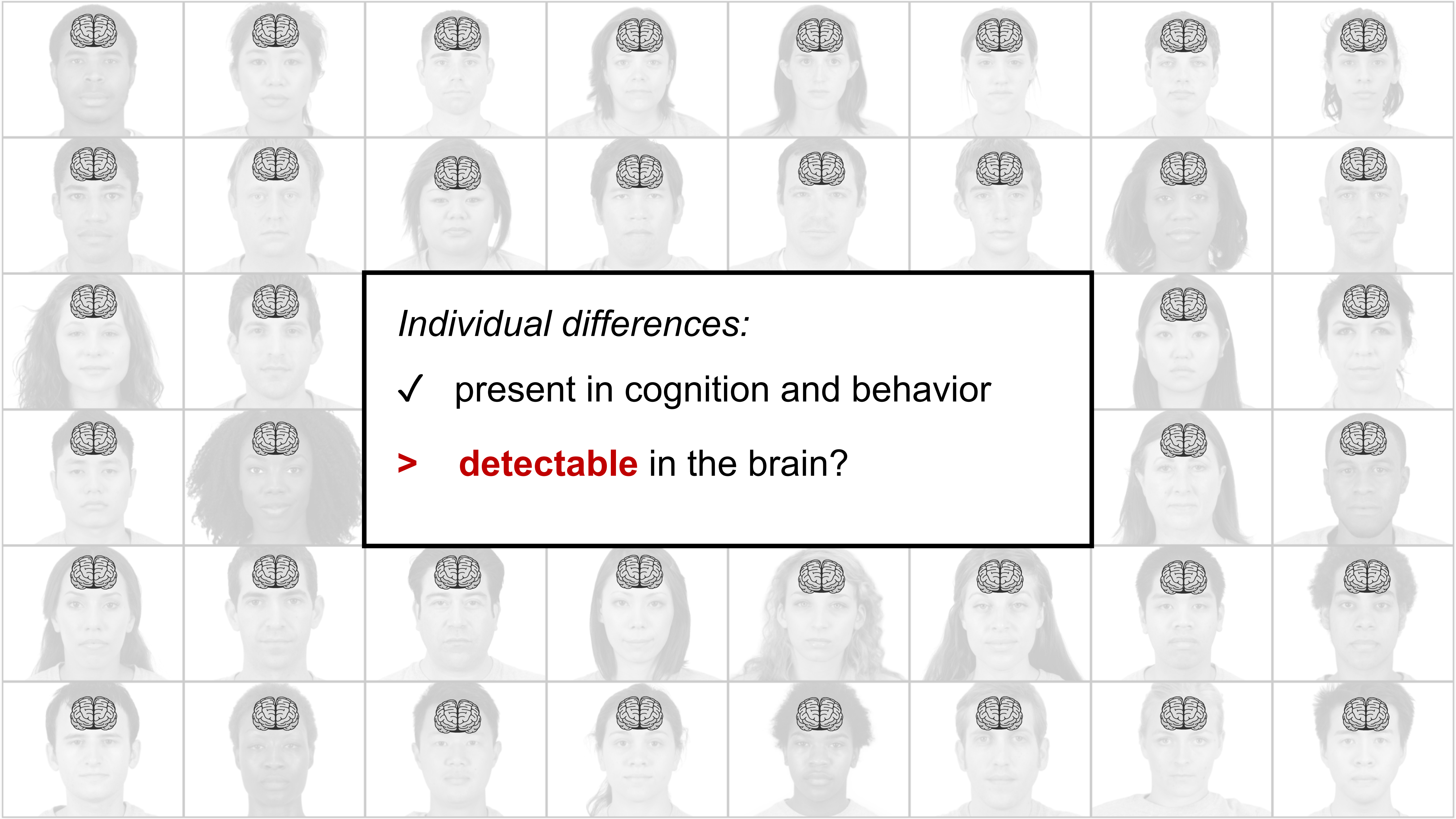
Individual differences:

- how we are **consistent** in our own behavior across **time** and **contexts**
- how we **reliably differ** from others

Individual differences:

✓ present in cognition and behavior


Individual differences:
✓ present in cognition and behavior
✓ present in the brain


Individual differences:
✓ present in cognition and behavior
> **detectable** in the brain?

Outline

1. **Why** should we care about individual differences?

2. **What** do we know about individual differences?

3. **Where** are the open questions & controversies?

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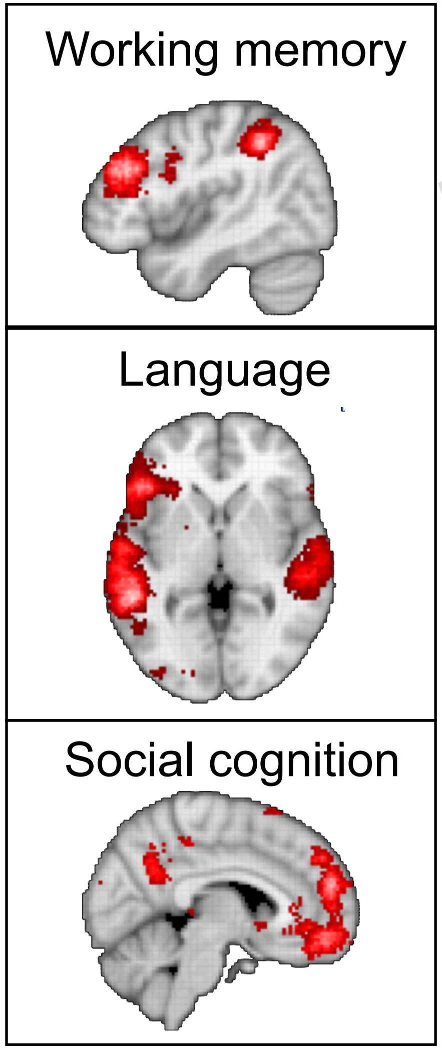
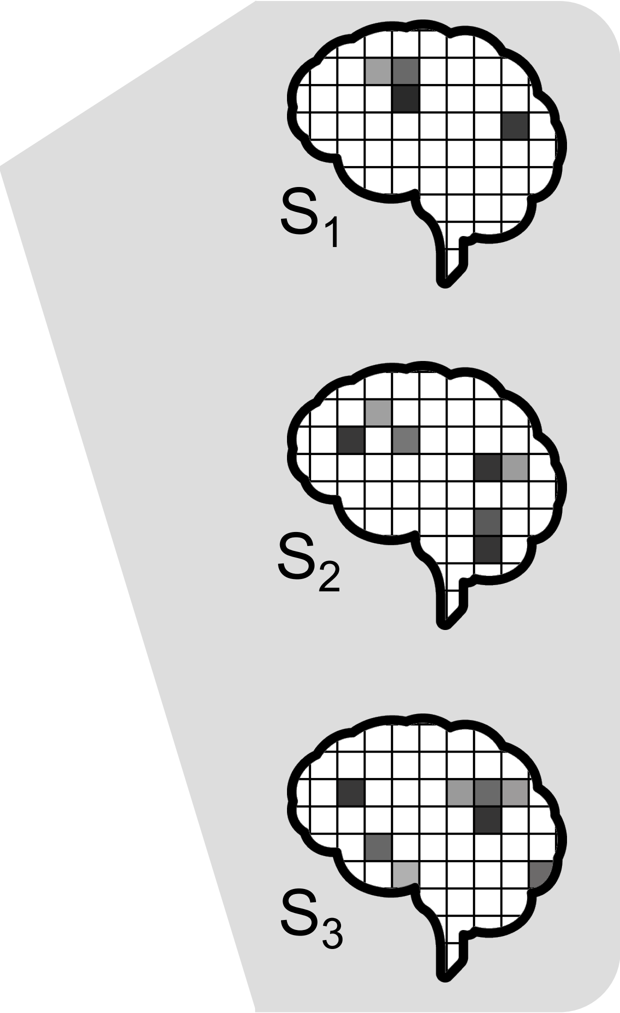
Toward a deeper understanding of cognition

Group average



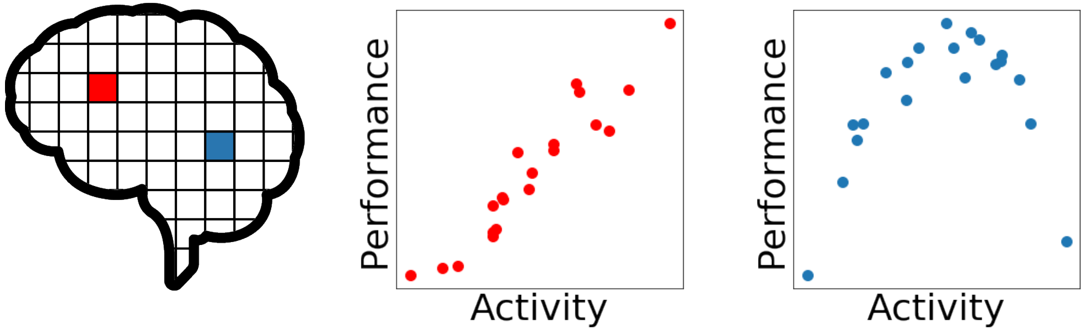
neurosynth.org

Individual maps



Degeneracy:

- Task performance?



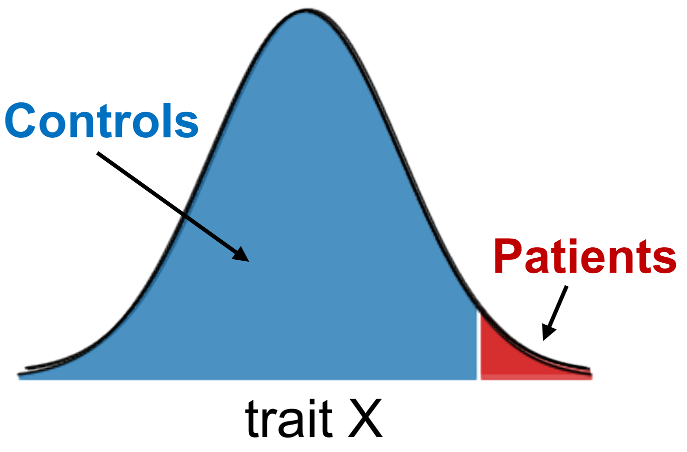
- Cognitive strategies, styles?
- Within-subject changes (i.e., learning)?

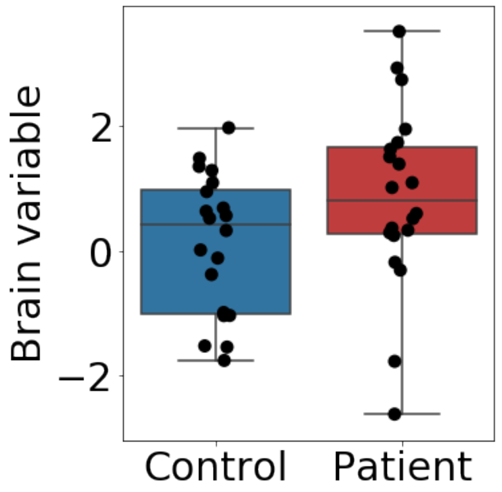
Univariate or multivariate relationships

Activity, connectivity, other features

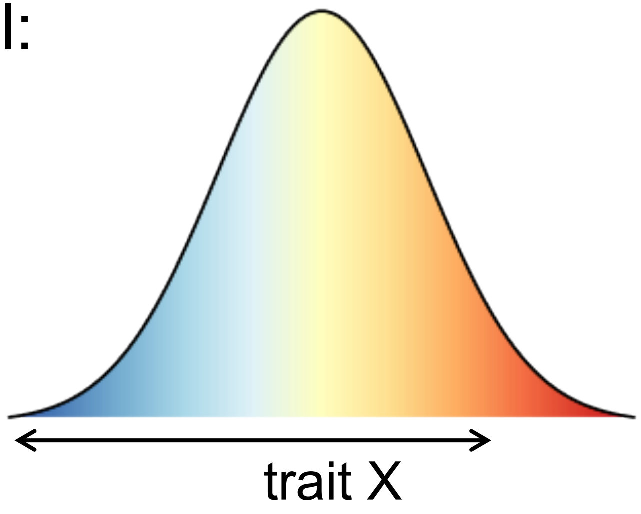
Insight into mental illness

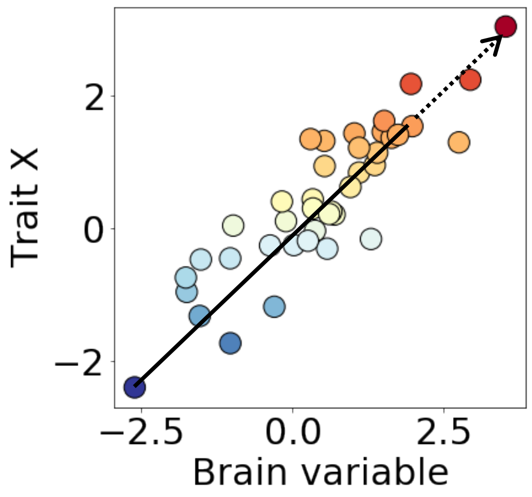
Categorical:





Dimensional:





Translational tools?

Insel et al., *Am J Psychiat* (2010)
Gabrieli et al., *Neuron* (2015)
Finn & Constable, *Dial Clin Neurosci* (2016)
Woo et al., *Nat Neurosci* (2017)

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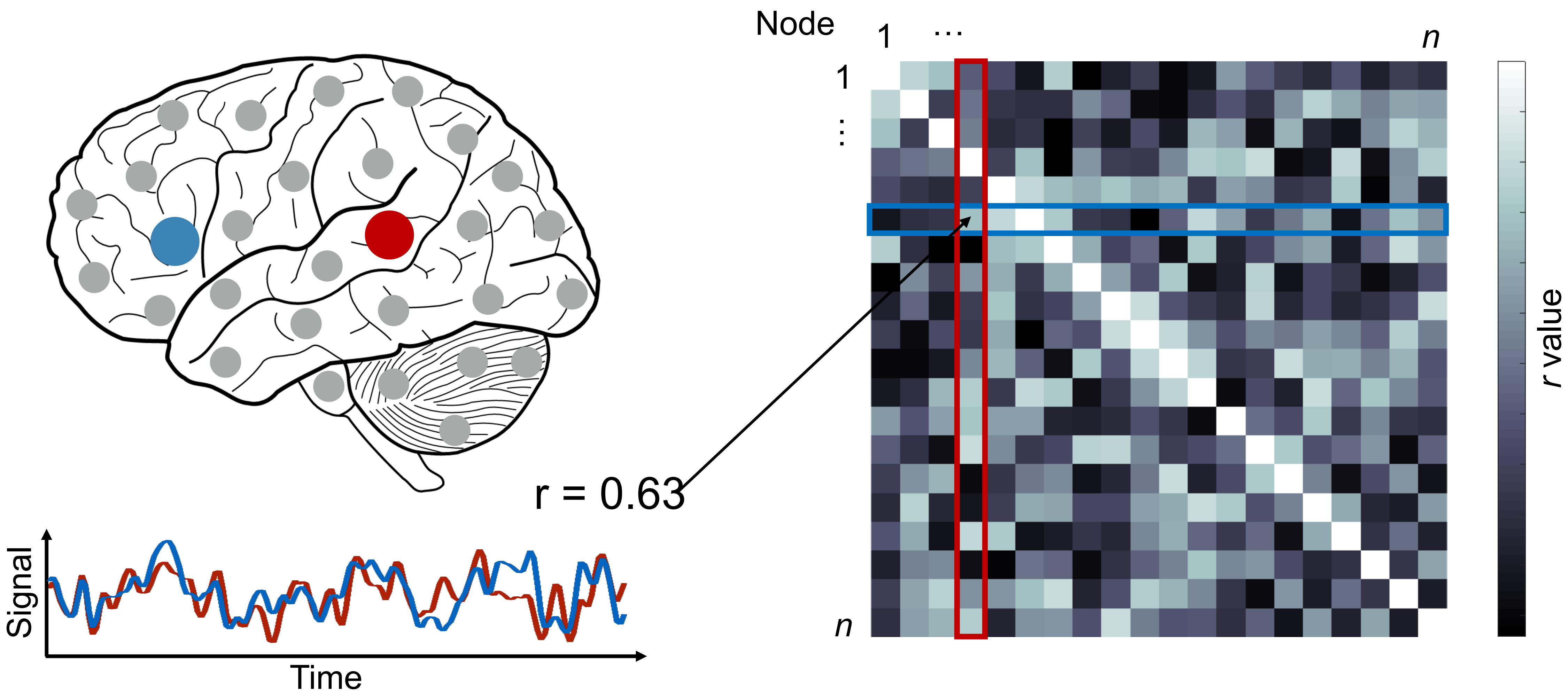
Functional connectivity



Functional connectome "fingerprints"

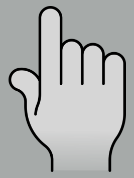
- n = 126 healthy adults
- 22-35 years old
- 50 sets of twins

Day 1

Resting (**R1**)

Working memory (**WM**)

Motor (**Mt**)

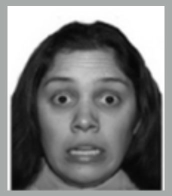


Day 2

Resting (**R2**)

Language (**Lg**)

Emotion (**Em**)



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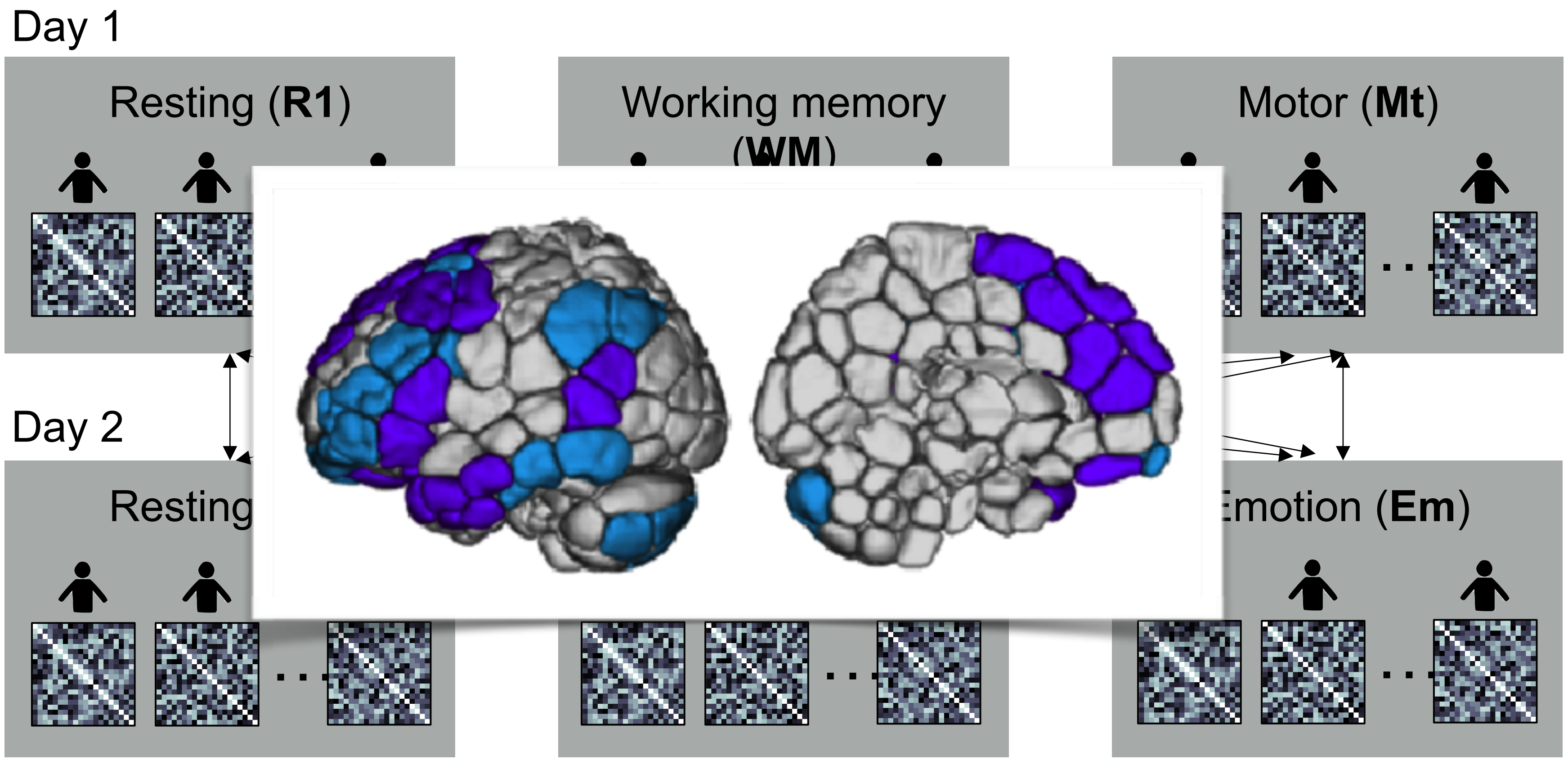
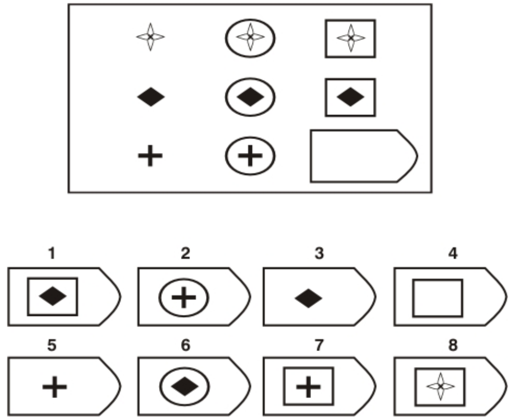


