

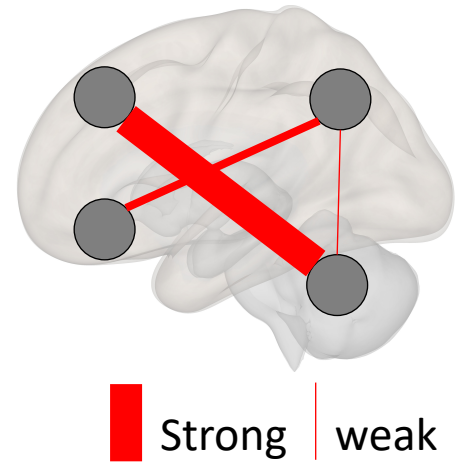
"Functional Connectivity:" What Do BOLD Correlations Tell Us About Brain Connectivity?

David Jangraw
Scientist, Emotion & Development Branch

*NIH Summer fMRI Course
August 13, 2019*

Outline

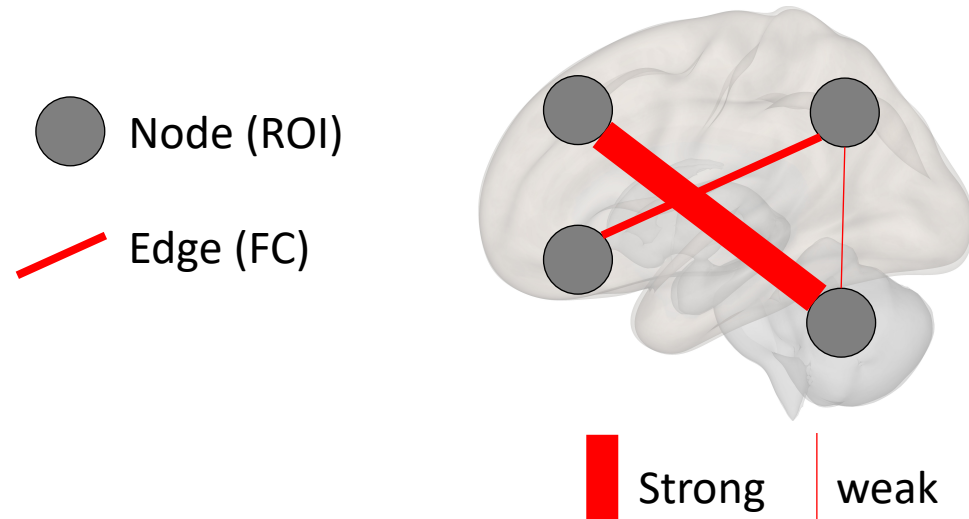
- What is functional connectivity (FC)?
- How are FC and structural connectivity (SC) measured?
- How different is FC from SC?
- Why do we use FC?
- How do we use FC?
- How might FC be used in the future?
- What controversies surround FC?



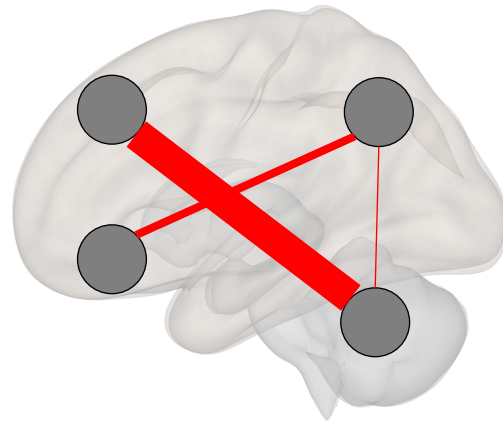
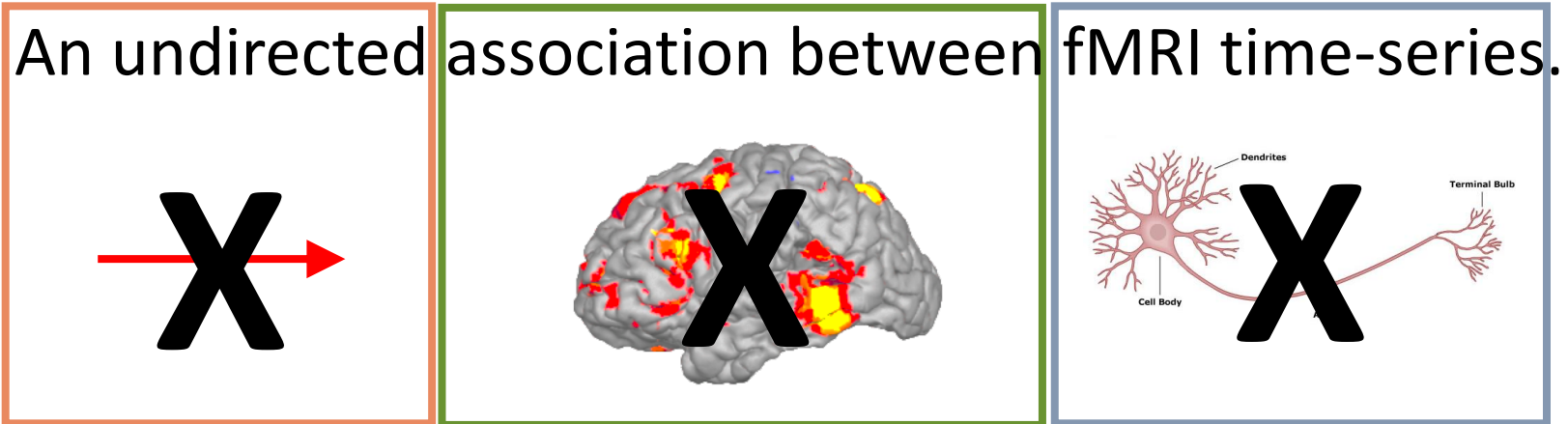
What is Functional Connectivity?


Functional Connectivity is:

An undirected association between fMRI time-series.



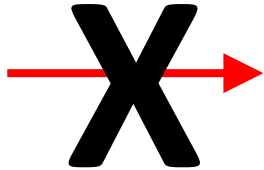
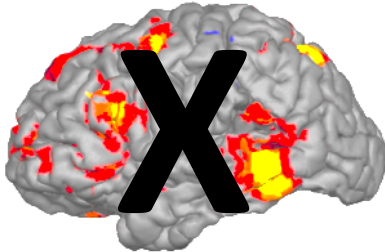
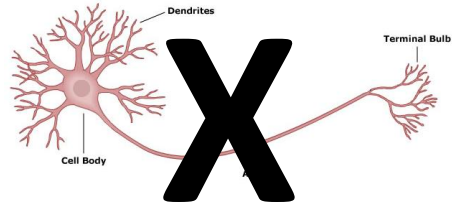
Functional Connectivity is:

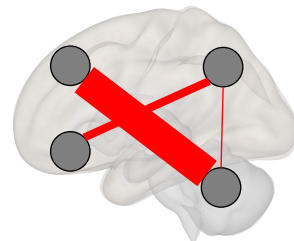


 Strong |  weak

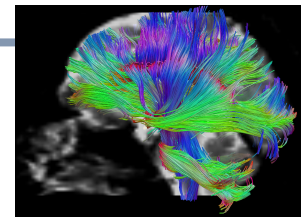
Functional Connectivity is:

An undirected association between fMRI time-series.

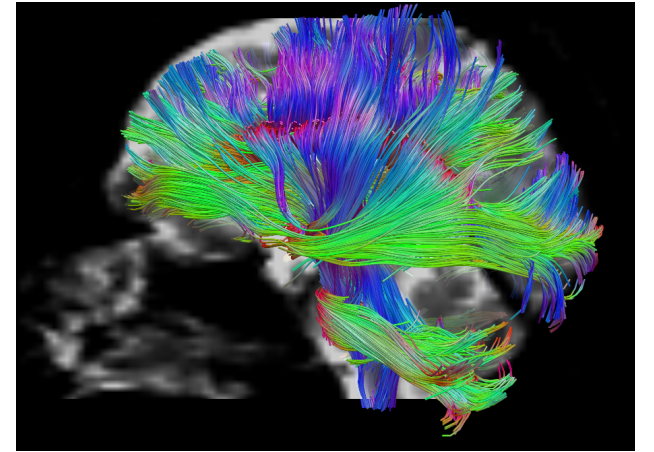
 <p>Unlike Effective connectivity</p>	 <p>Unlike BOLD magnitude</p>	 <p>Unlike Diffusion Tensor Imaging</p>
----------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------



Strong | weak



A measure of SC!



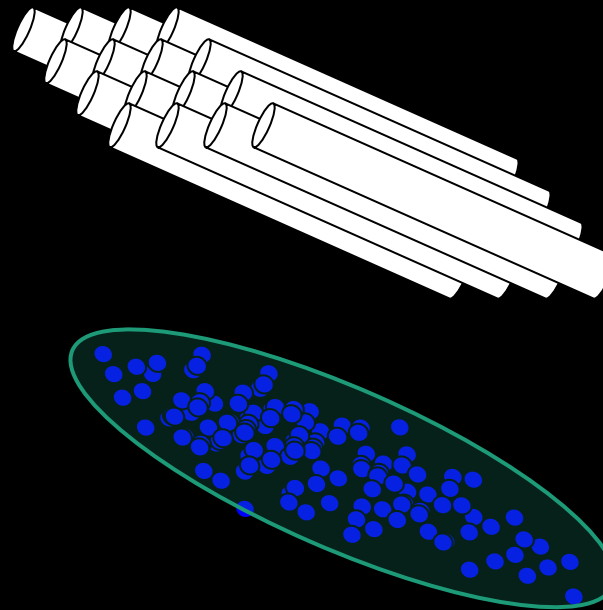
How are SC and FC measured?

Structural Connectivity: Diffusion Tensor Imaging

Water molecules diffuse randomly
in a homogenous space

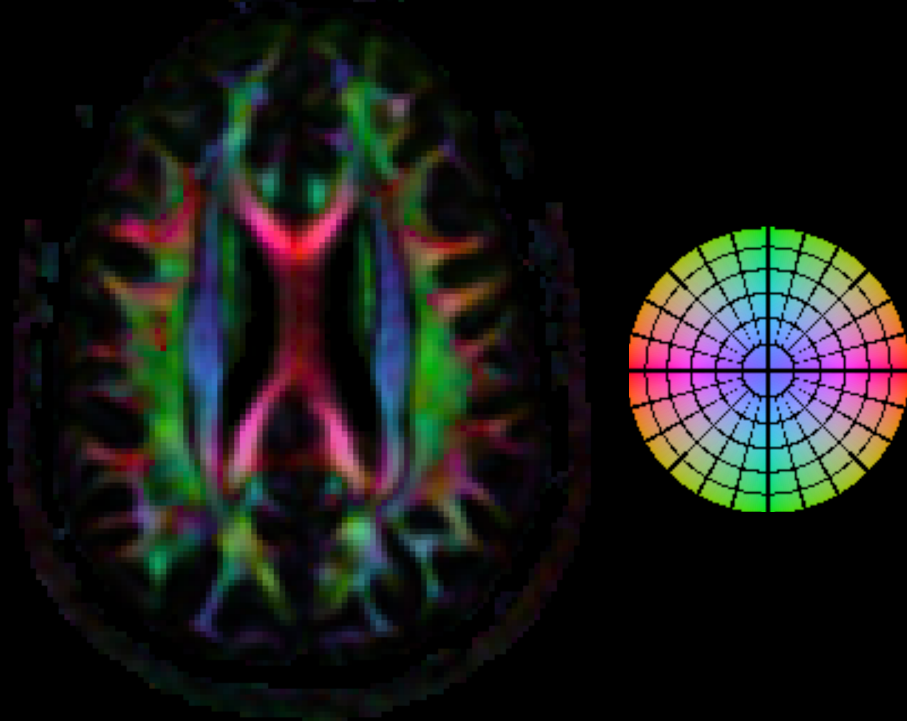


They're more likely to diffuse along
an axon than orthogonal to it:
Their **diffusion** is represented by a different tensor

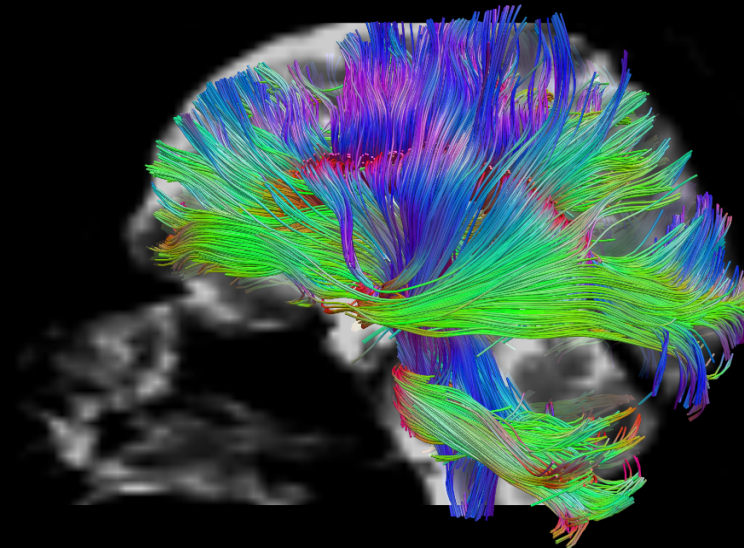


Structural Connectivity: Diffusion Tensor Imaging

You can estimate the primary axis of the diffusion tensor
and assign the voxel a corresponding color



And you can trace white matter
tracts (bundles of axons).