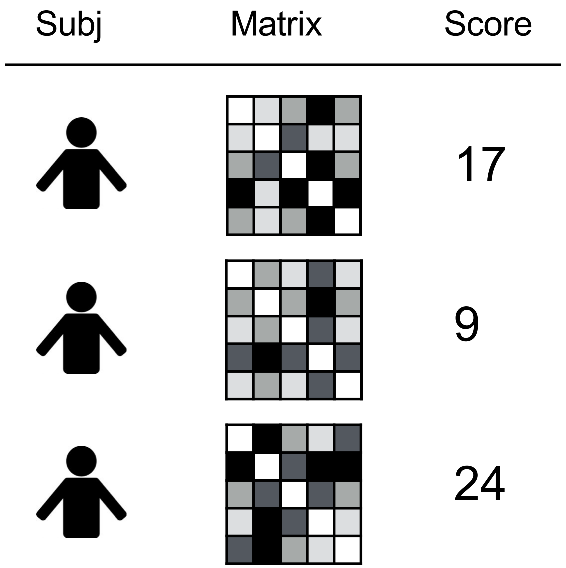
Accuracy: **54 – 94% (mean: 76%)** *chance < 1%*

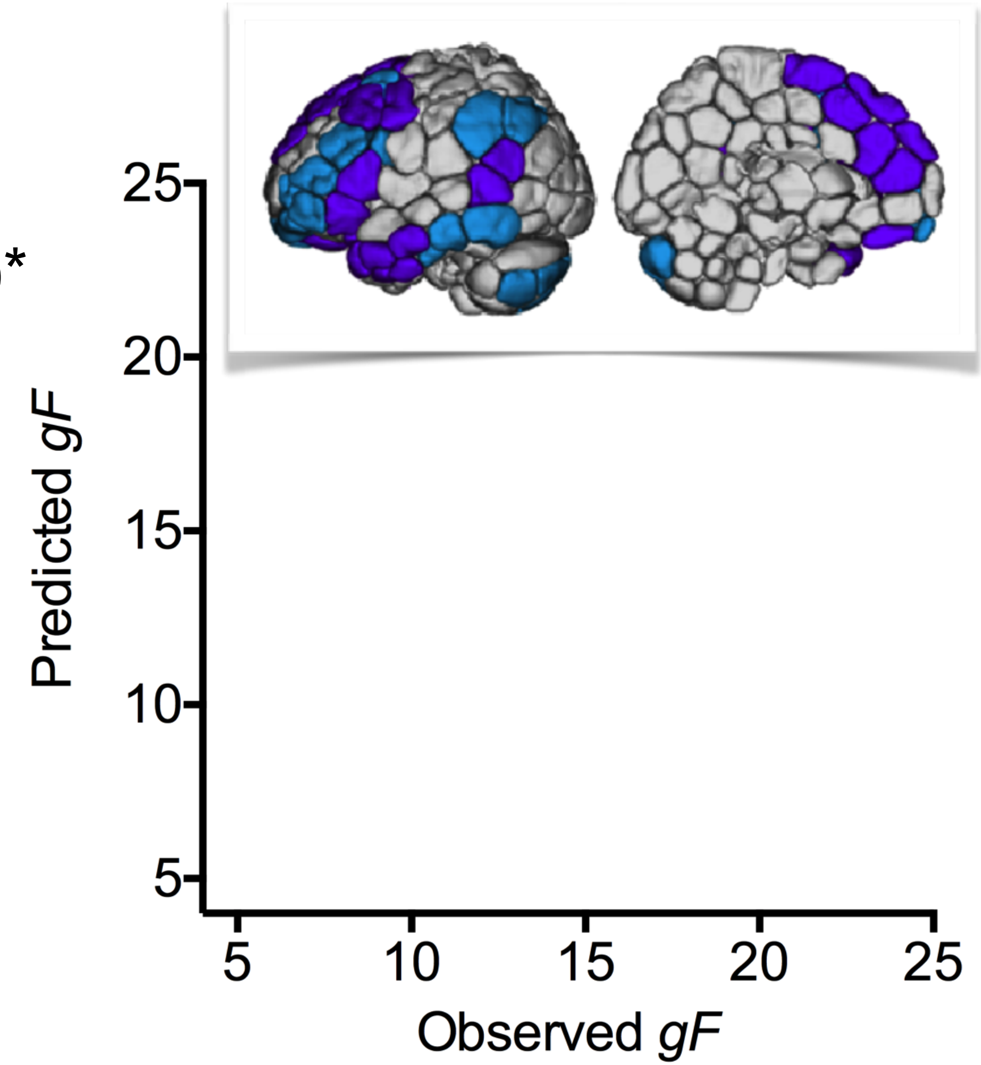
Finn, Shen et al., *Nat Neurosci* (2015)

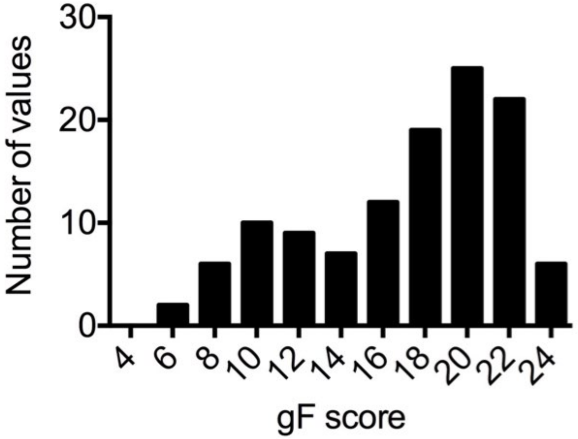
Functional connectomes predict fluid intelligence



Connectome-based
Predictive Modeling (CPM)*







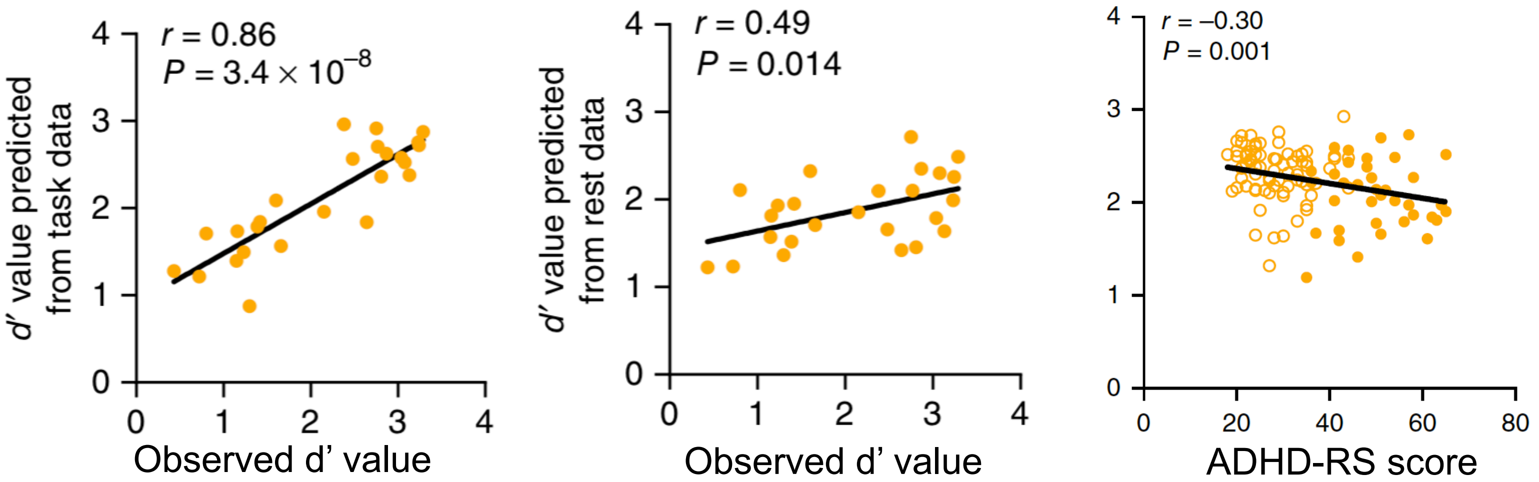
*Shen, Finn et al. *Nat Protoc* (2017)

Finn, Shen et al., *Nat Neurosci* (201

Predicting behavior from functional connectomes

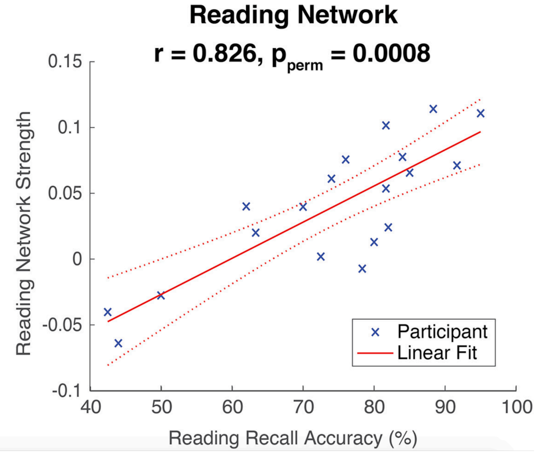
Sustained attention & ADHD symptoms

Rosenberg, **Finn** et al., *Nat Neurosci* (2016)



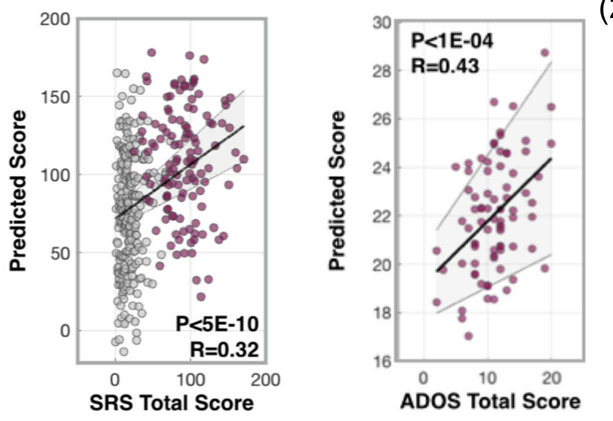
Reading ability

Jangraw et al., *NeuroImage* (2017)



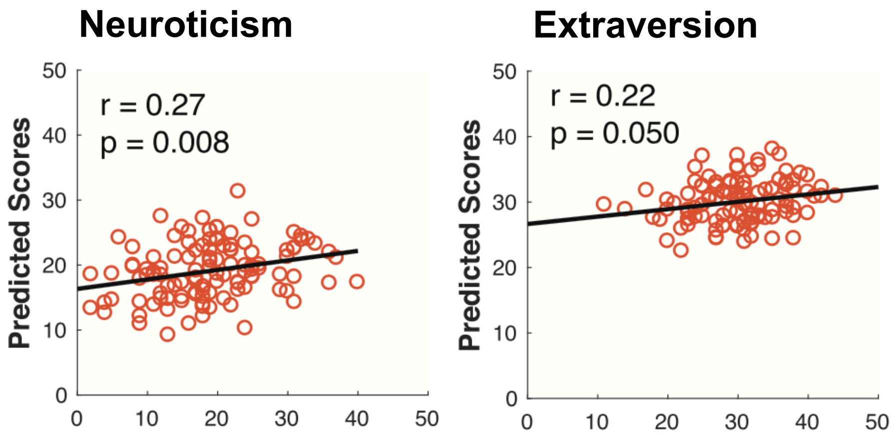
Autism symptoms

Lake, **Finn** et al., *Biol Psychiat* (2019)



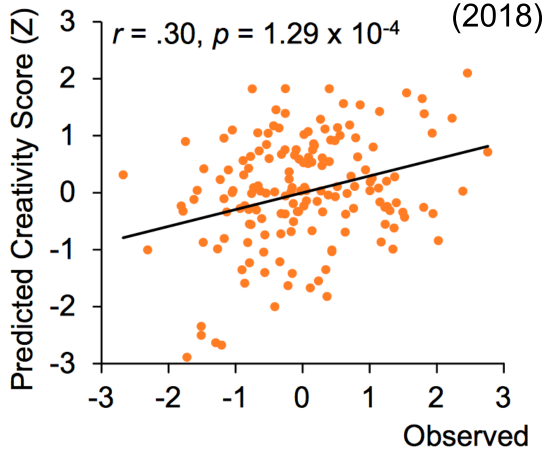
Personality traits

Hsu et al., *Soc Cogn Aff Neurosci* (2018)



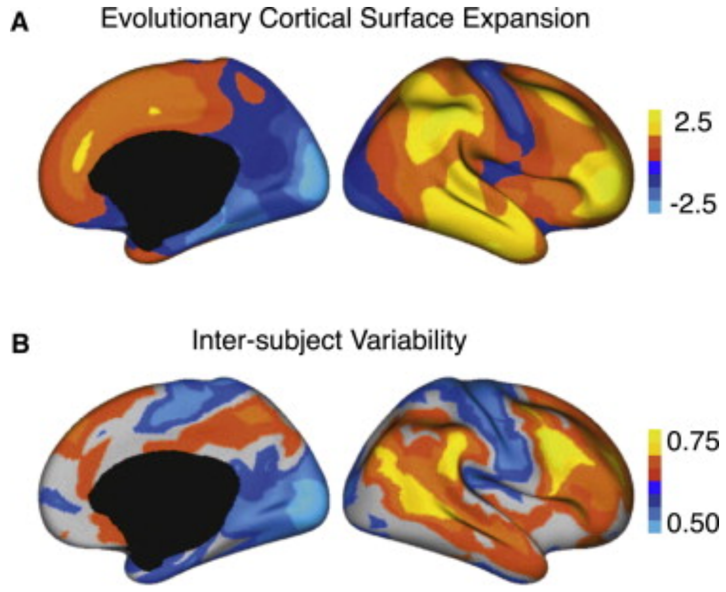
Creativity

Beaty et al., *PNAS* (2018)

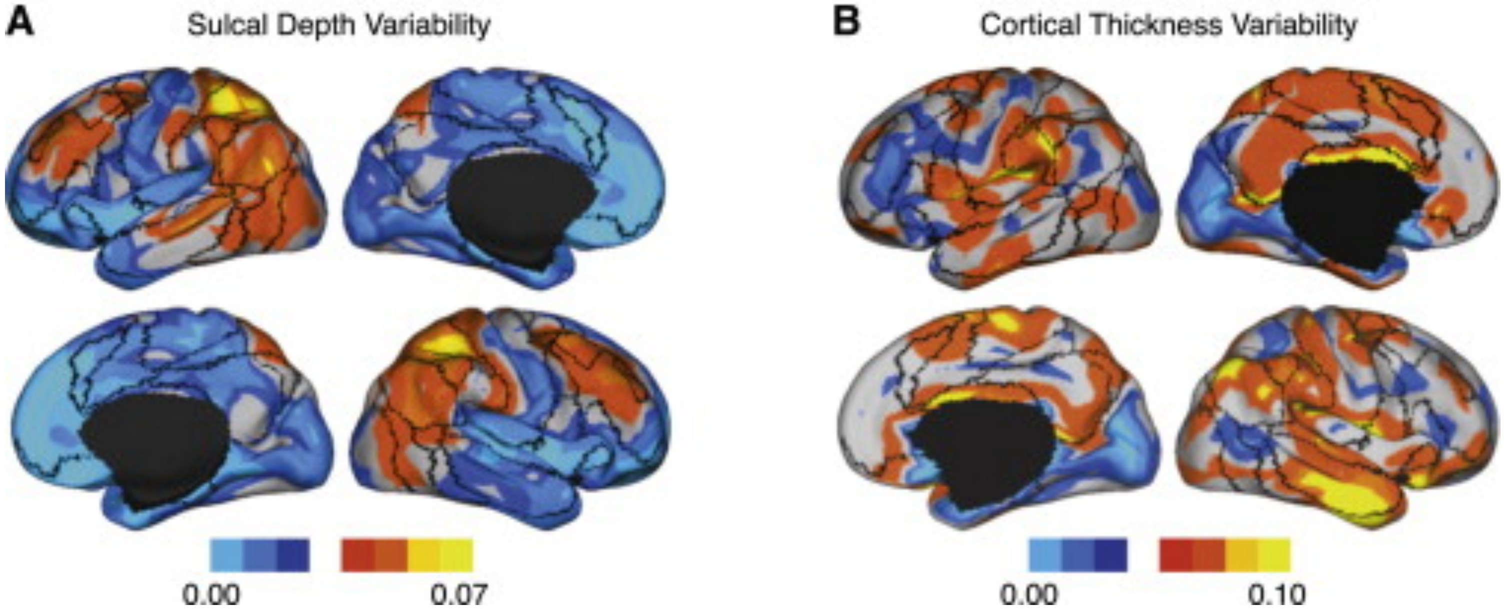


Localizing individual differences

Biggest differences found in most evolutionarily recent regions:

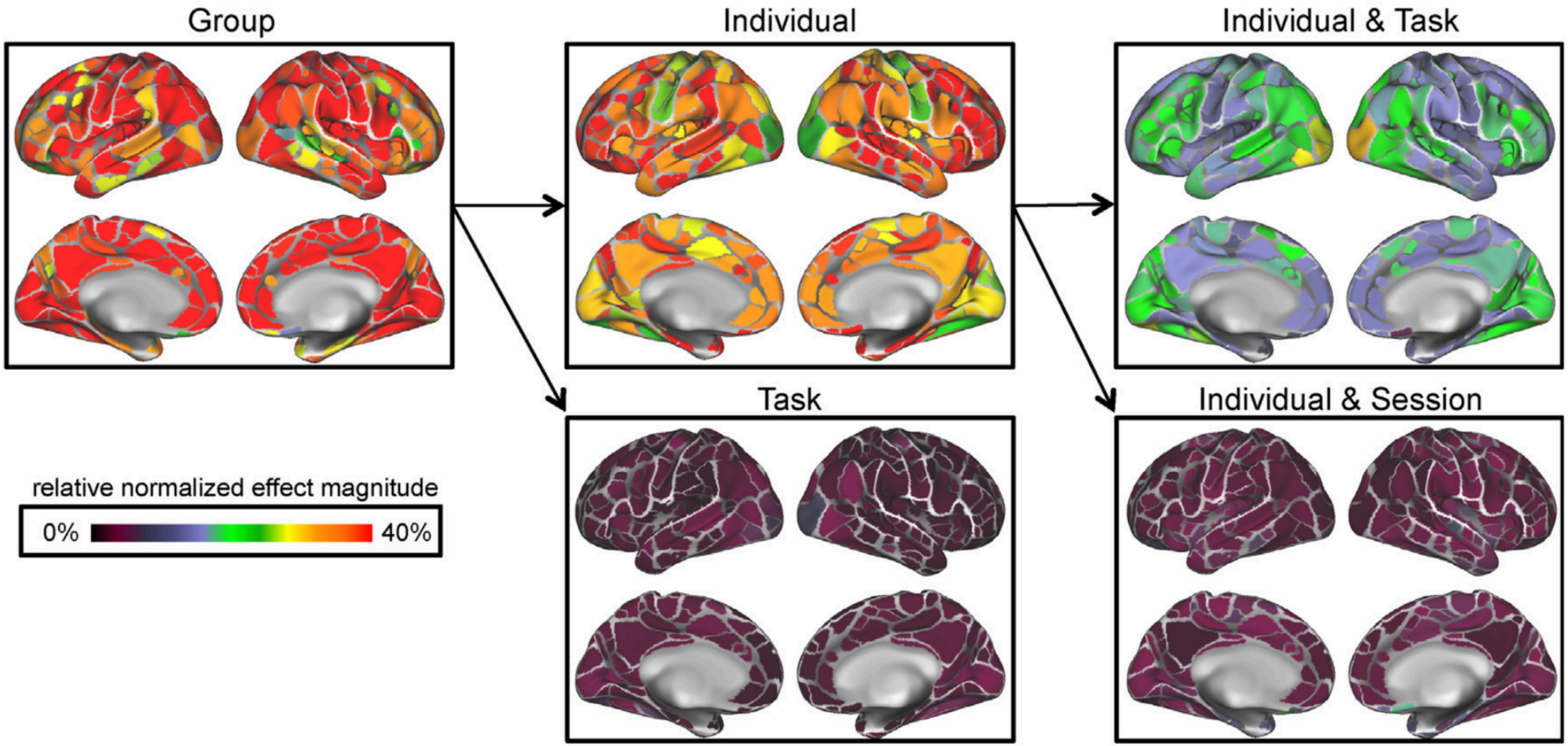


Anatomical differences also play a (large) role:



Mueller et al., *Neuron* (2013)

Individuals account for the most variance!



Gratton et al., *Neuron* (2018)

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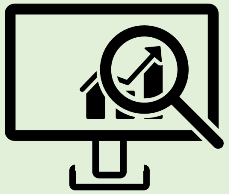
Questions & controversies

Data acquisition

Subjects

- High n, sparsely sampled or low n, densely sampled?
- Which populations?

Data analysis



Applications

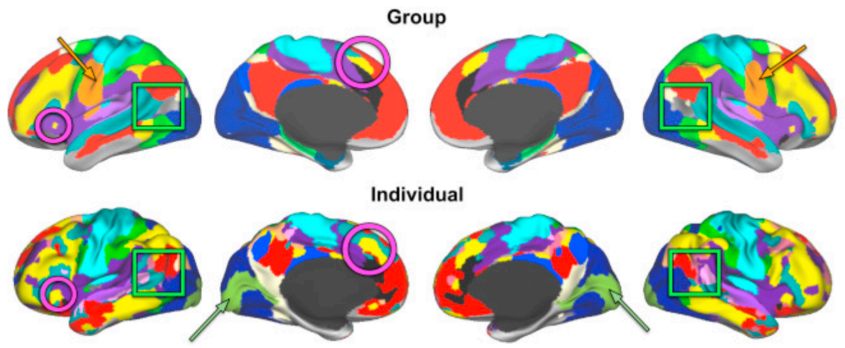
High *n*, sparsely sampled? Or low *n*, densely sampled?

Dense sampling helps characterize:

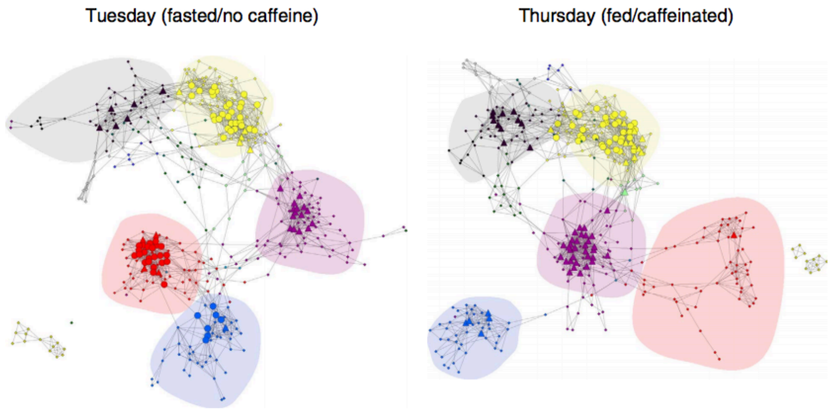
"MyConnectome"

Midnight Scan Club

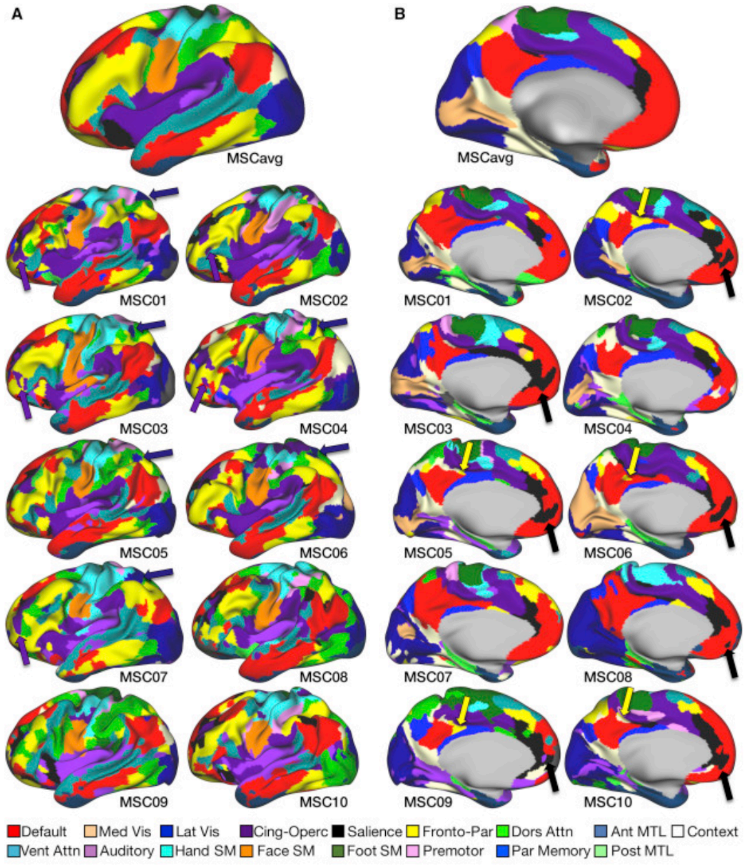
- Within-subject variability
  → *understand fluctuations in psychiatric illness*
- Between-subject variability



Laumann et al., *Neuron* (2015)



Poldrack et al., *Neuron* (2015)

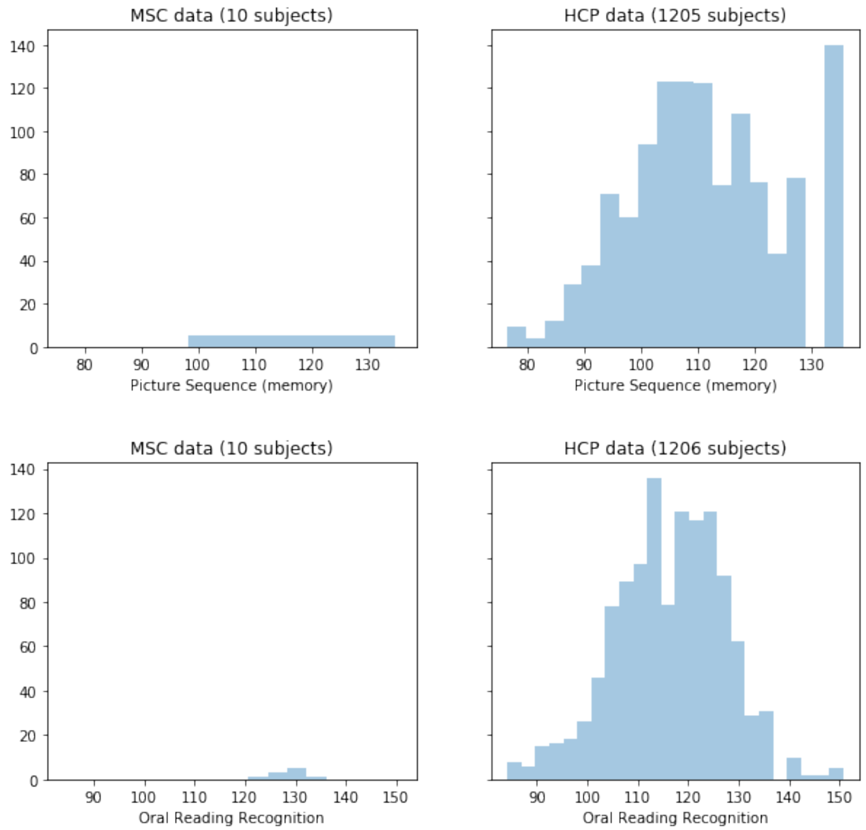


Gordon et al., *Neuron* (2017)

High *n*, sparsely sampled? Or low *n*, densely sampled?

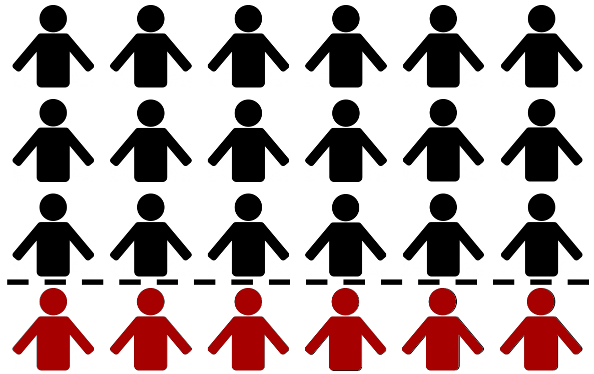
Advantages of high *n* sampling:

- Wider distribution of behavior/phenotypes
- Allows for cross-validated model building
- More realistic for real-world applications

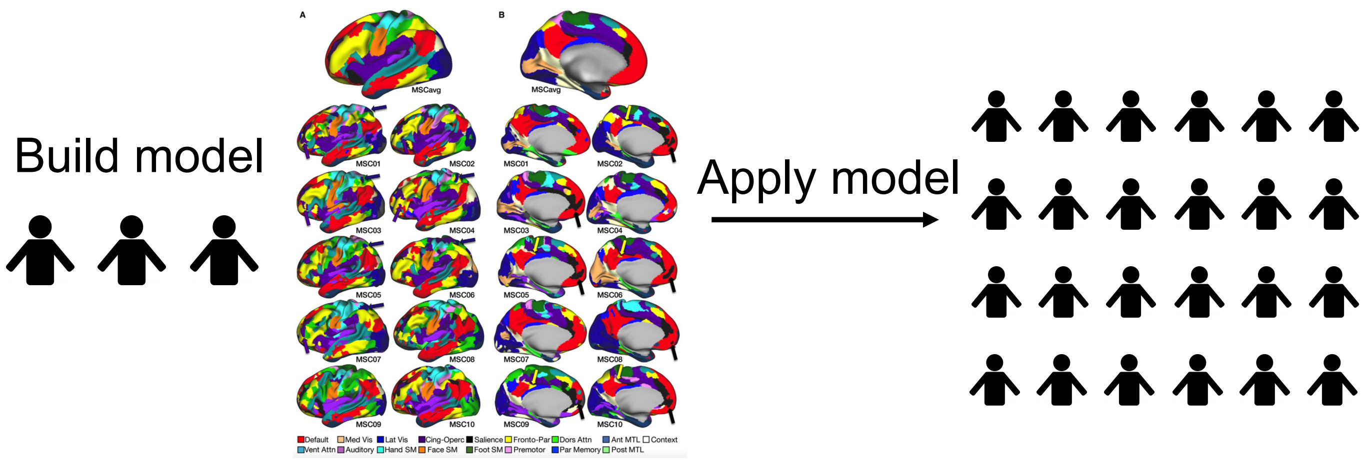


Training set

Test set

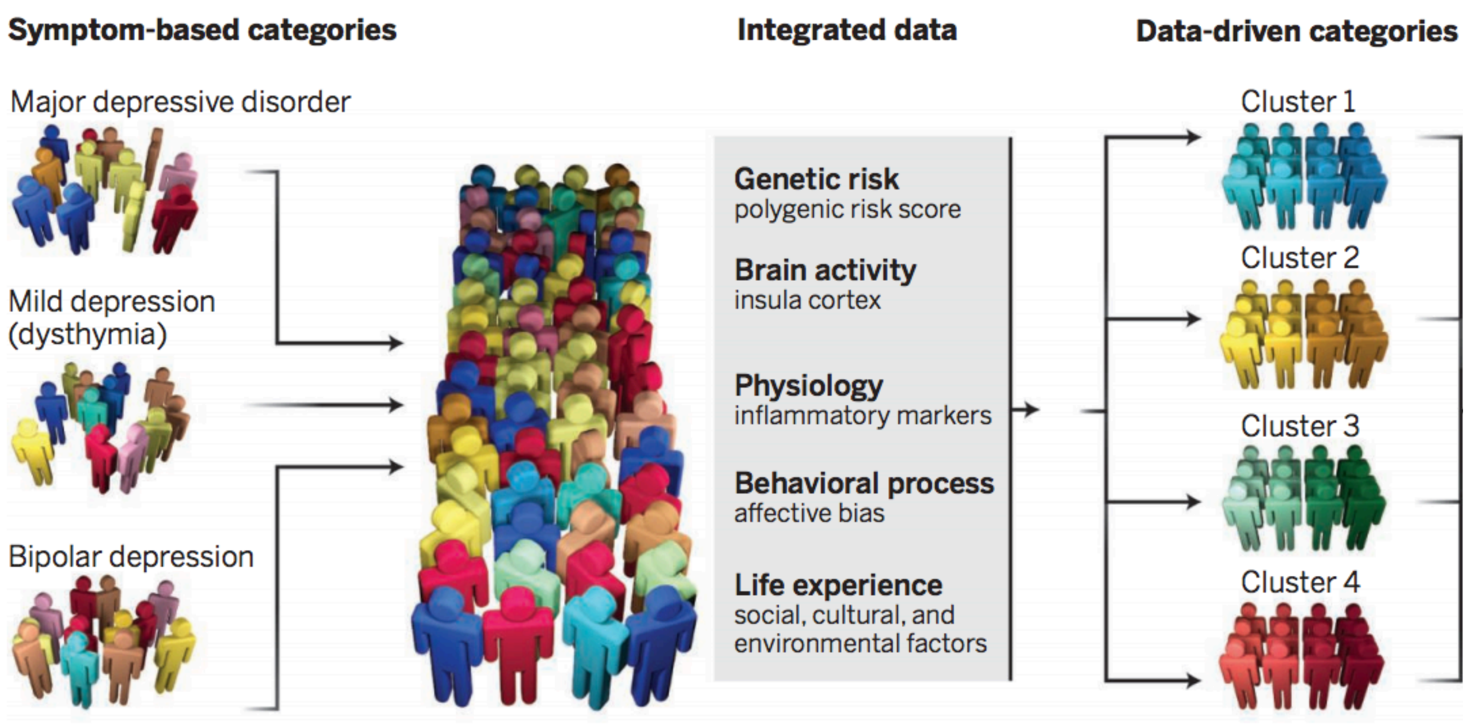


Combination approach?



Who should we recruit?

- Patients or controls? Ideally both
- Which diagnosi(e)s to target? Ideally several
- A "help-seeking" model can enrich samples for pathology
- Longitudinal studies are key (recruit patients while they're still controls!)



Insel & Cuthbert, *Science* (2015)

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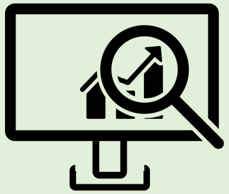
Imaging
- Data quality?
- Brain state (“stress test”)?
- Multisite studies?

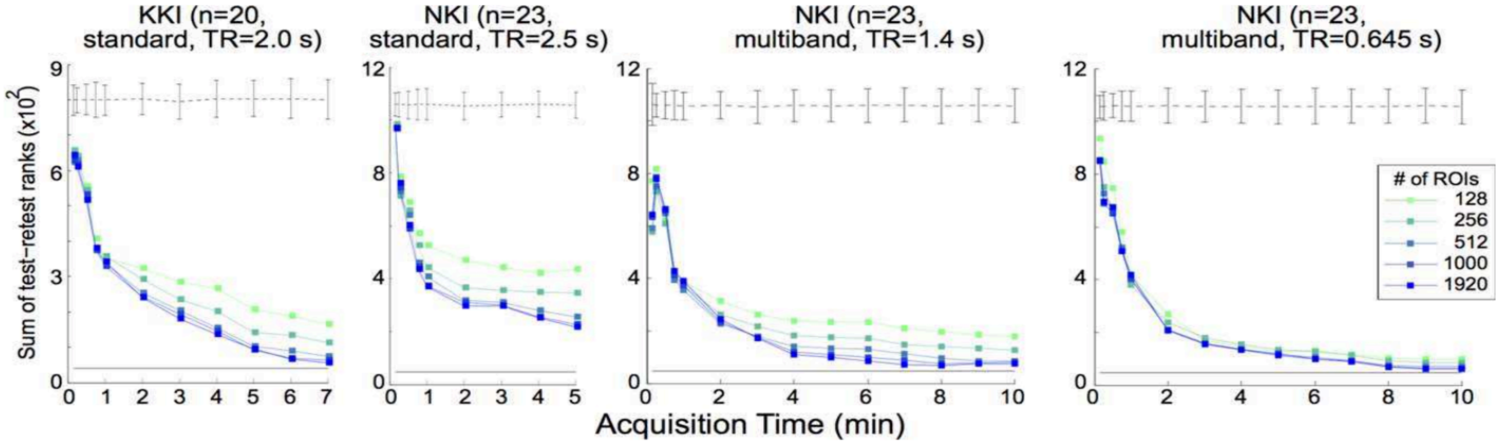
Data analysis



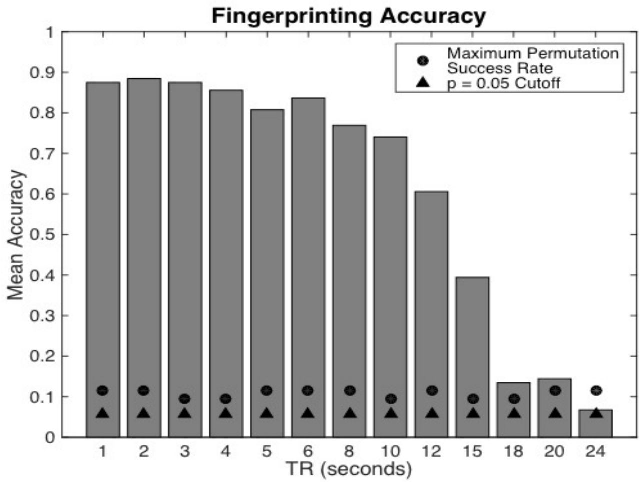
Applications

Q. Do you need HCP-quality data?
A. Not really

ID is fairly robust even at more standard spatial & temporal resolutions:



Airan et al., Hum Brain Mapp (2016)

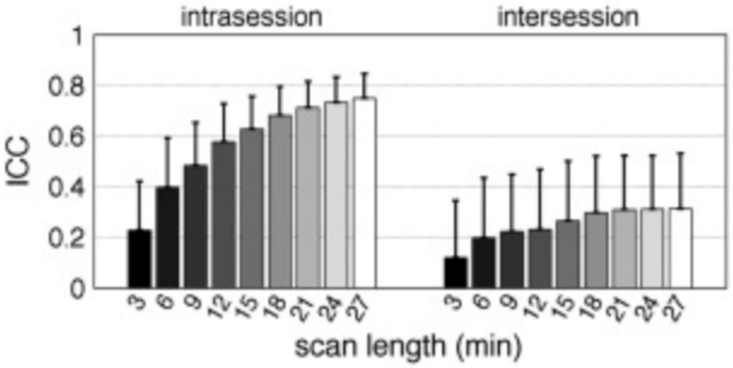


Courtesy of Jason Druzgal

Q. What about amount of data?
A. Scan duration matters!

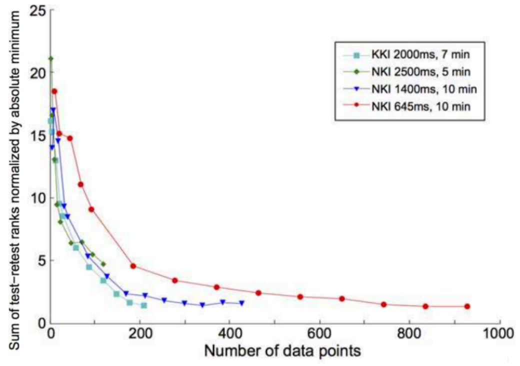
Longer acquisitions are better:

- higher reliability within subjects



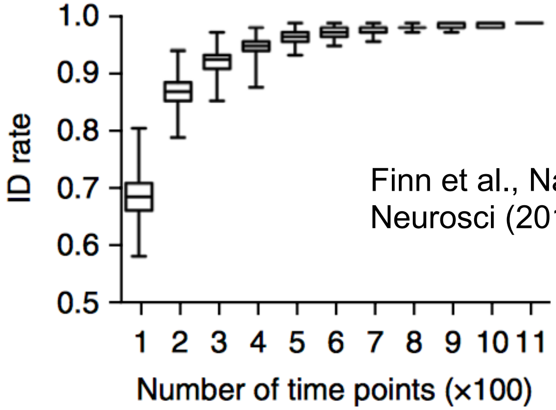
Birn et al., NeuroImage (2013)