FC is correlation

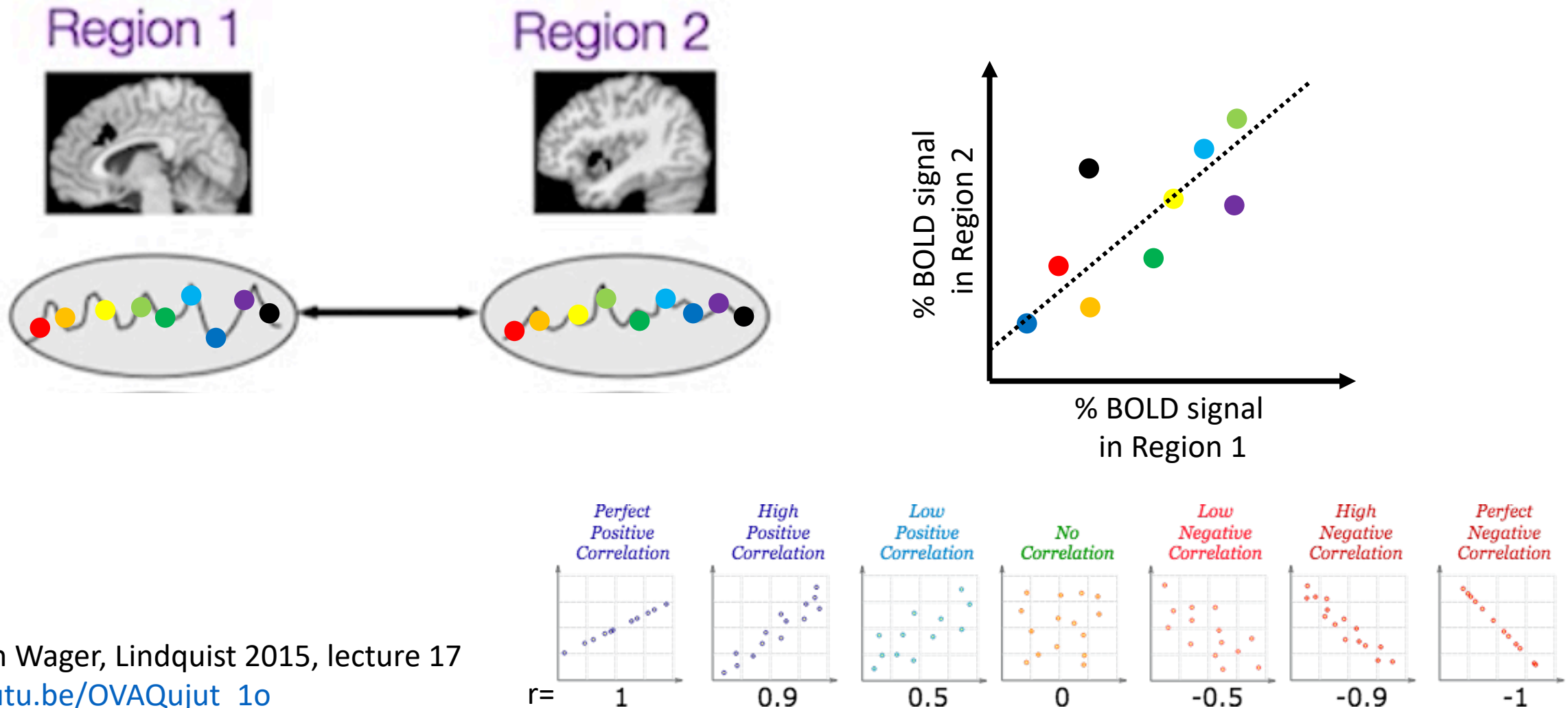


Figure from Wager, Lindquist 2015, lecture 17
https://youtu.be/OVAQujut_1o

Two-Region FC Analysis:

Do these regions have significant FC?

Is FC greater in one group than another?

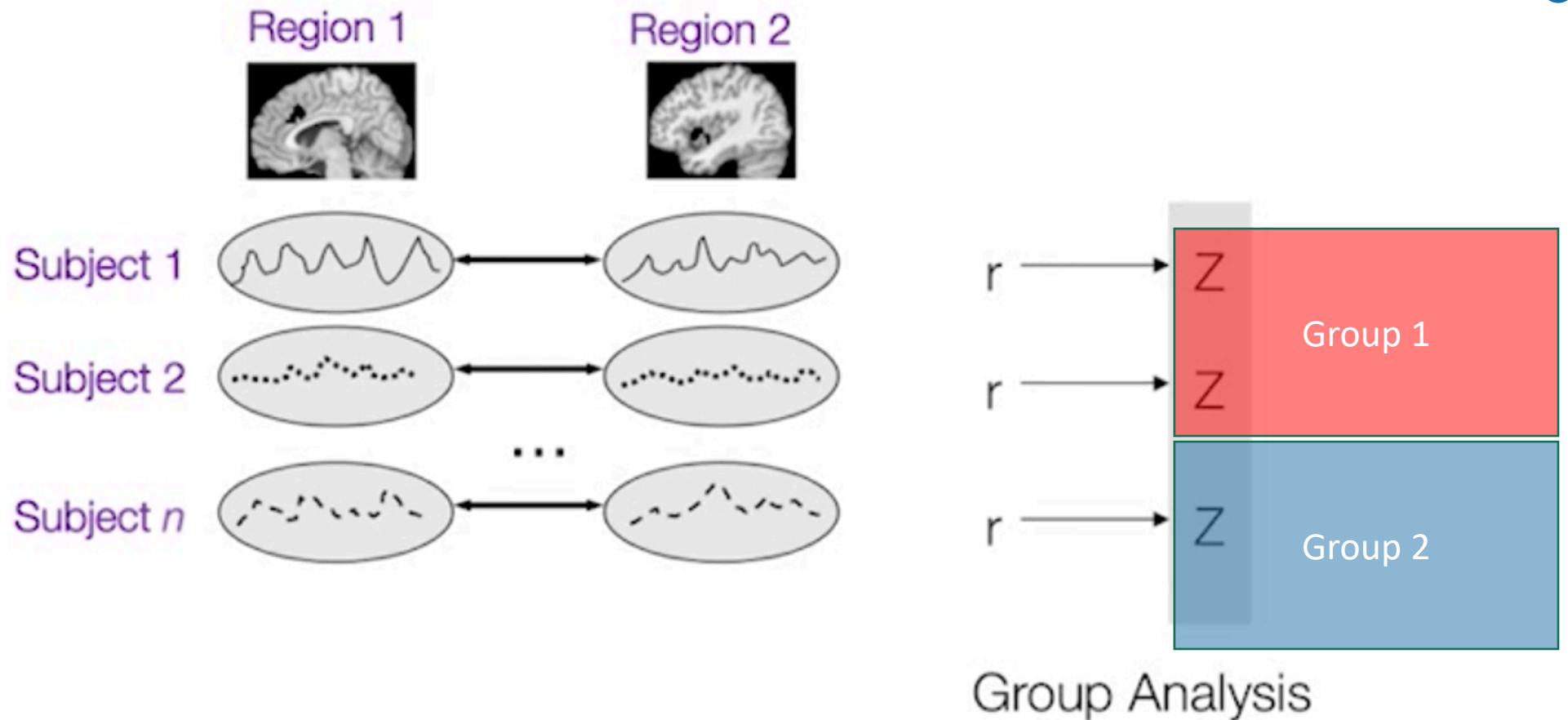


Figure from Wager, Lindquist 2015, lecture 17

https://youtu.be/OVAQujut_1o

Seed-Based FC Analysis:

With what other voxels does this region have strong FC?