- higher sampling rate (shorter TR) cannot make up for shorter scan duration

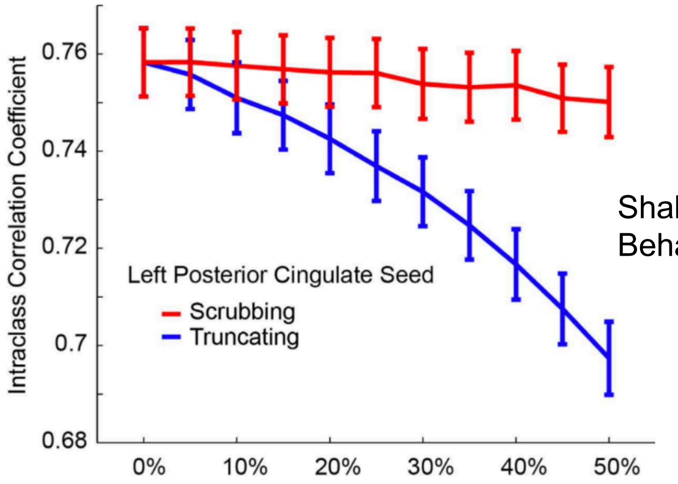


Airan et al., Hum Brain Mapp (2016)

- higher identifiability across subjects



Finn et al., Nat Neurosci (2015)

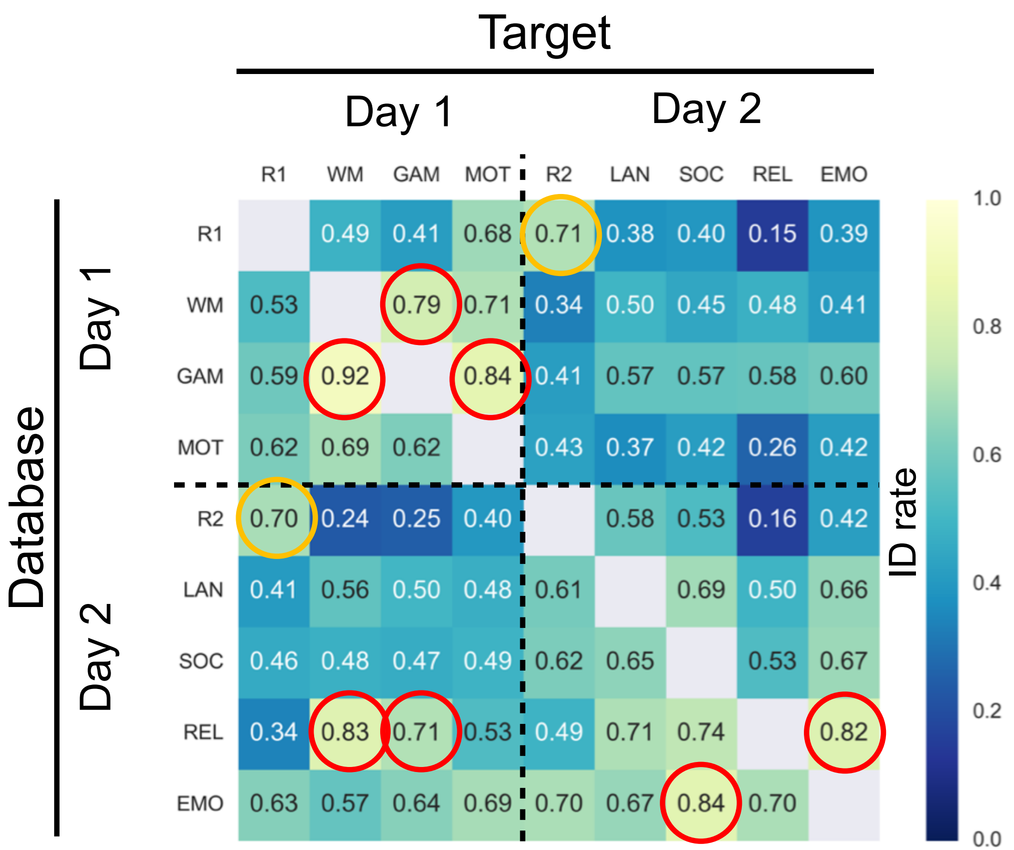


Shah et al., Brain & Behav (2016)

Q. Does scan condition matter?
A. Yes!

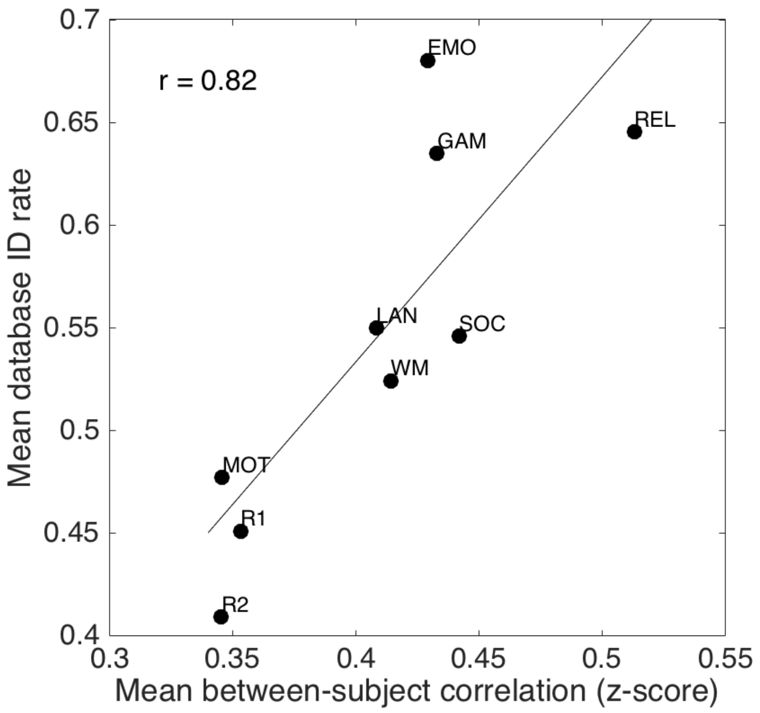
Rest has become the default condition for FC & individual differences, but tasks may increase signal-to-noise

Replicating identification experiments:



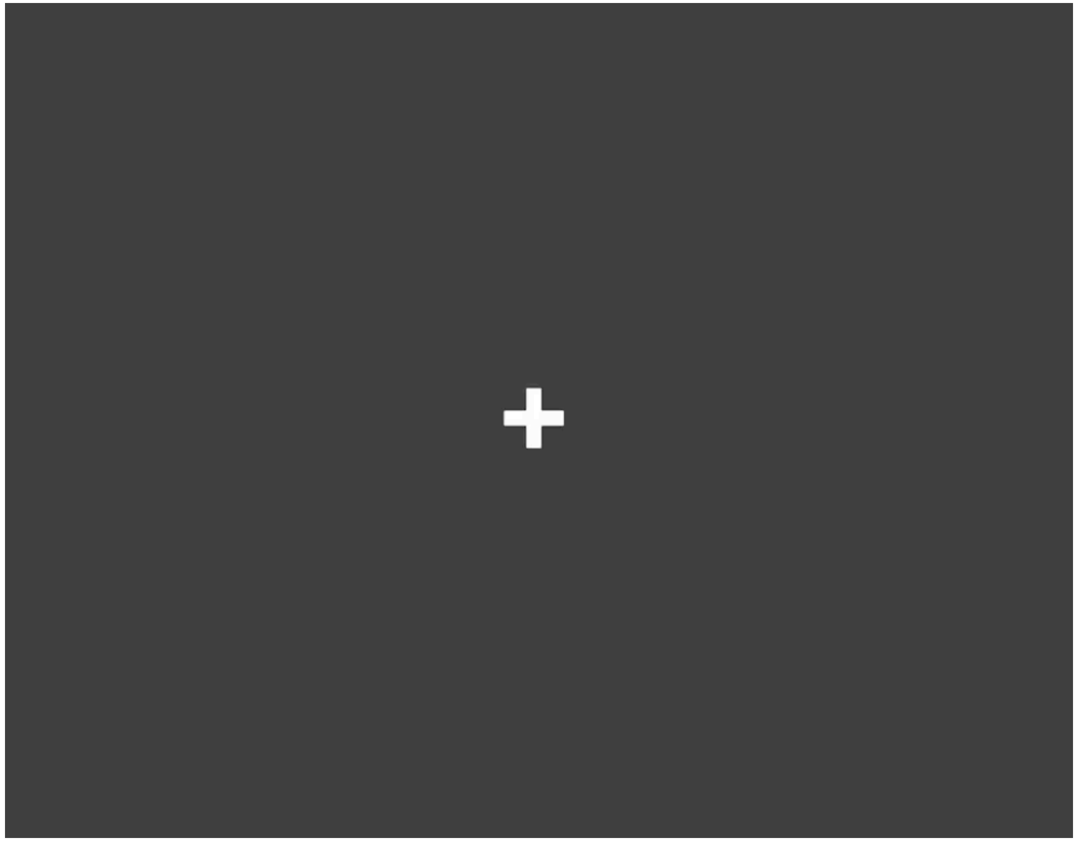
Chance ~ 0.001

Conditions that make subjects look **more similar** to one another actually make **better databases** for identification:



Q. Is rest best?
A. Probably not

Consider naturalistic tasks:



Inscapes: Vanderwal et al., *NeuroImage* 2015
headspacestudios.org

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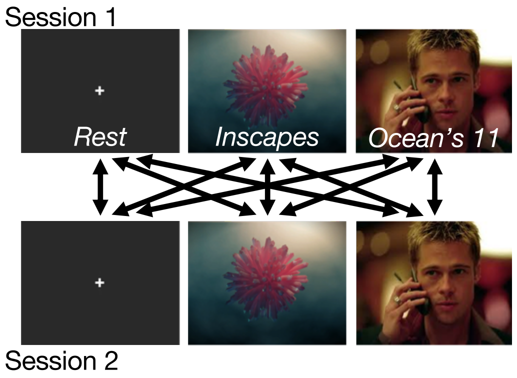
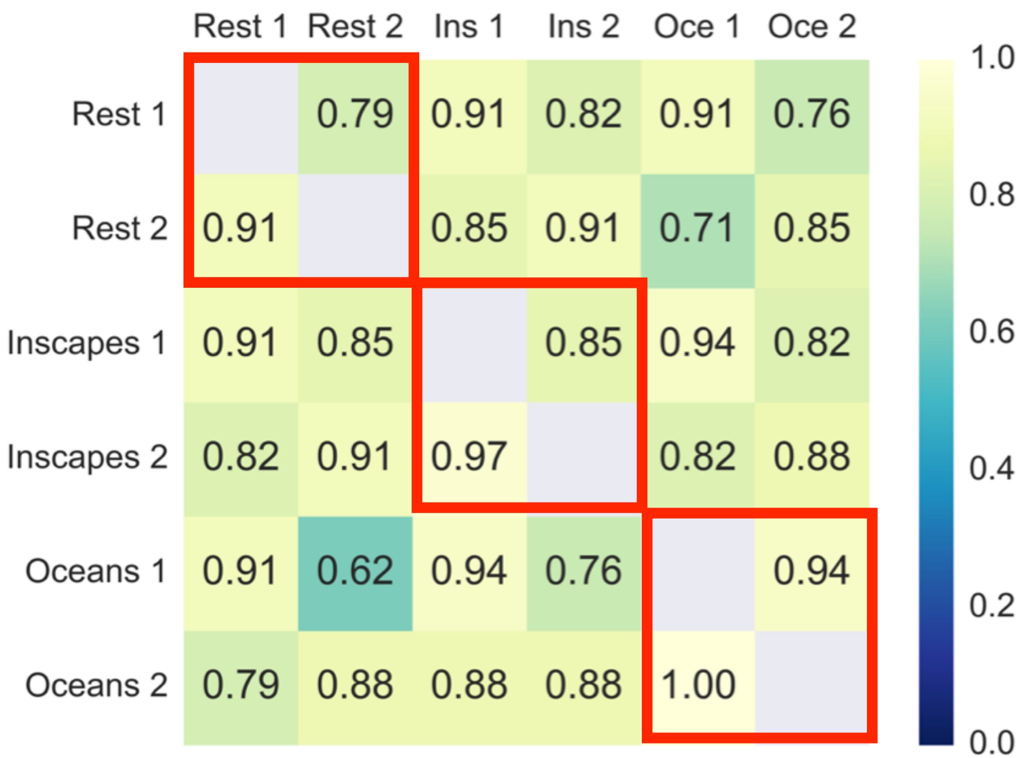
A. Probably not

Consider naturalistic tasks:

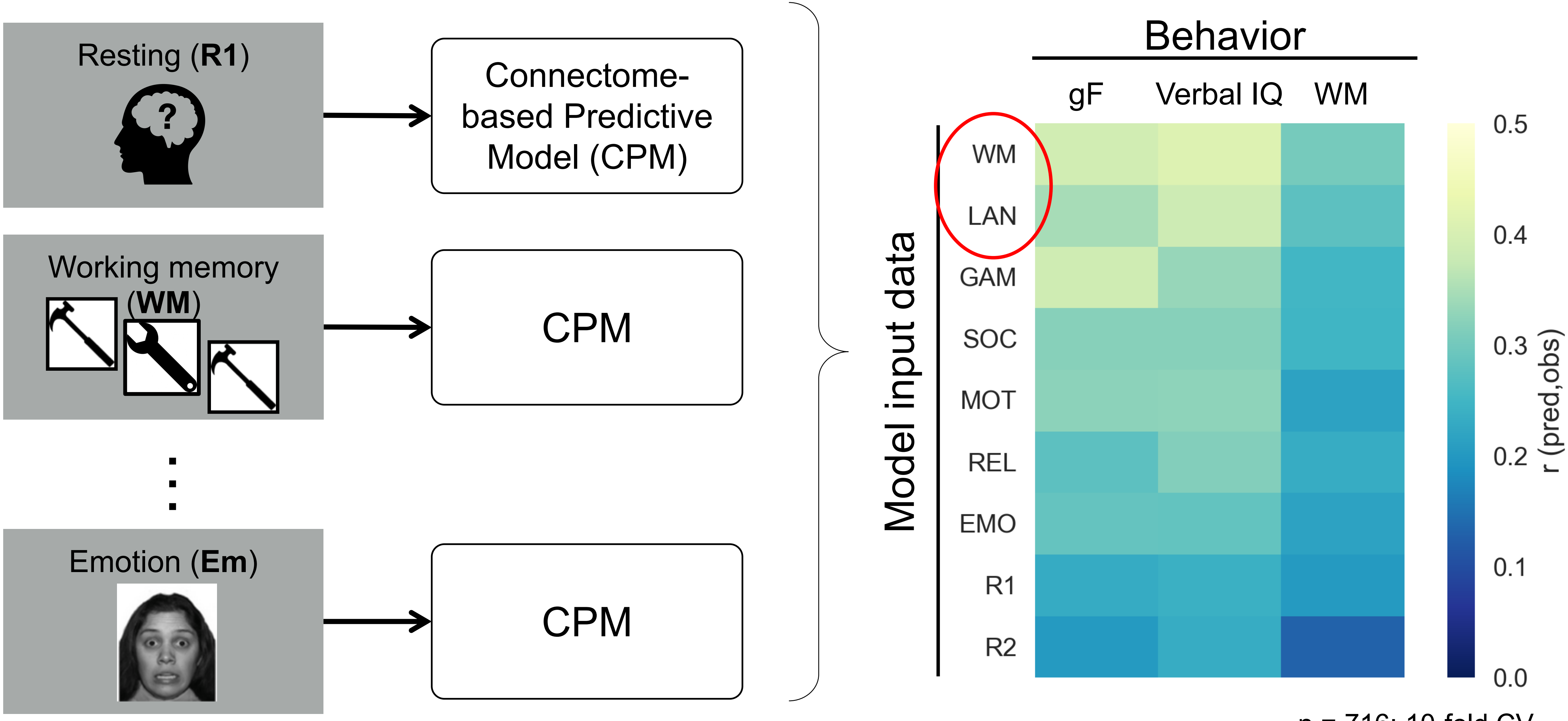
- ID rate is just as good as (if not better than) rest





Vanderwal et al., NeuroImage (2017)

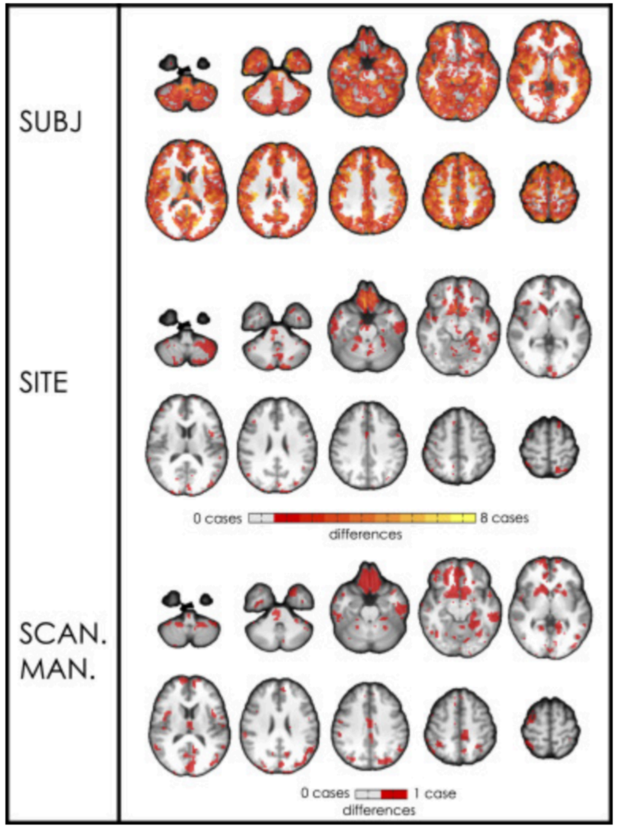
Cognitive brain states best predict cognitive ability



n = 716; 10-fold CV

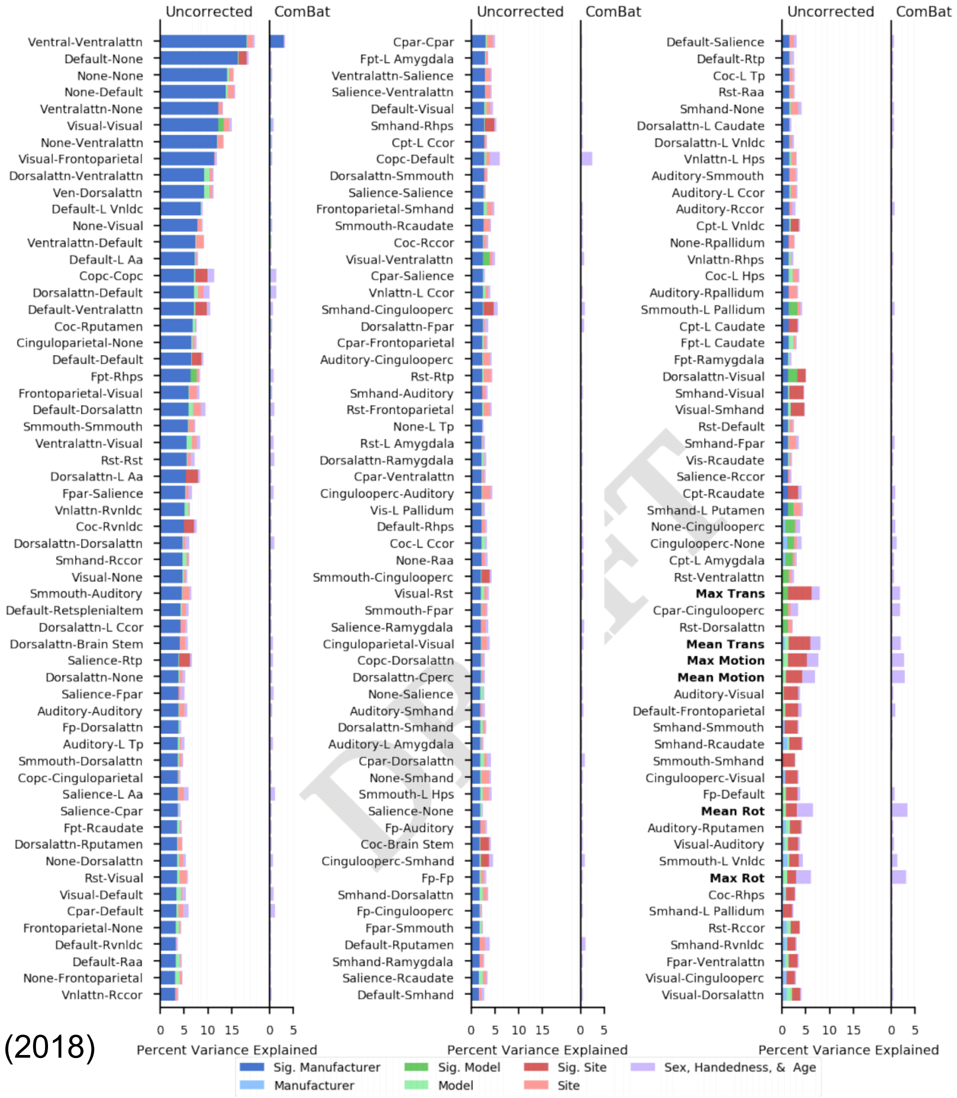
Multisite studies?