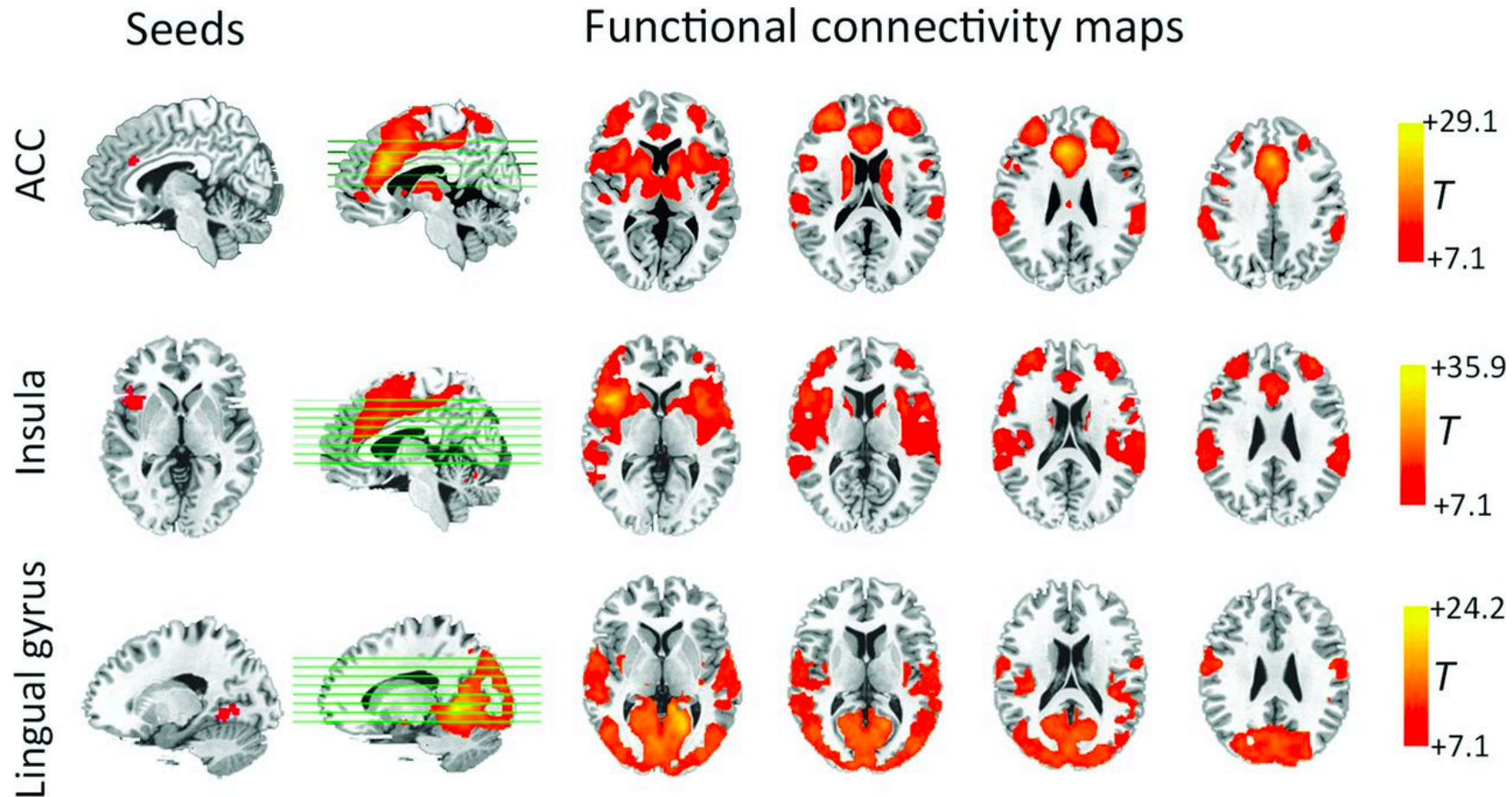


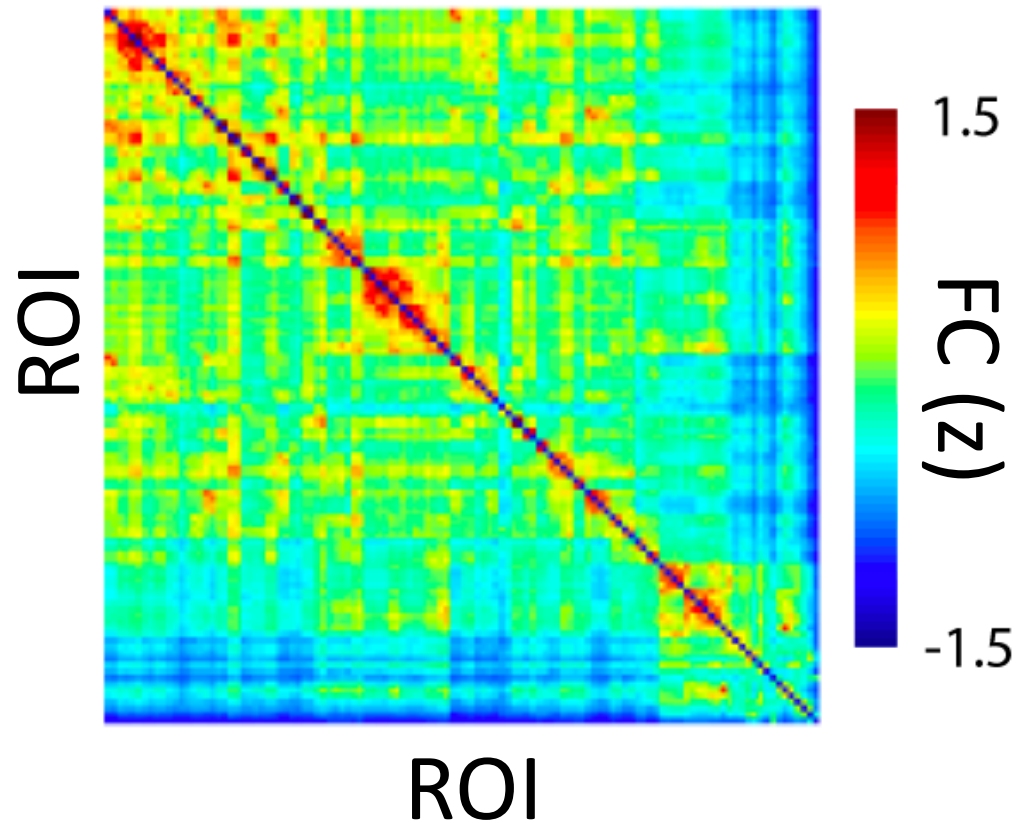
Figure from Cui 2016

<http://www.ajnr.org/content/37/11/2115>

Functional Connectome:

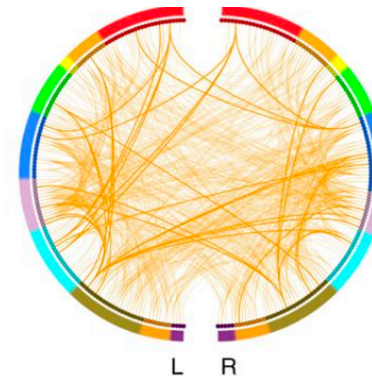
What is the FC of each parcel with every other?