- Multisite studies help increase *n*
- But site and scanner effects can introduce added variance
- Ultimately, biomarkers need to be robust to site



Noble et al., *NeuroImage* (2017)

- Harmonization techniques are promising:



Nielson et al., *bioRxiv* (2018)

Questions & controversies

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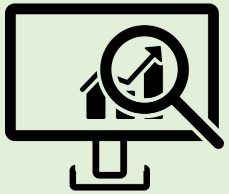
Behavior
- Self-report or task-based?
- *Inter-* vs *intra*-subject variability?

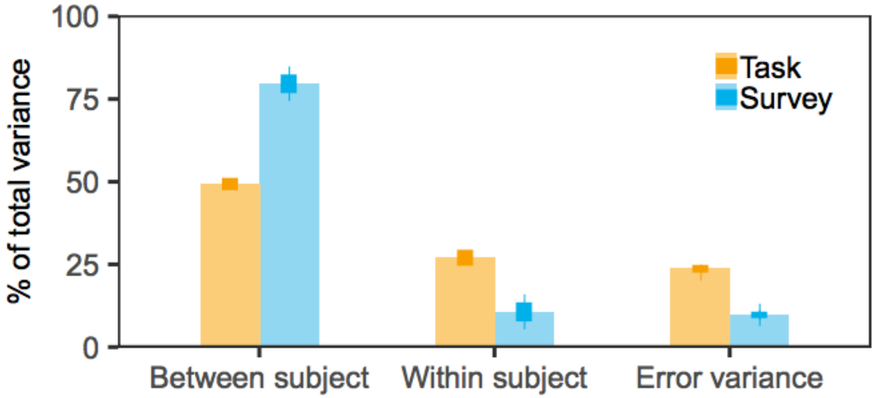
Data analysis

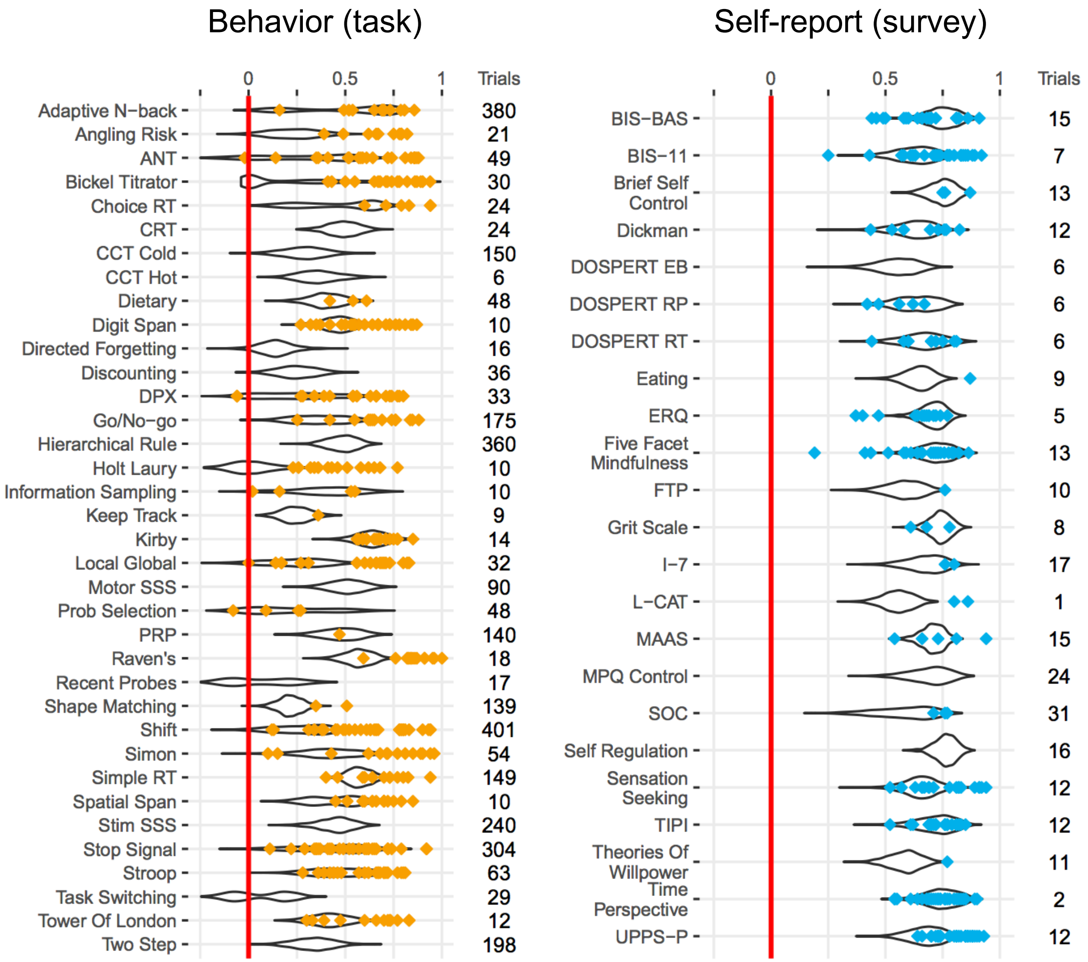


Applications

Self-report or behavior?

- Self-report is subject to demand characteristics, limited by people's ability to introspect accurately
- Behavior may be less biased
- But self-report may be more stable within individuals (and more variable across individuals)
- Predicting "real-world" behavior (e.g., outcomes) will be gold standard



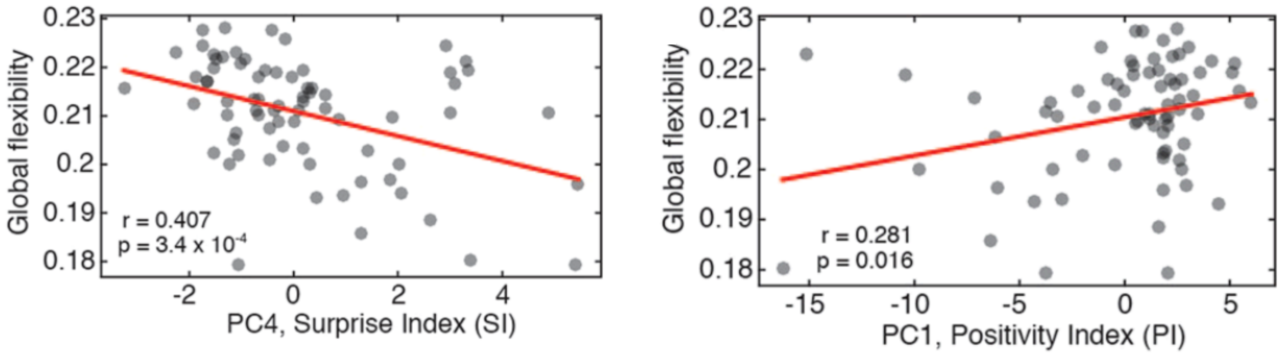


Enkavi et al., PNAS (2019)

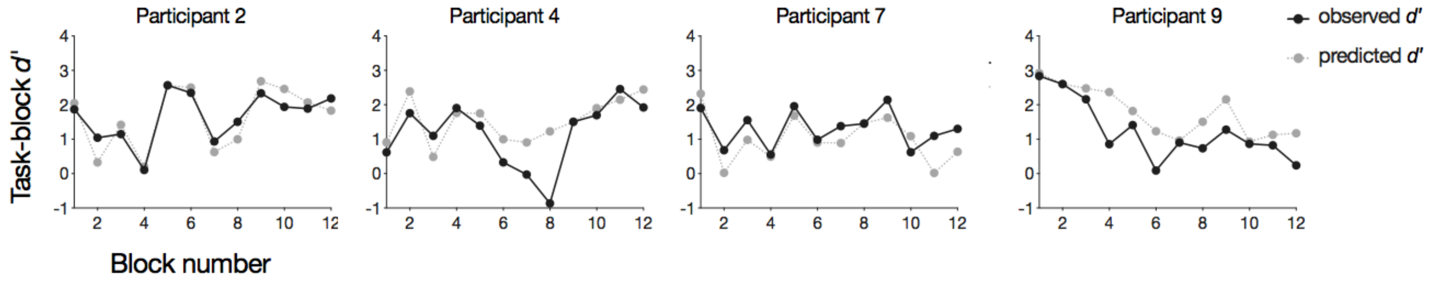
Inter- versus *intra*-subject variability

Is your behavior stable?

- Trait vs. state
- State variables may be better suited to within-subject analysis

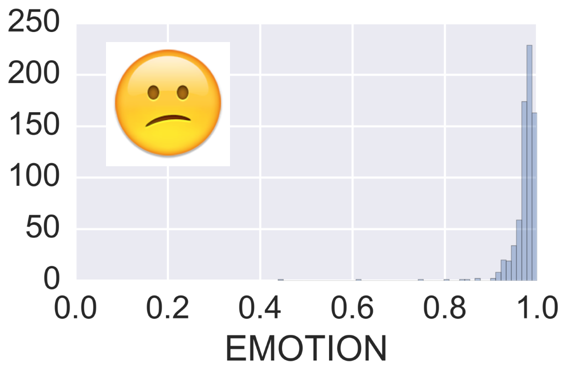


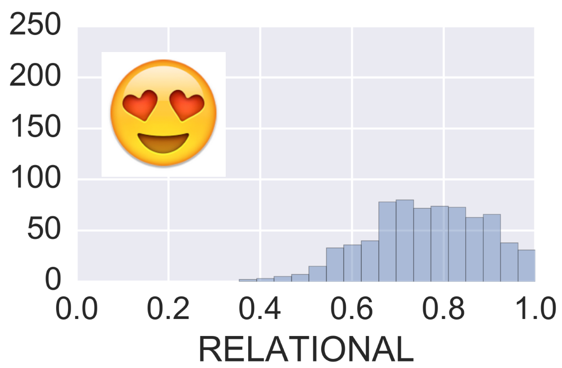
Betzel et al., Sci Rep (2017)



Rosenberg et al., bioRxiv (2019)

Does it show a good distribution in your population?





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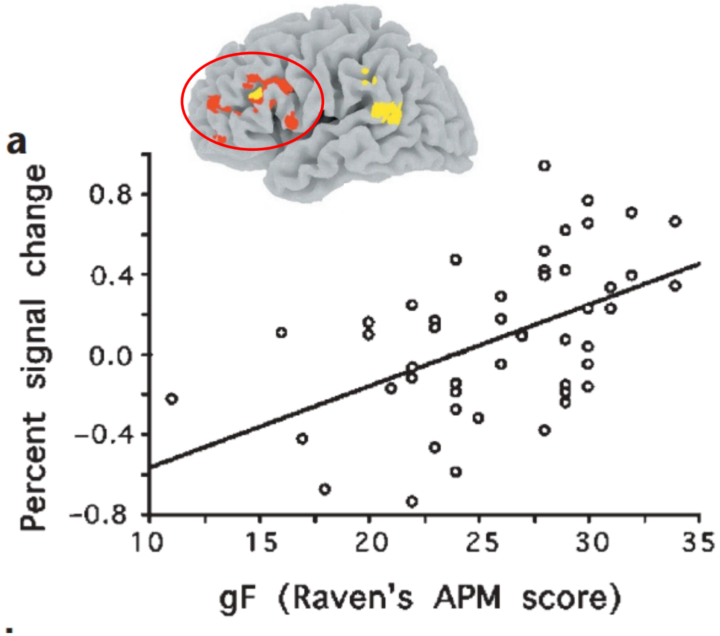
Data analysis

Features / level of analysis
- Functional connectivity? Activation? Combo?
- Parcel boundaries? Connections between parcels? Both?

Applications

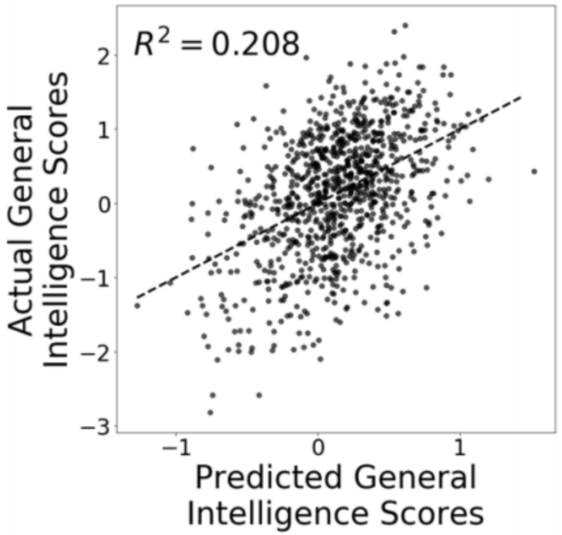
Connectivity? Activation? Both? Something else?

- Current focus on functional connectivity stems from explosion of resting-state & large-scale datasets
- But many task-based studies have shown parametric relationships between activity and behavior
- Combining the two may be most powerful
- Other non-traditional approaches such as inter-subject correlation (ISC) have potential

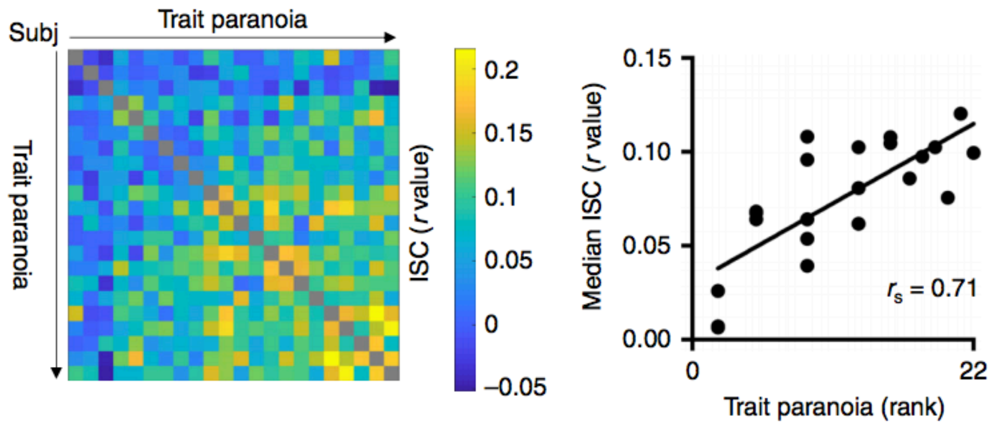


Gray et al., *Nat Neuro* (2003)

Model based on
[FPN activity – DMN activity]
during n-back task



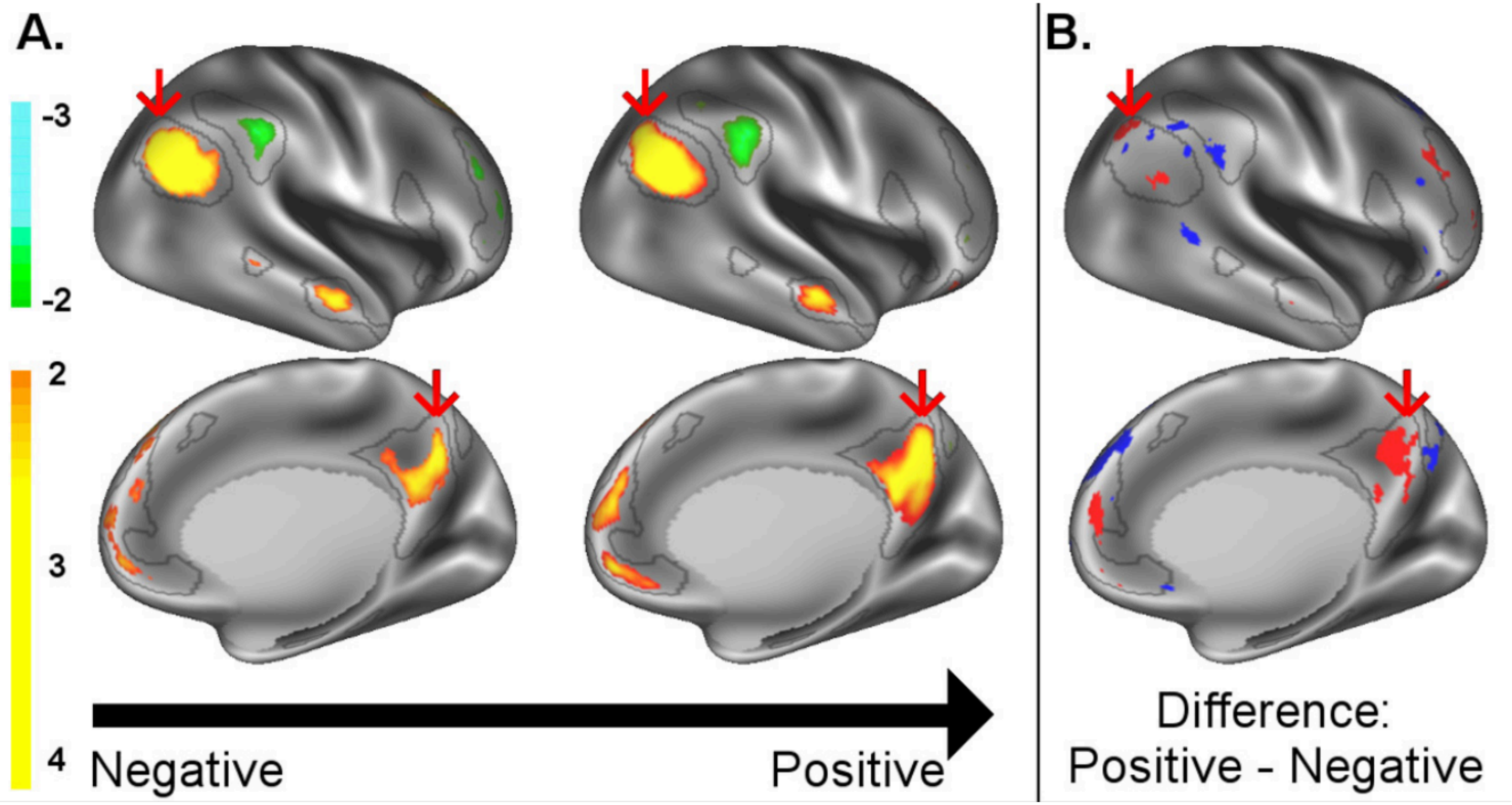
Sripada et al., *bioRxiv* (2019)



Finn et al., *Nat Commun* (2018)

Node boundaries or functional connections?