FC Matrix



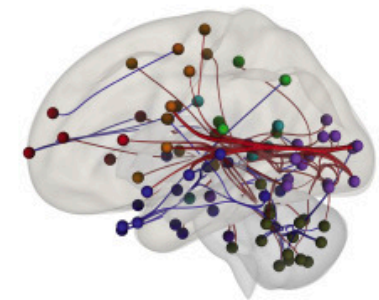
Circle Plot

(aka Connectome Ring)
(aka Spaghetti Plot)

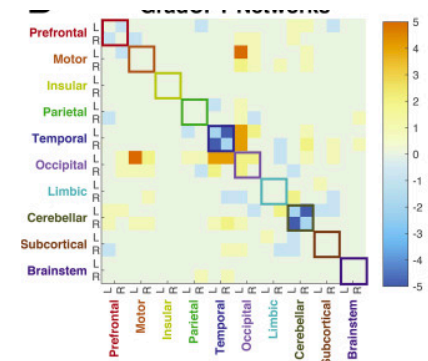


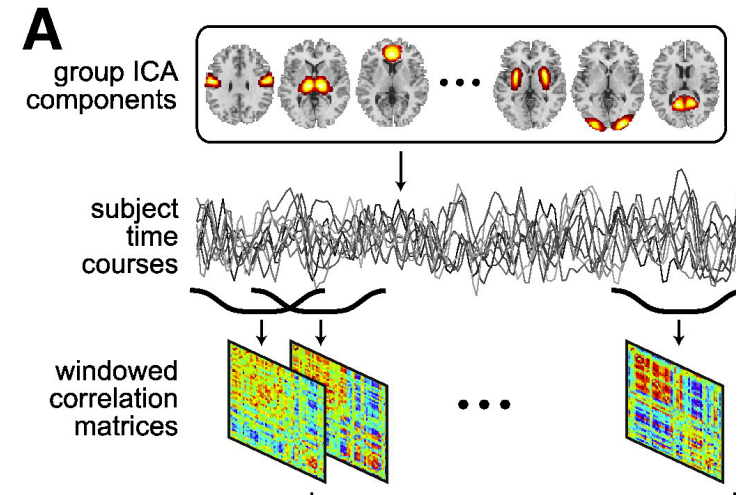
Brain Template Plot

(aka Ball and Stick Plot)
(aka Hairball)



Region Summary Matrix





How different is FC from SC?

rsFC and Structural Connectivity are Related

Raw SC explains about 1/4 of the variance of FC.

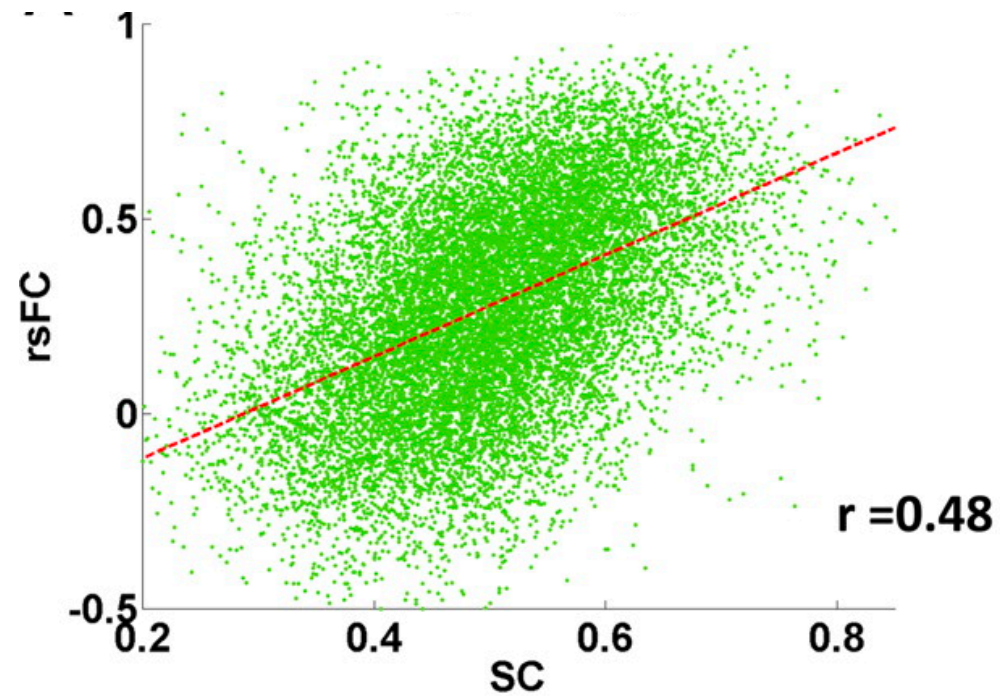
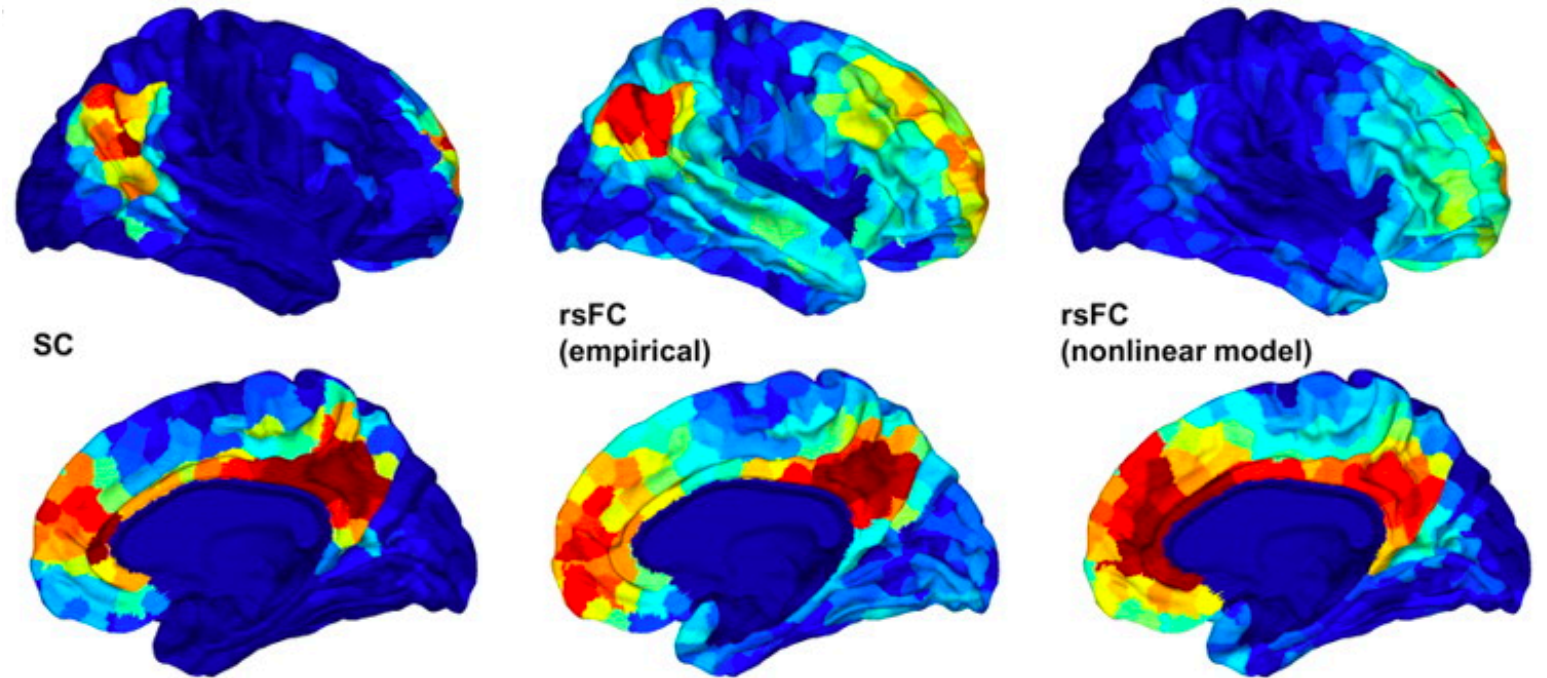
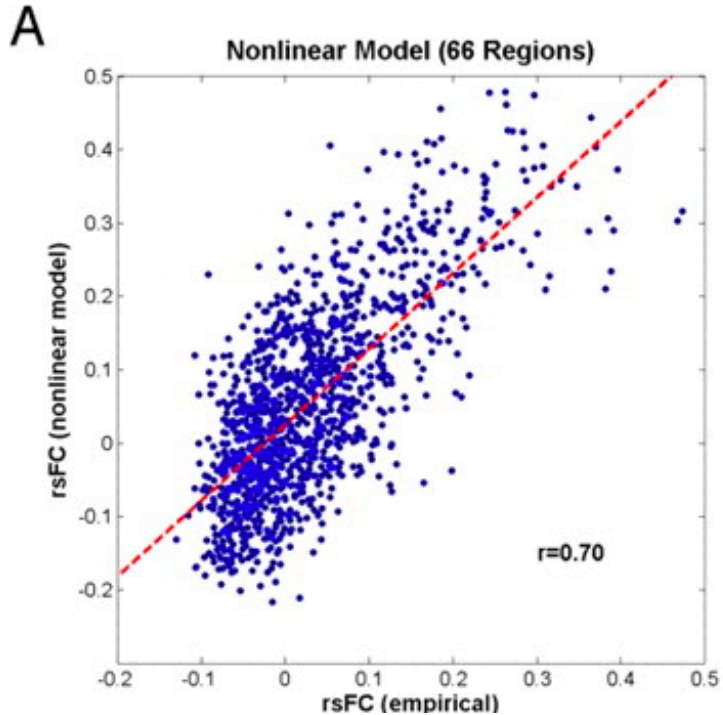


Figure from Honey, 2009

<https://www.pnas.org/content/106/6/2035/>

Predicting rsFC from Structural Connectivity

**A nonlinear model of how SC affects FC
can explain about 1/2 of the variance of FC.**



Figures from Honey, 2009

<https://www.pnas.org/content/106/6/2035/>

FC can be negative

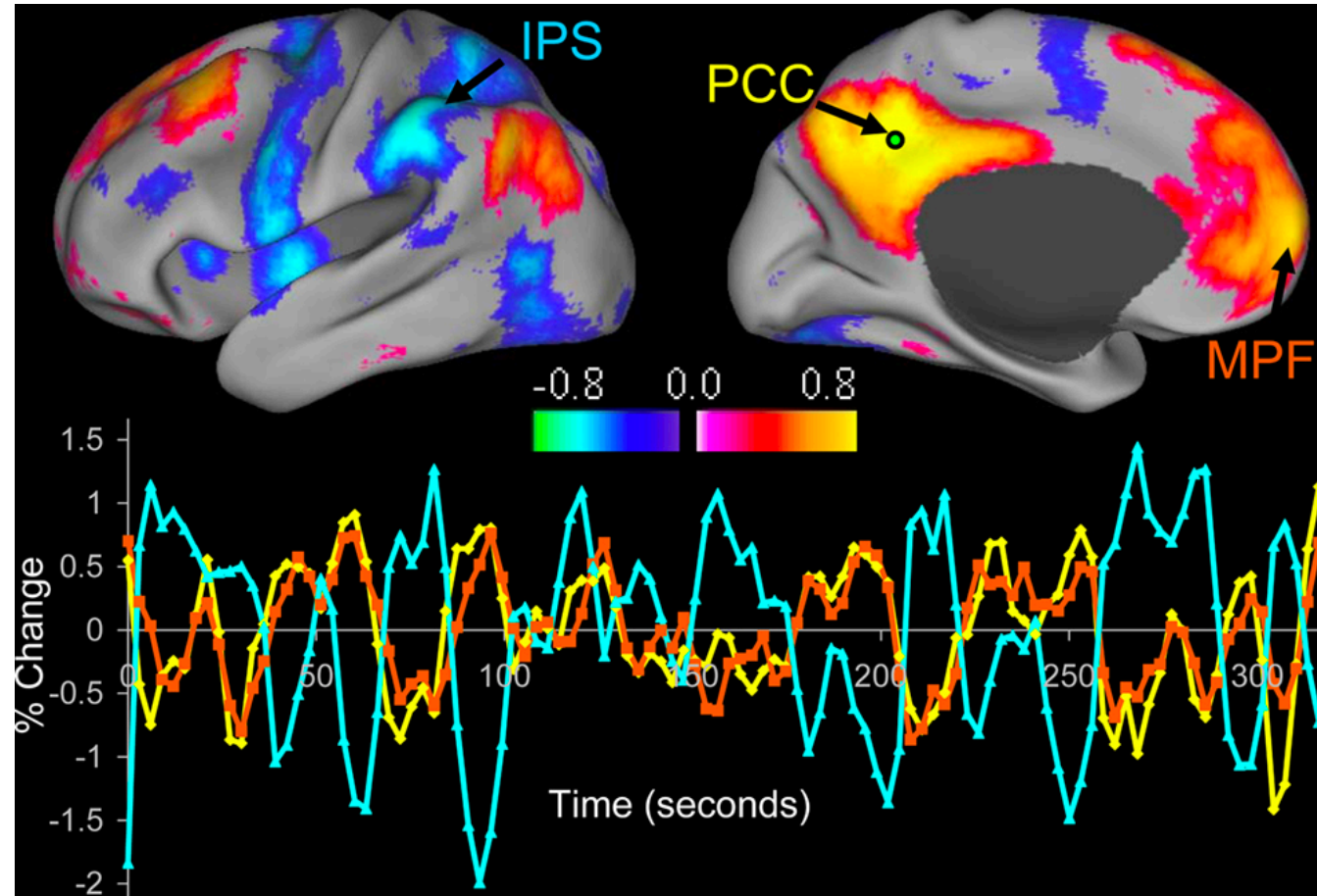
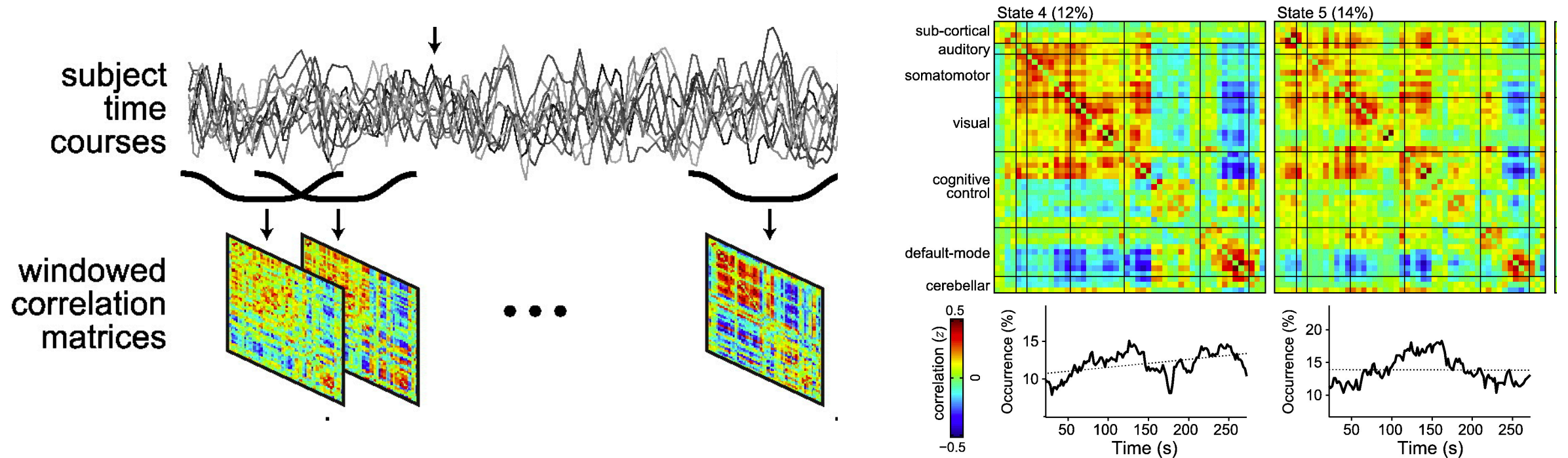