- Imposing a group atlas can obscure individual differences in node boundaries
- Node boundaries themselves may contain meaningful information



Bijsterbosch et al., *eLife* (2018)

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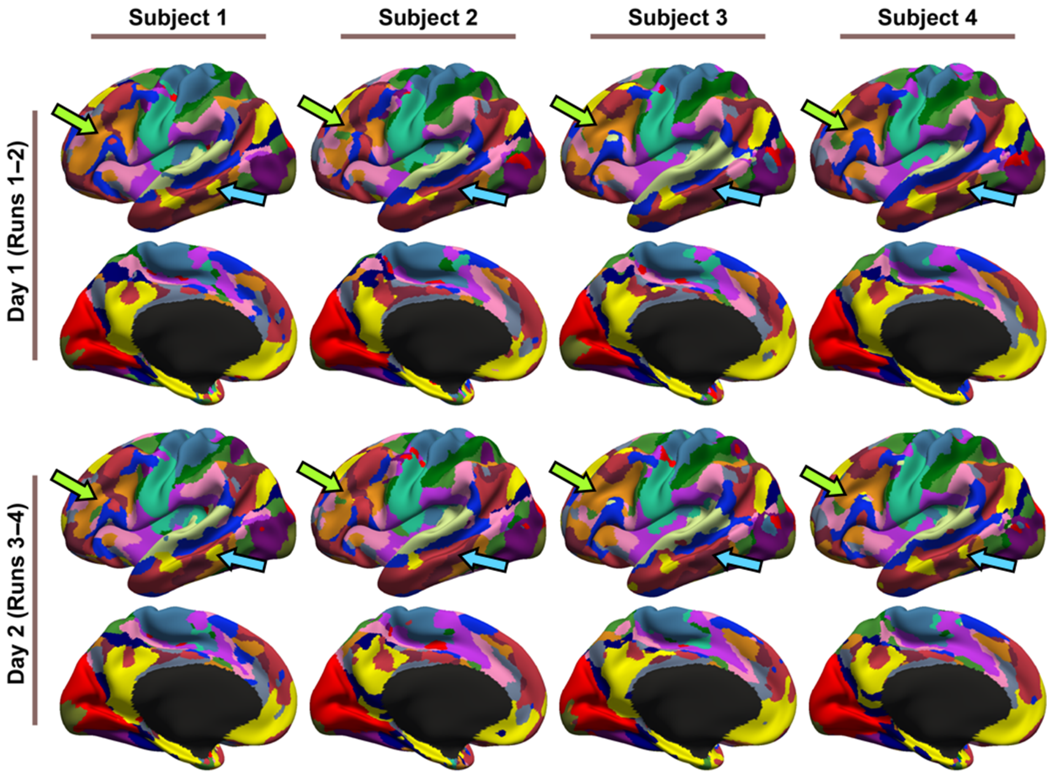
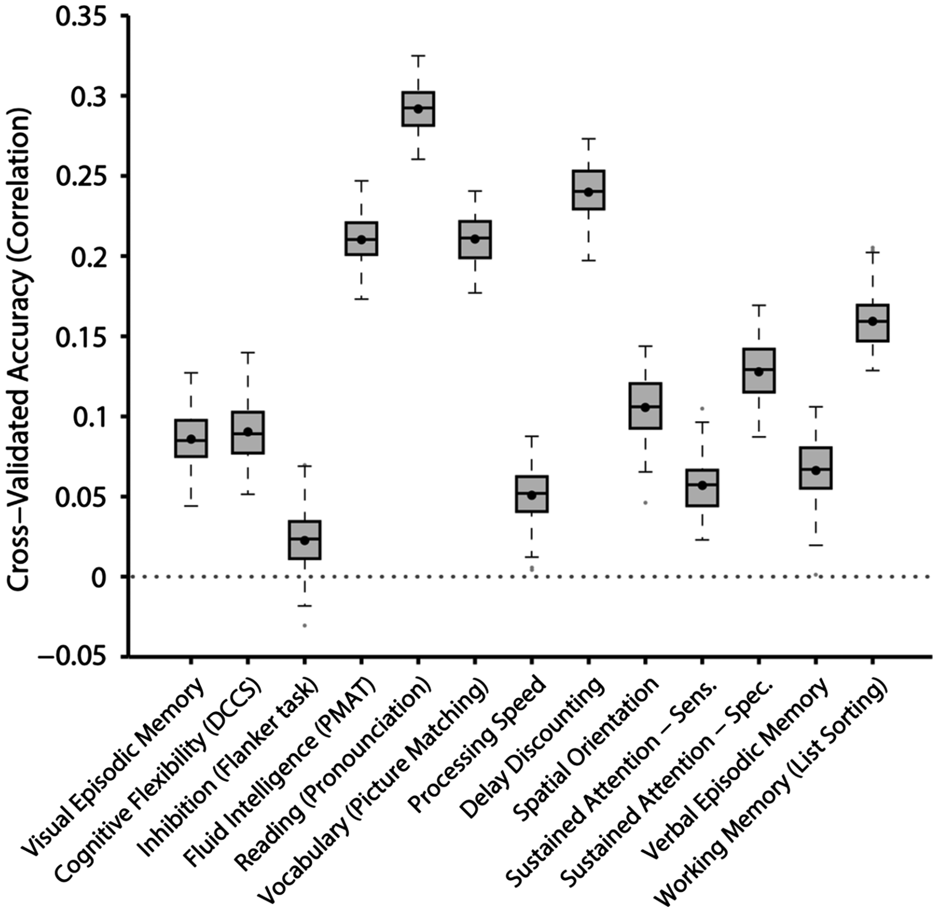
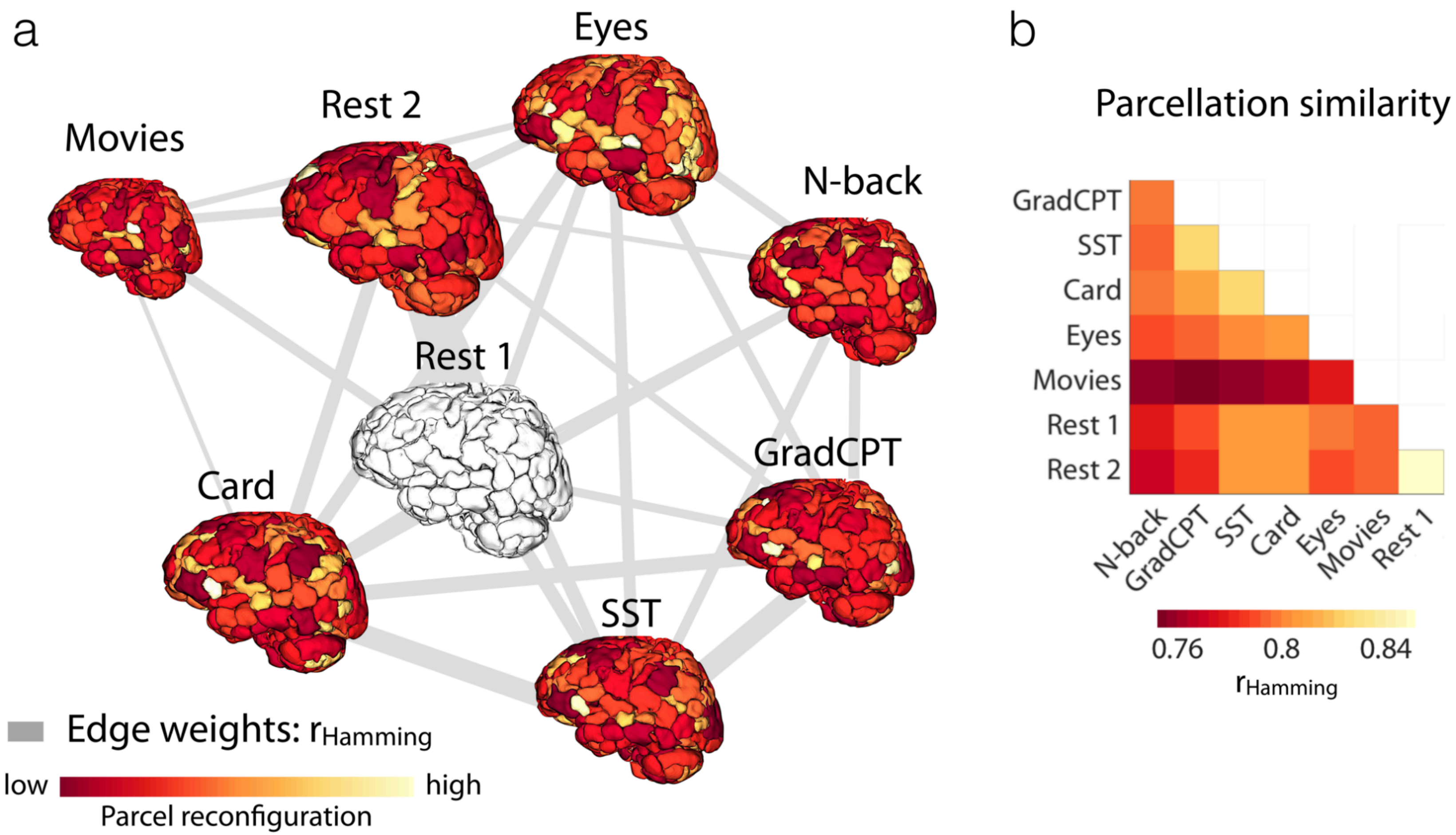




Kong et al., *Cereb Cortex* (2018)

Node boundaries or functional connections?

Even individual-specific parcellations may be task-dependent:



Salehi et al., *bioRxiv* (2019)

Questions & controversies

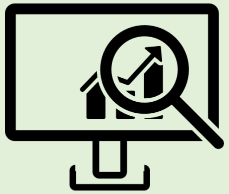
Data acquisition

Subjects
- High *n*, sparsely sampled or low *n*, densely sampled?
- Which populations?

Imaging
- Data quality?
- Brain state (“stress test”)?
- Multisite studies?

Behavior
- Self-report or task-based?
- *Inter-* vs *intra*-subject variability?

Data analysis



Features / level of analysis
- Functional connectivity? Activation? Combo?
- Parcel boundaries? Connections between parcels? Both?

Confounds
- Head motion, others

Applications

Behavior: Mitigating confounds

Many behaviors/phenotypes are correlated with head motion!

Negatively:

Subject measures	Pearson *r*
ReadEng (AgeAdj)	−0.23
ReadEng (Unadj)	−0.23
Vocabulary (AgeAdj)	−0.19
Dexterity (Unadj)	−0.18
CardSort (Unadj)	−0.18
Dexterity (AgeAdj)	−0.18
CardSort (AgeAdj)	−0.18
Education	−0.17
Fluid intelligence	−0.17
Spatial orientation	−0.17
Vocabulary (unadjj)	−0.17
Emotion recognition	−0.16

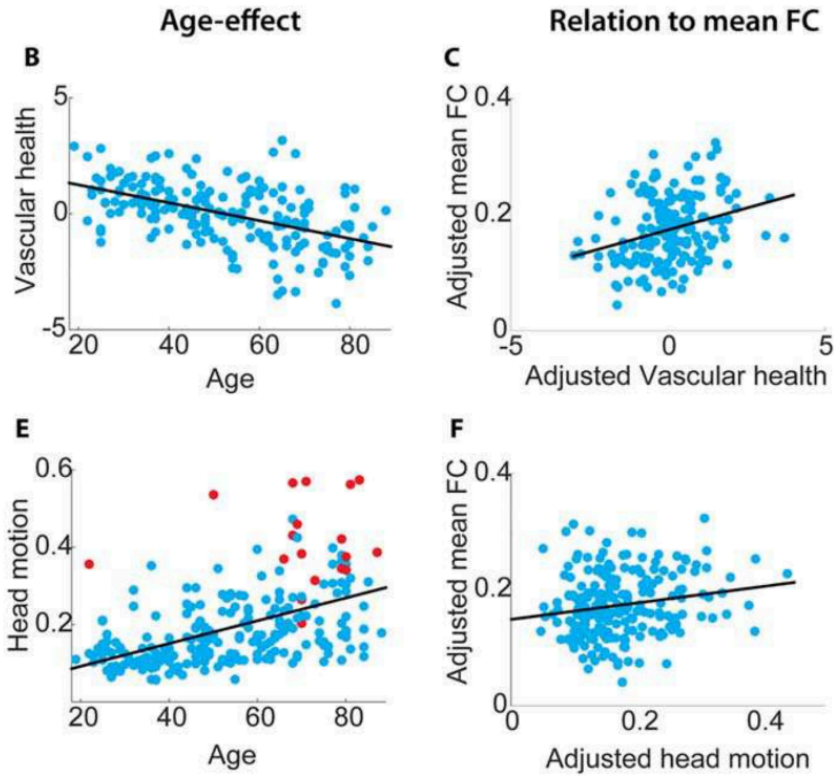
Positively:

DSM somatic problems (pct)	0.16
DSM antisocial (raw)	0.16
ASR externalizing (raw)	0.16
DSM somatic problems (raw)	0.16
Tobacco use 7 day	0.18
Diastolic blood pressure	0.18
ASR externalizing	0.18
Tobacco use today	0.2
Systolic blood pressure	0.23
Weight	0.52
Body mass index (BMI)	0.66

Siegel et al., *Cerebral Cortex* (2016)

- Patients of any kind move more
- Children & older adults move more

Age, vascular health:

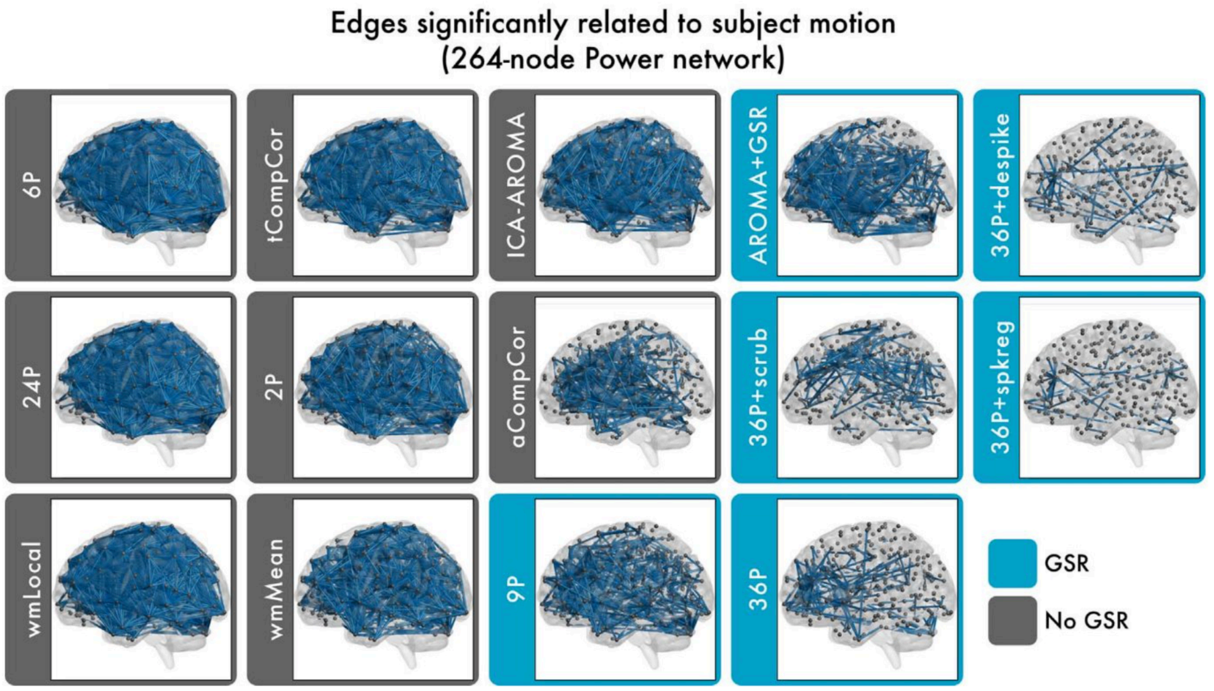


Geerligs et al., *Hum Brain Mapp* (2017)

Behavior: Mitigating confounds

Many behaviors/phenotypes are correlated with head motion!

- Check correlation in your sample
- Consider excluding very high-motion subjects
- Choose appropriate preprocessing techniques
- Use motion as an explicit covariate



Ciric et al., NeuroImage (2017)

Questions & controversies

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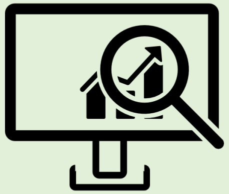

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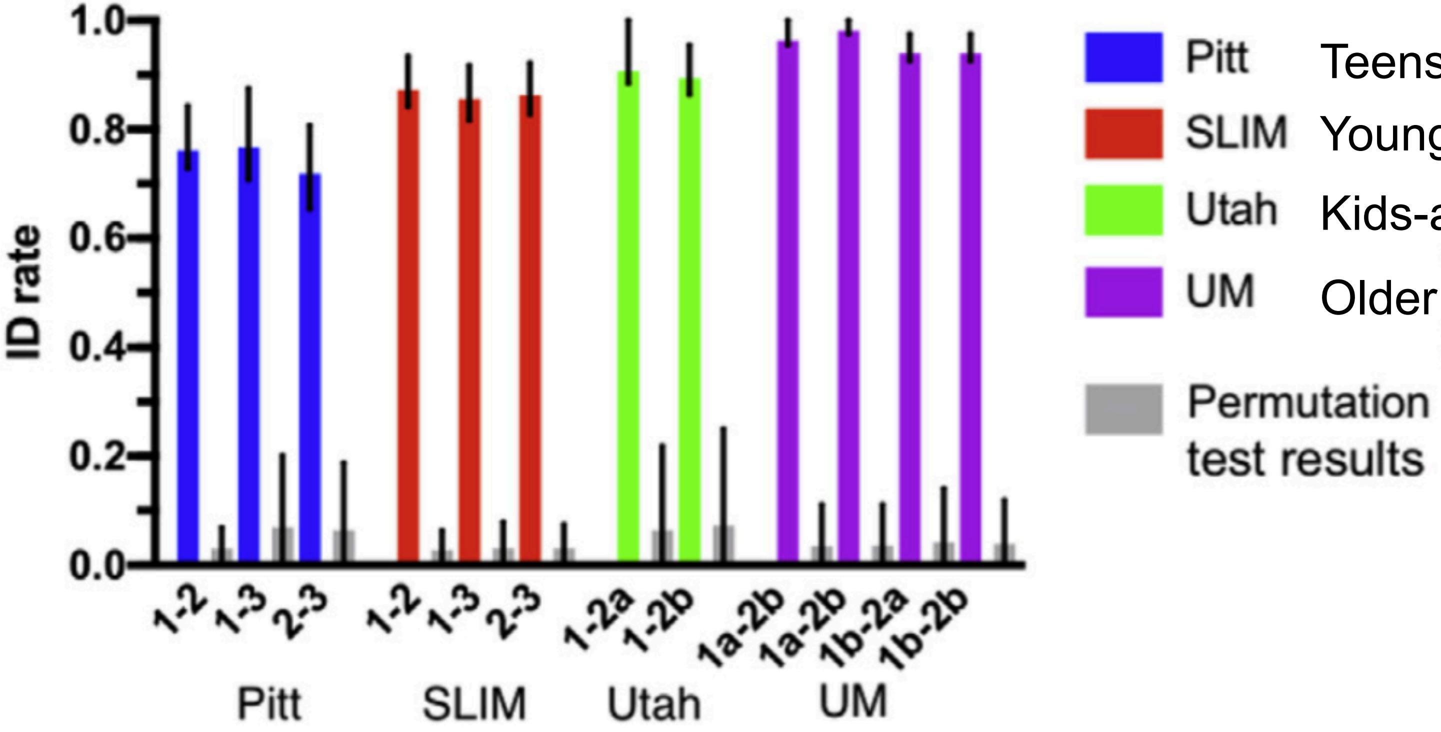
Applications

Mutability
- Development? Disease? Plasticity/training?

"Fingerprinting" across development, aging

- Identification is possible across sessions separated by a period of years:

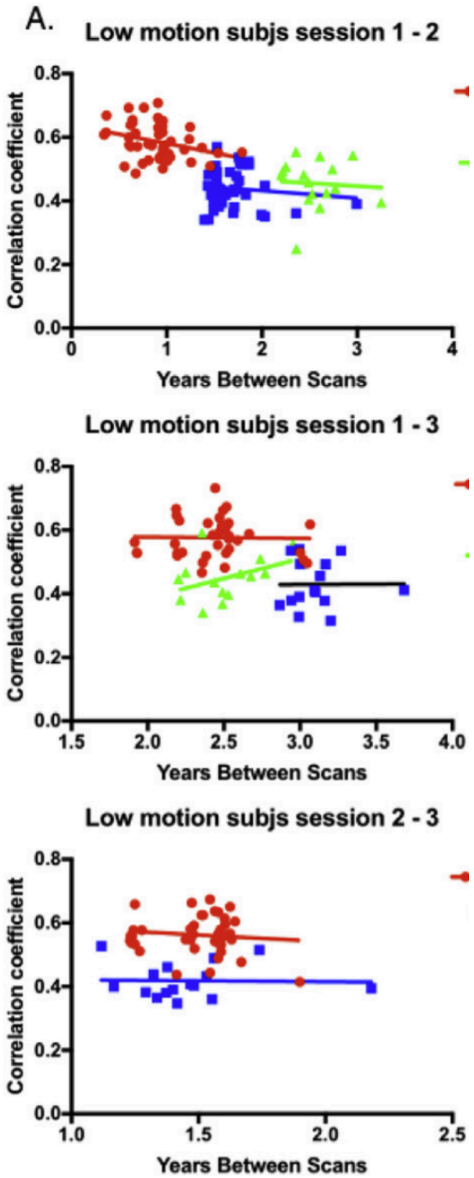


Teens (~15 yrs)

Young adults (~20 yrs)

Kids-adults (~10-30 yrs)

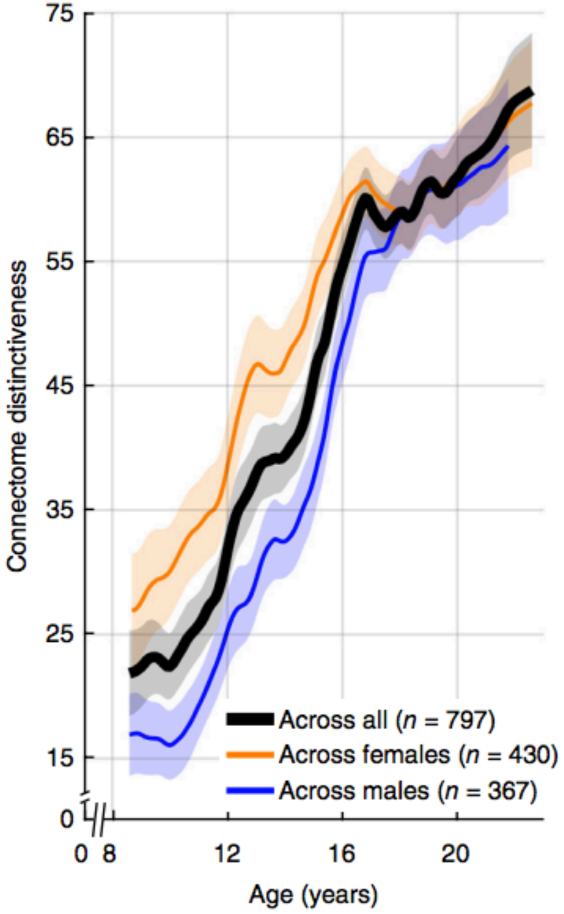
Older adults (~65 yrs)

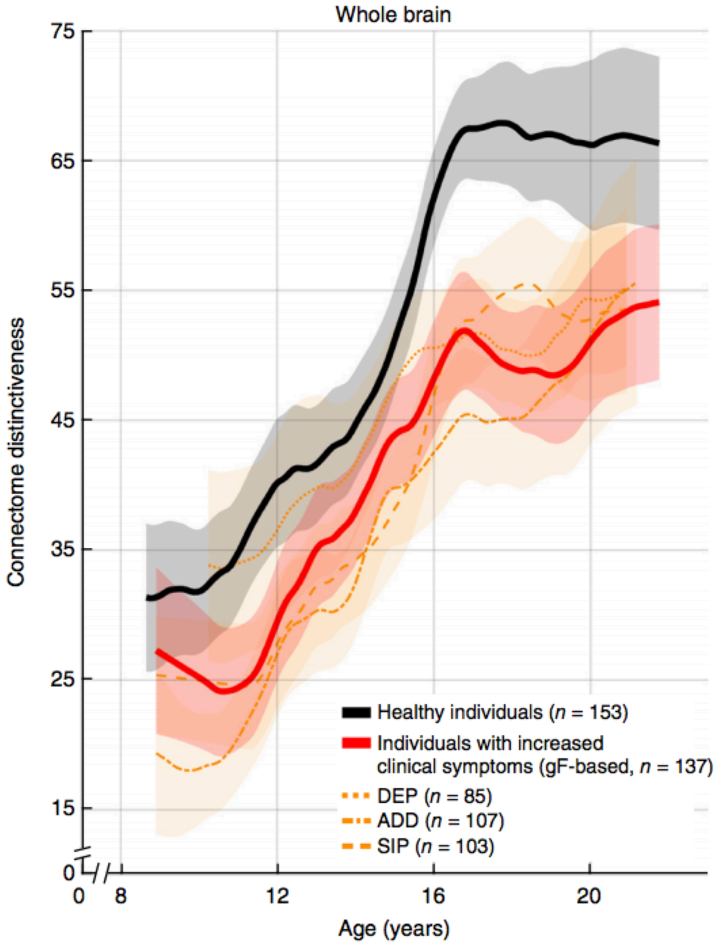


“Fingerprinting” across development, disease

- Connectomes grow more distinct with age
- This process is delayed in mental illness
- Need longitudinal data!

Adolescent Brain Cognitive Development®
Teen Brains. Today’s Science. Brighter Future.





Kaufmann et al., *Nat Neuro* (2017)

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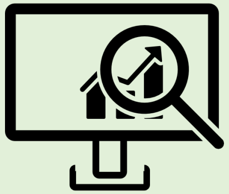

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- Ethics?

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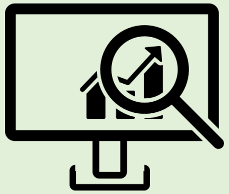

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Further reading & open data sets

Selected reviews:

Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience
Gabrieli, Ghosh & Gabrieli, *Neuron* (2015)

Building a science of individual differences from fMRI
Dubois & Adolphs, *Trends in Cognitive Sciences* (2016)

From regions to connections and networks: new bridges between brain and behavior
Misic & Sporns, *Current Opinion in Neurobiology* (2016)

Can brain state be manipulated to emphasize individual differences in functional connectivity?
Finn et al., *NeuroImage* (2017)

Open data sets with brain and behavior:

HUMAN Connectome PROJECT

biobank uk
Improving the health of future generations

ADHD 200

ABIDE
Autism Brain Imaging Data Exchange

nki ROCKLAND SAMPLE

Philadelphia Neurodevelopmental Cohort
dbGaP GENOTYPES and PHENOTYPES

CHILD MIND® INSTITUTE
healthy brain network

Adolescent Brain Cognitive Development®
Teen Brains. Today's Science. Brighter Future.

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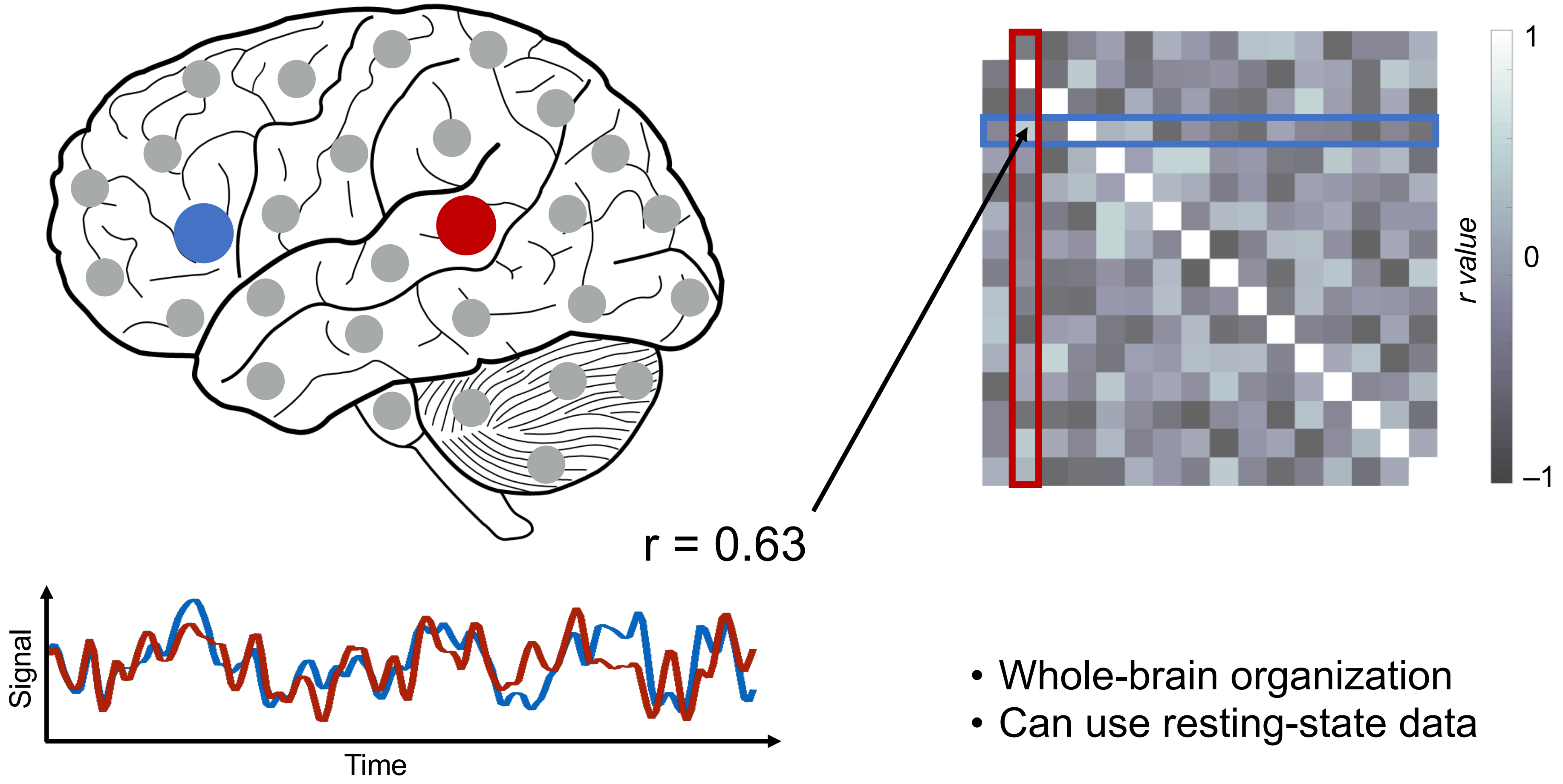
Ramya Varadarajan

Todd Constable
Xilin Shen
Dustin Scheinost
Xenophon Papademetris
Marvin Chun
Monica Rosenberg
Tamara Vanderwal

emily.finn@nih.gov

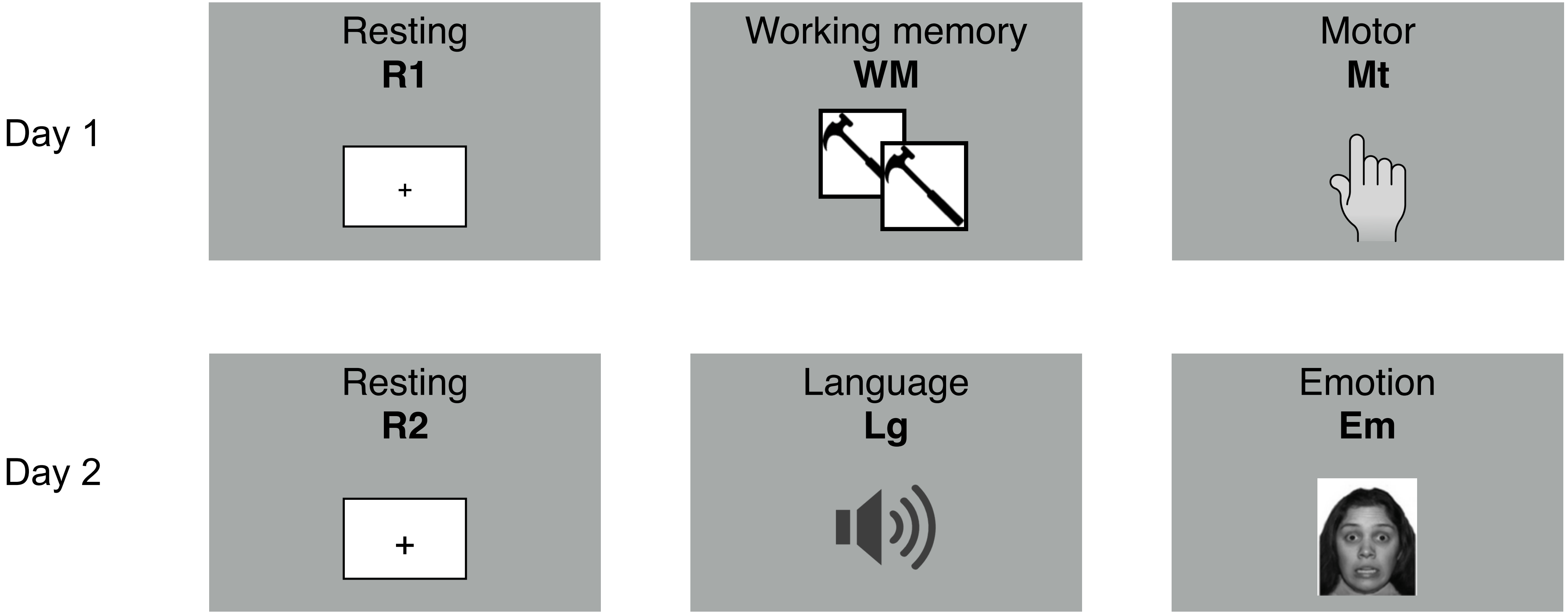
Functional connectivity



- Whole-brain organization
- Can use resting-state data

Identification experiments

Human Connectome Project
- 126 healthy subjects (50 sets of twins)
- Age 22-35 years old



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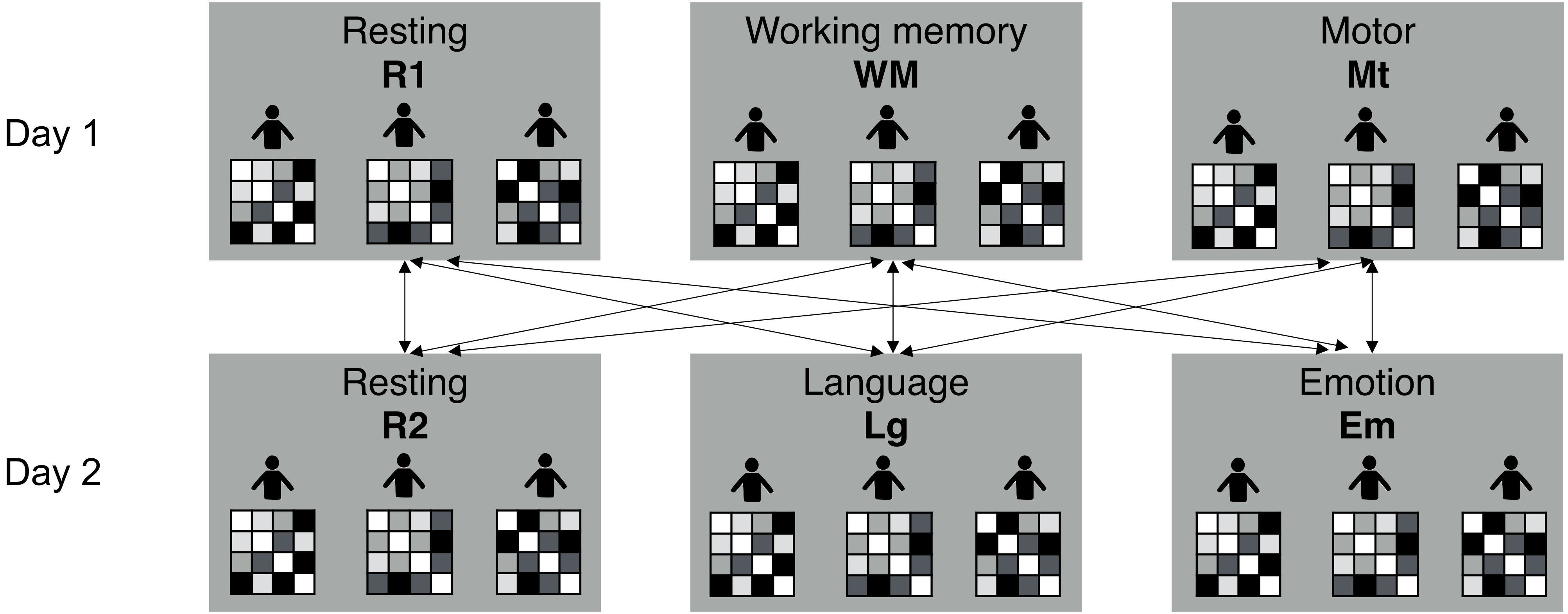
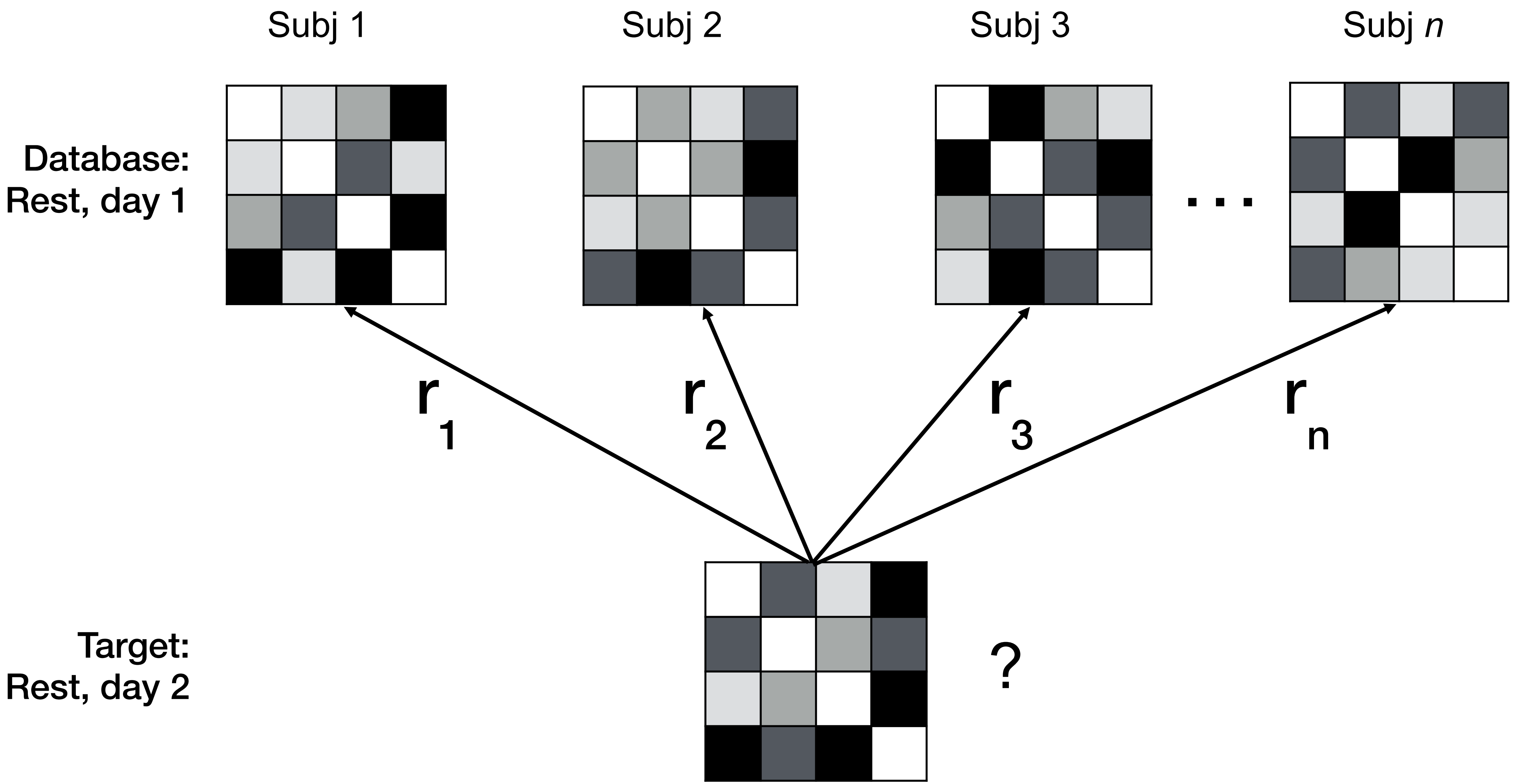
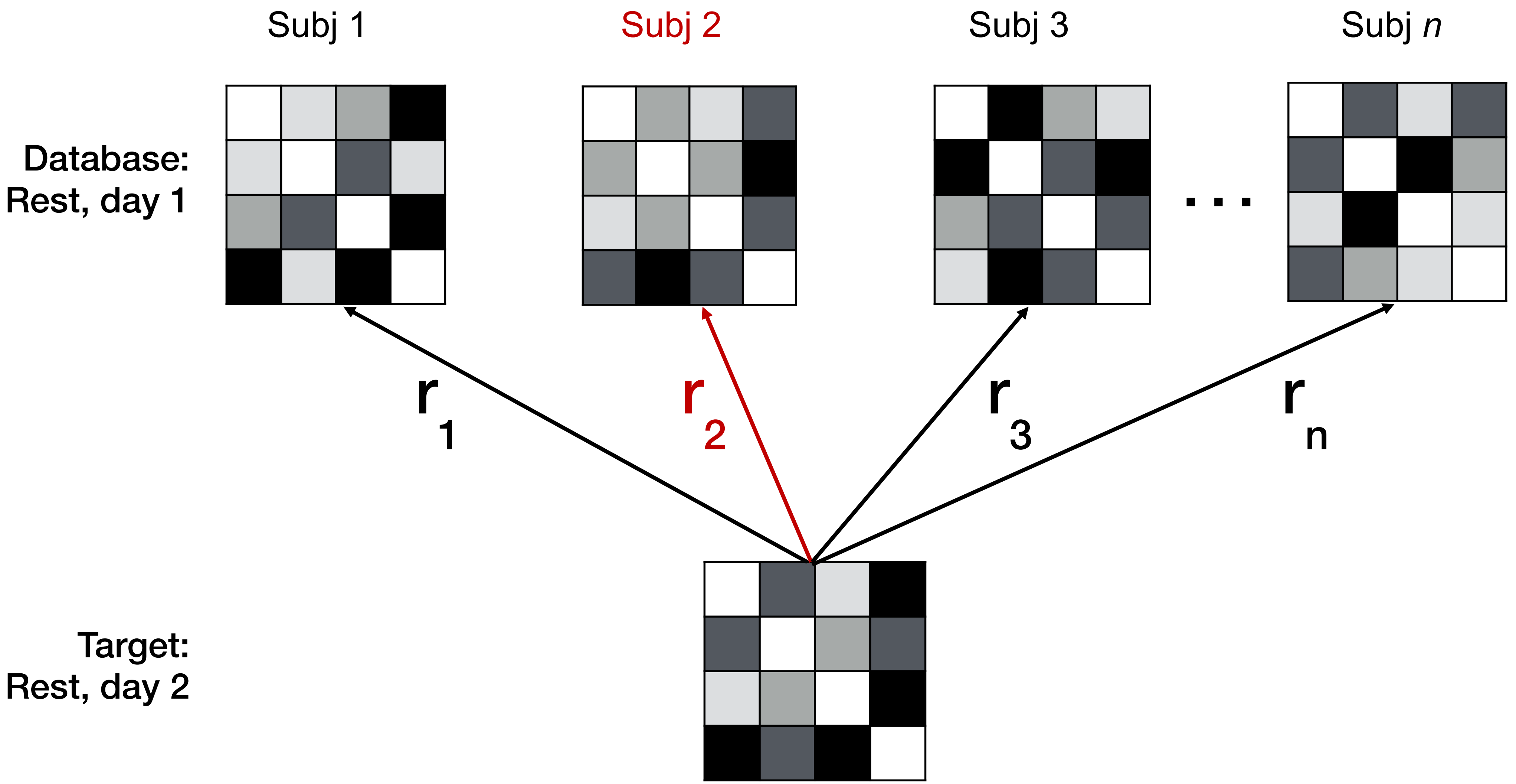