Figure from Fox 2005

<https://www.pnas.org/content/102/27/9673.long>

FC is dynamic



FC is dynamic

- <https://www.youtube.com/watch?v=o5WoiUGsh3E>

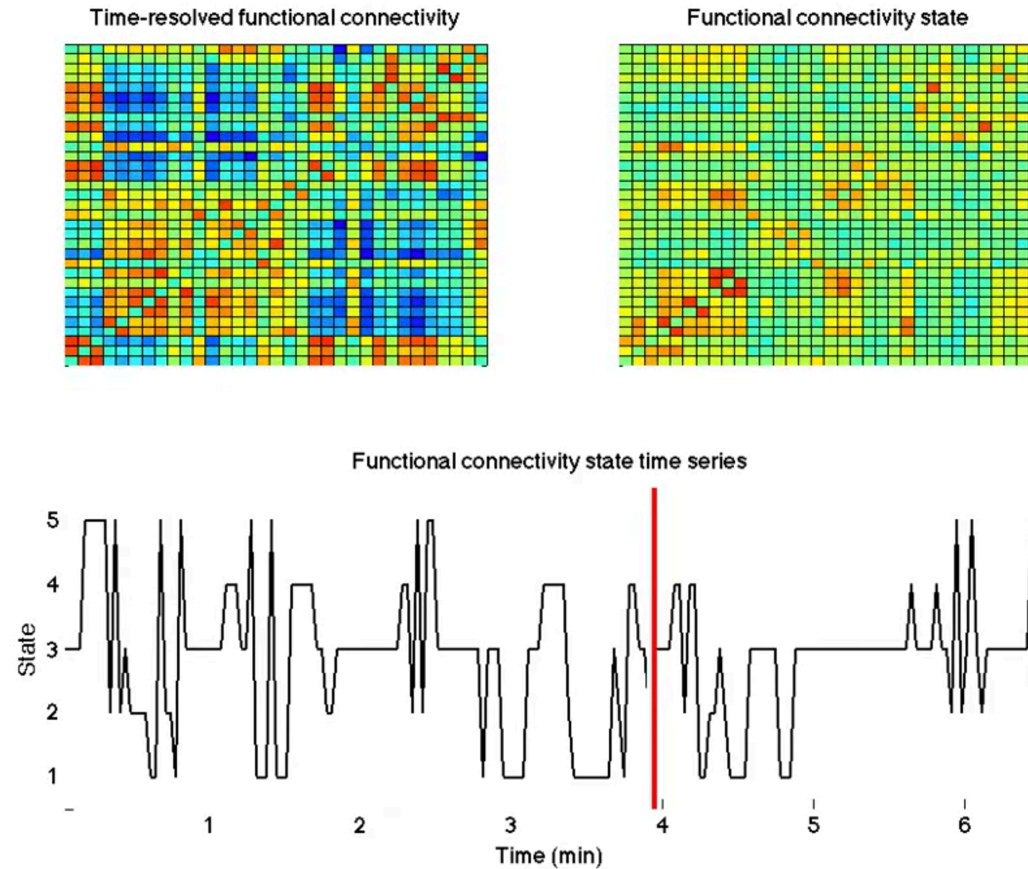
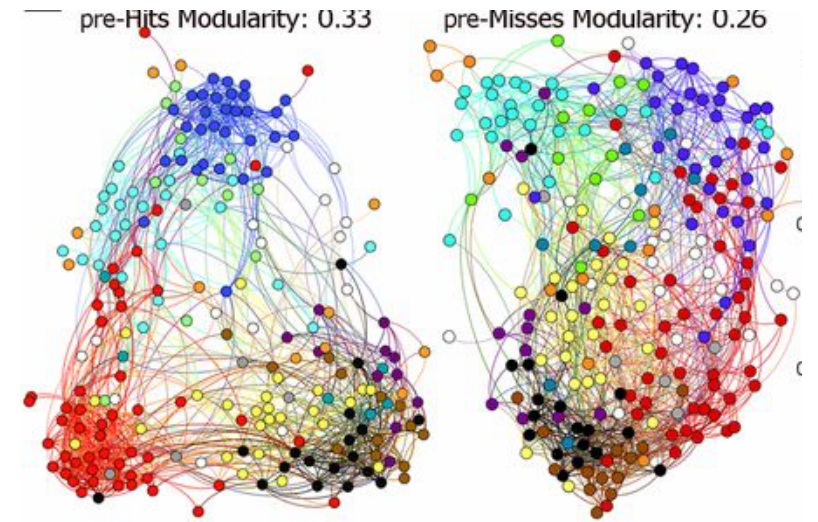