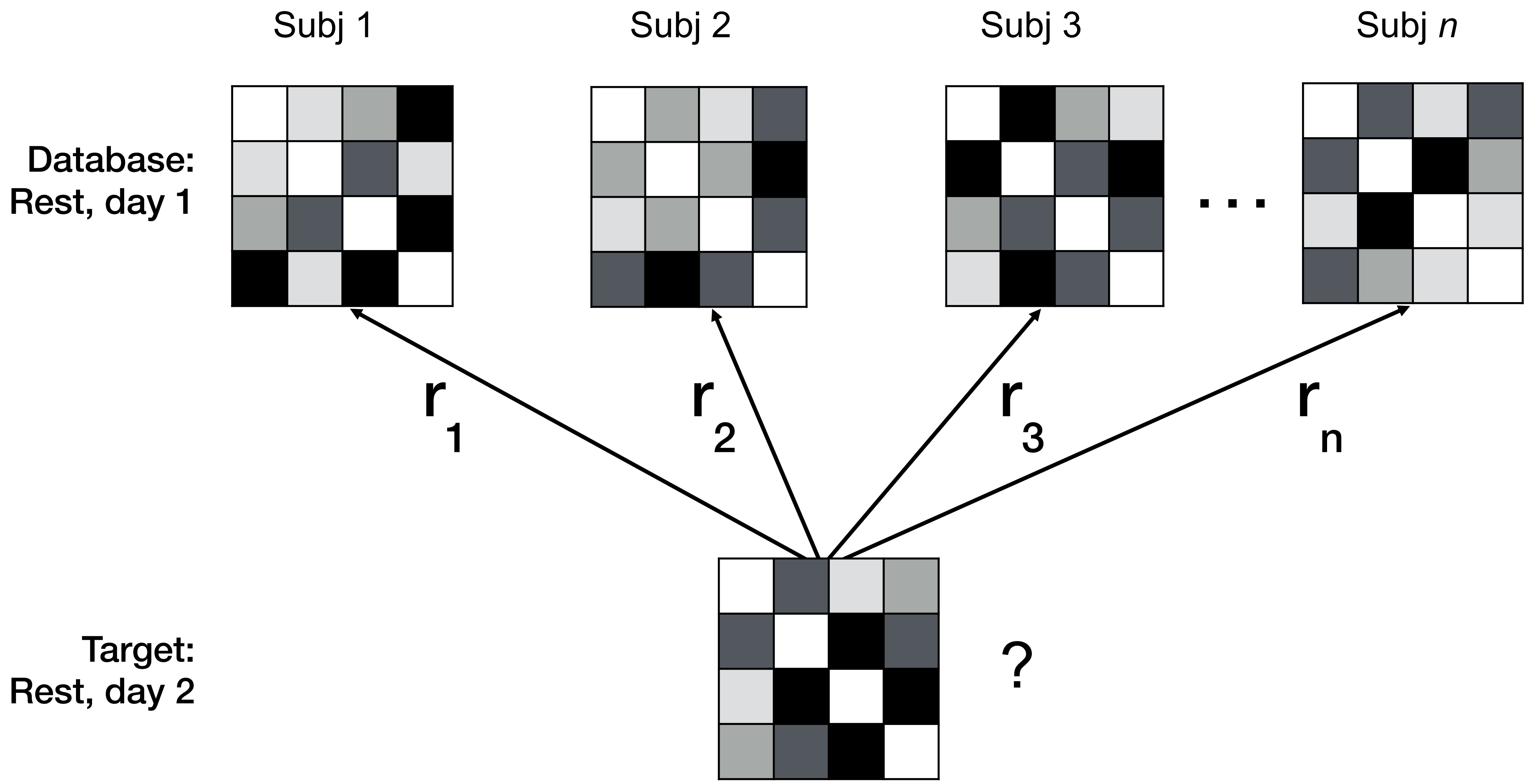
Identification experiments



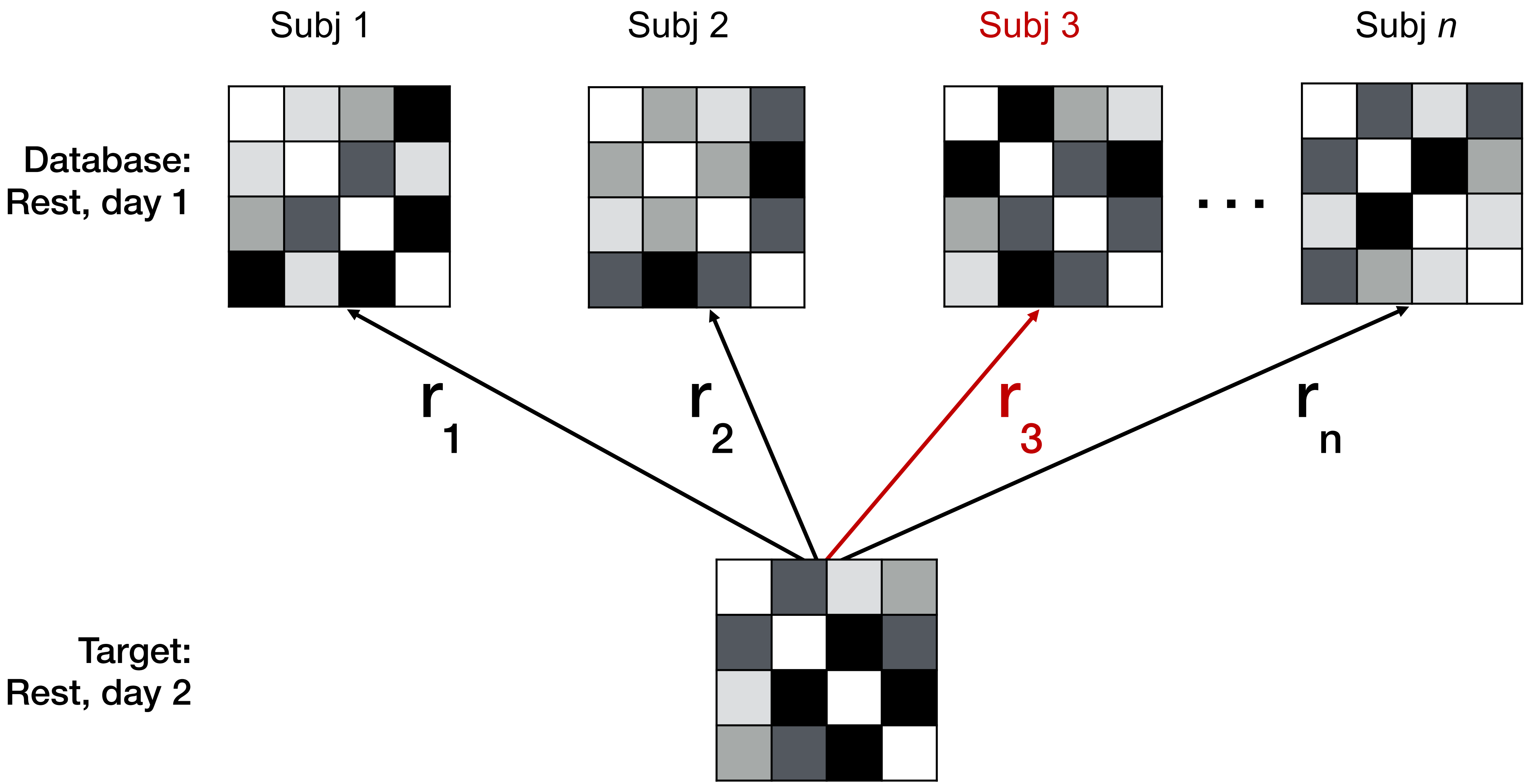
Identification experiments



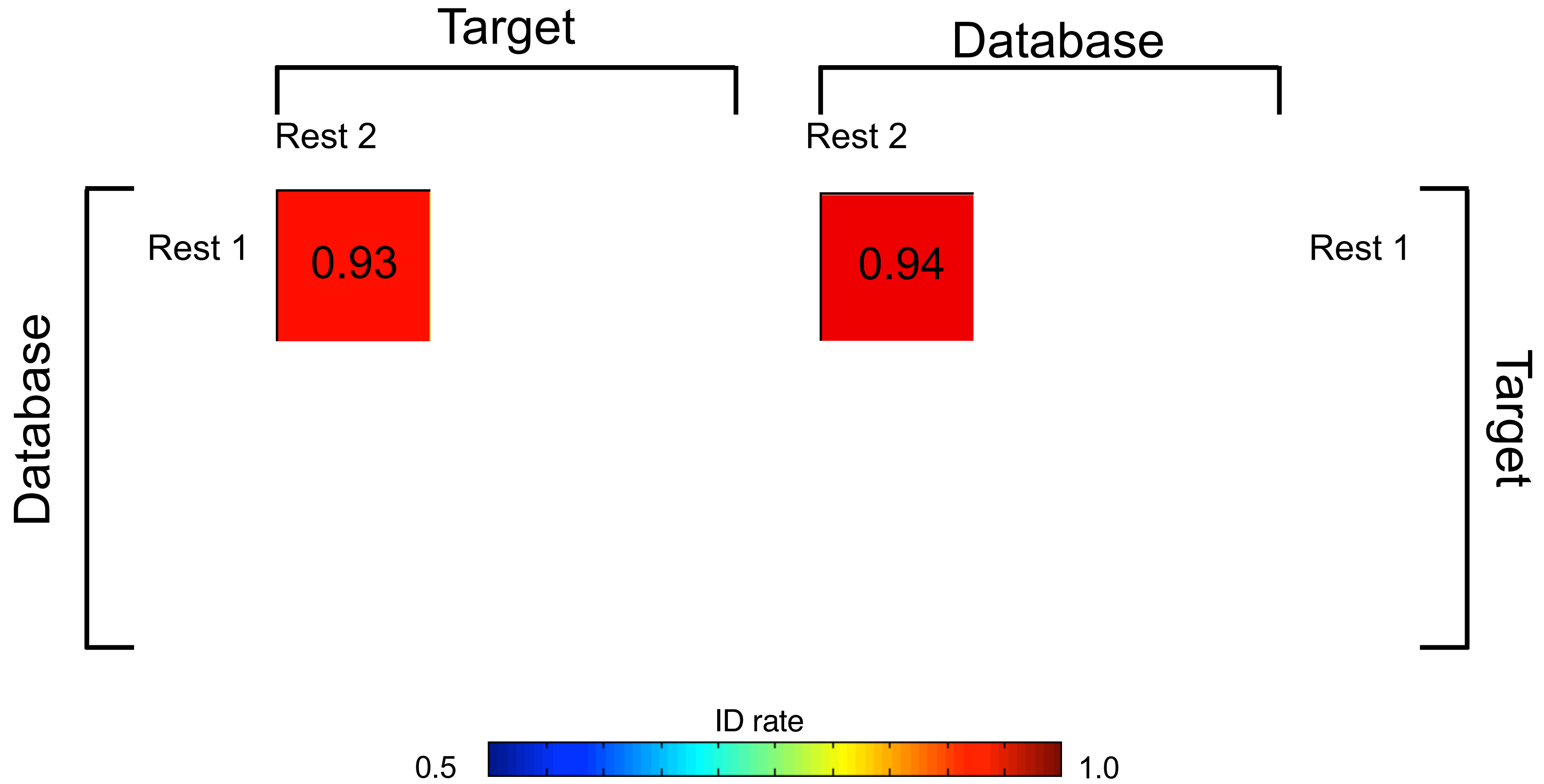
Identification experiments



Identification experiments



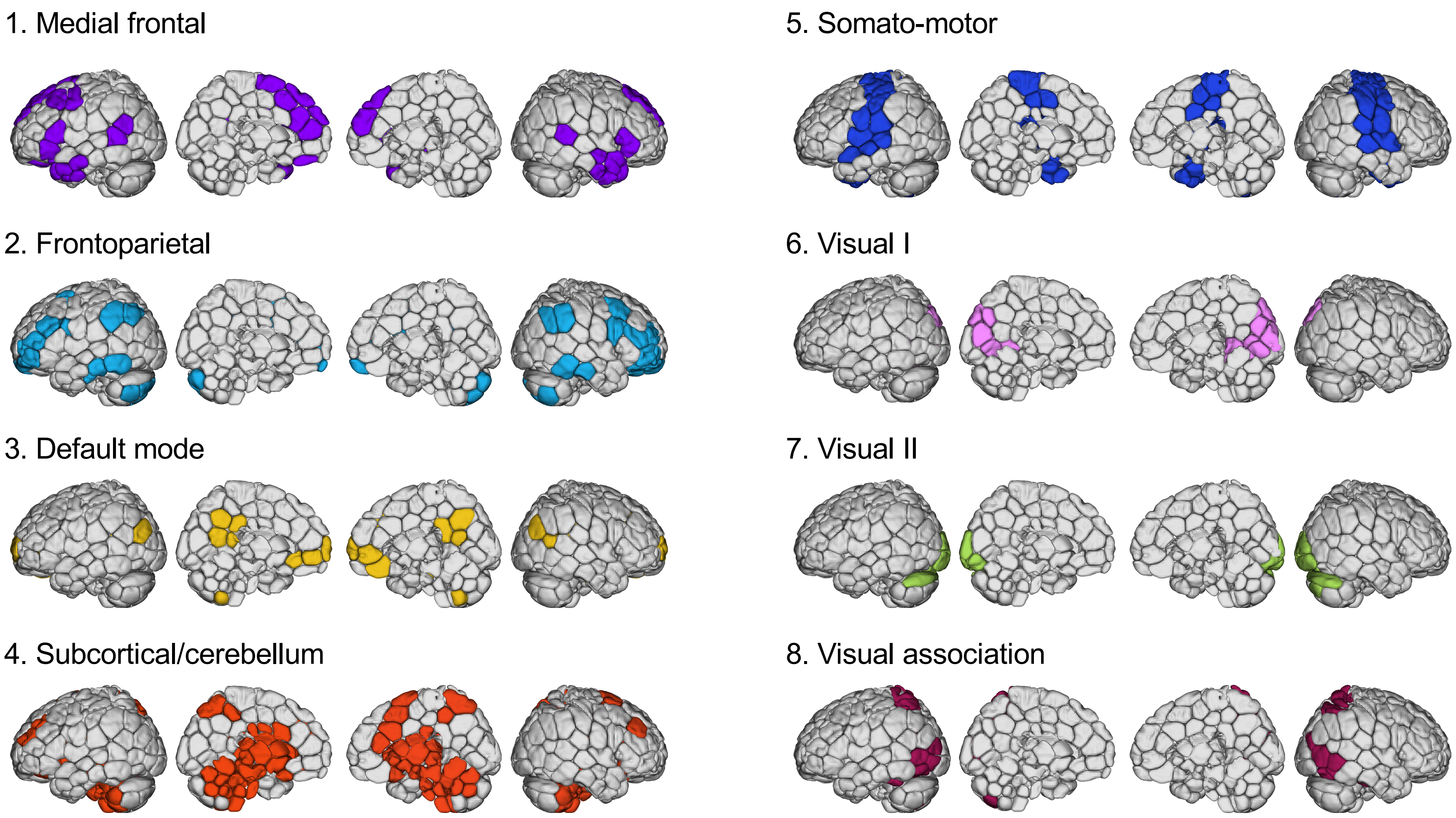
Identification results



Chance: ~0.008

Finn, Shen et al., *Nat Neurosci* (2015)

Network-based identification



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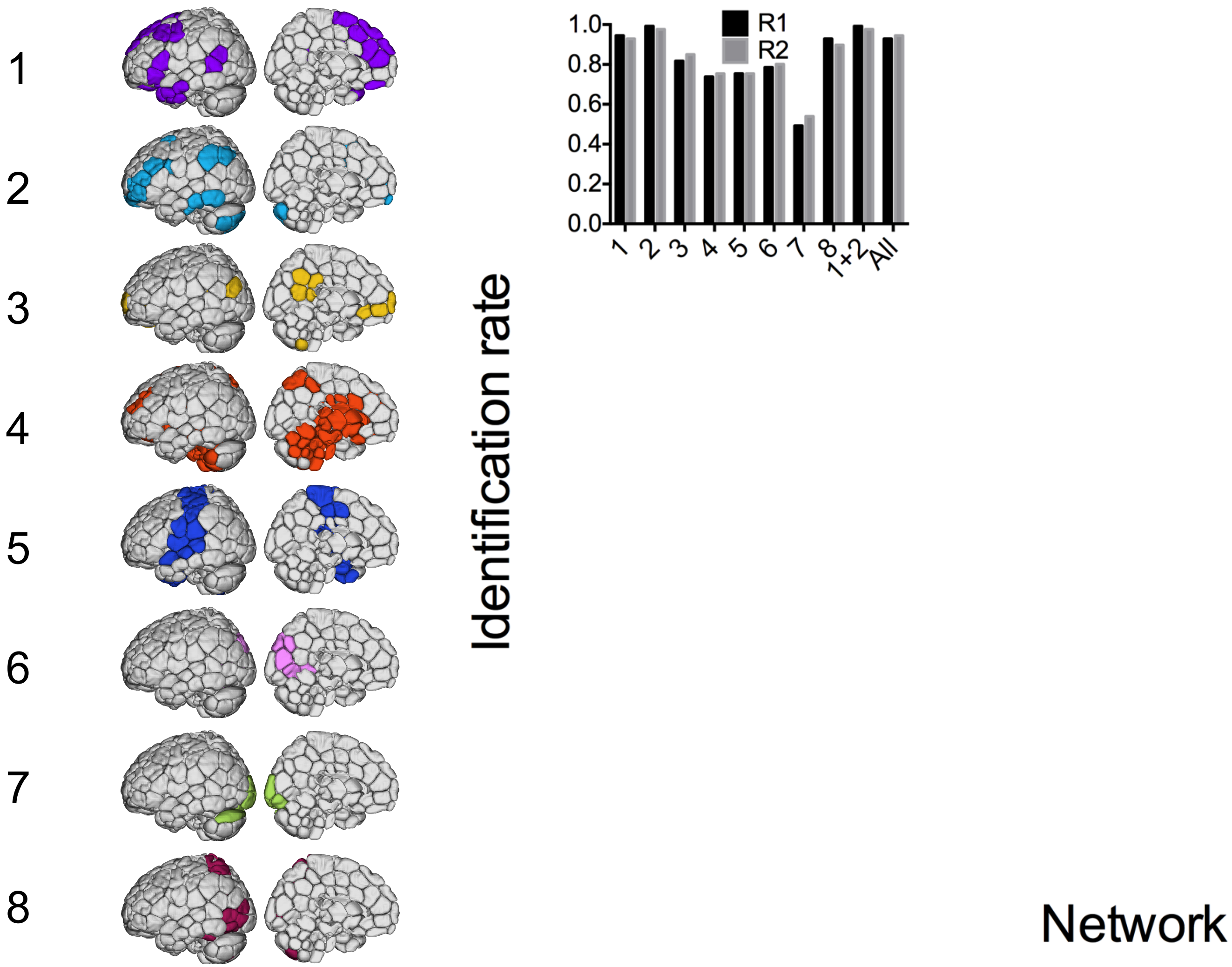

Finn, Shen et al., *Nat Neurosci* (2015)