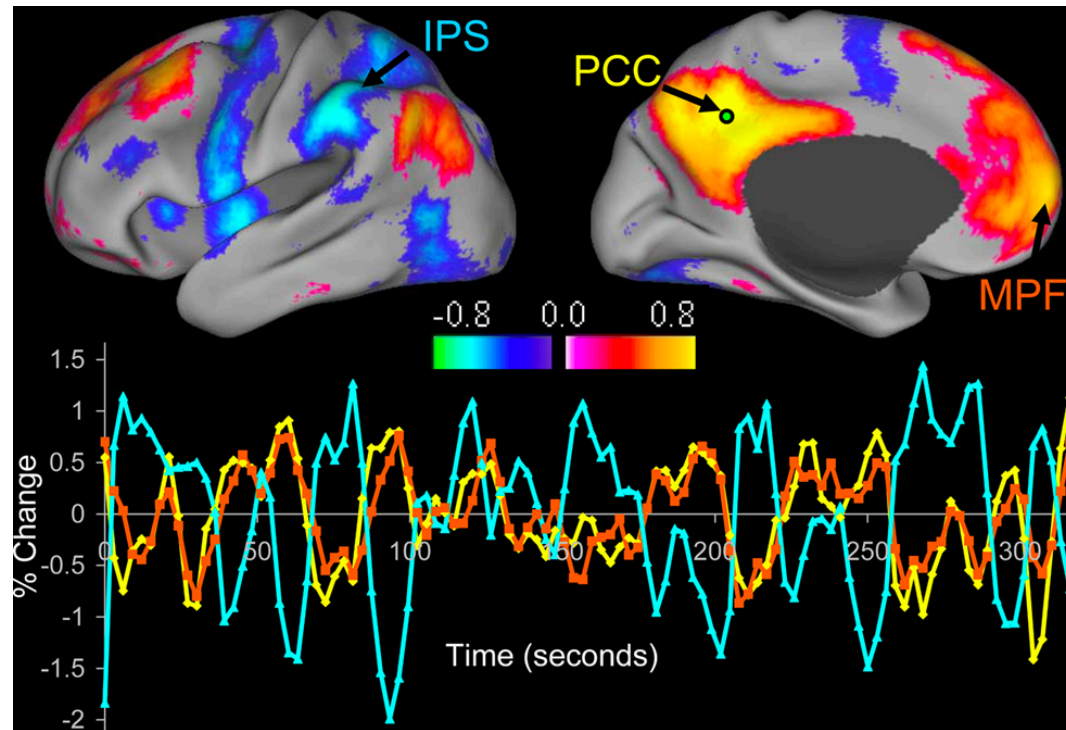
Figure from Tagliazucchi, 2015

<https://www.youtube.com/watch?v=o5WoiUGsh3E>



Why do we use FC?

FC is there (and big) even at rest



Task activations are small additions to resting activity: they account for only 1-5% of the BOLD signal.

Figure from Fox 2005

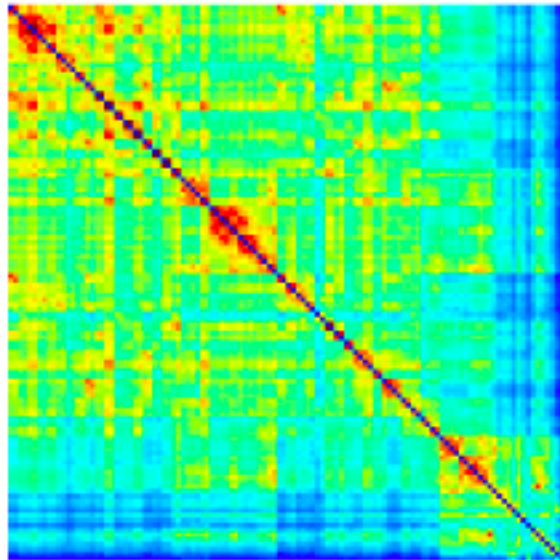
<https://www.pnas.org/content/102/27/9673.long>

Info from Damoiseaux, 2009

<https://link.springer.com/article/10.1007/s00429-009-0208-6>

FC is stable across scans

Resting 1



Resting 2

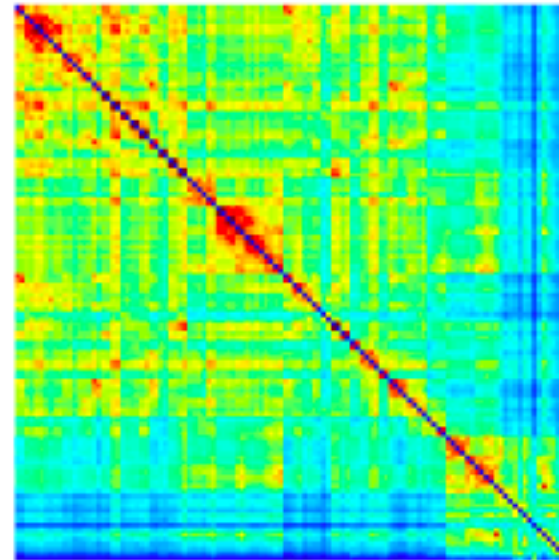
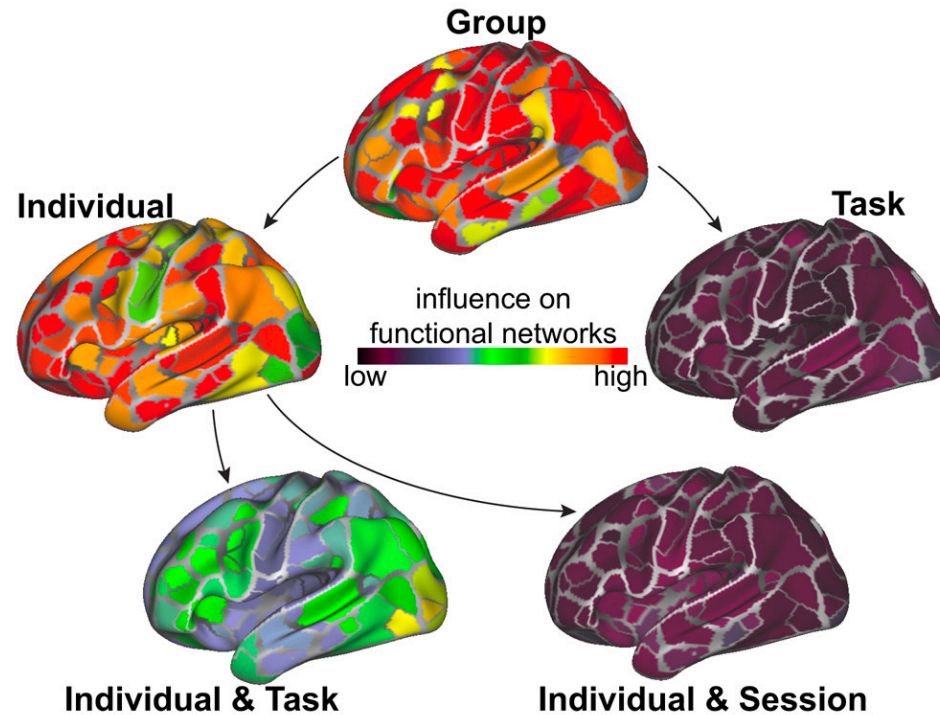


Figure from Masic 2014

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0111007>

FC varies across individuals and tasks

Variance in human functional brain networks attributable to:



Stability and sensitivity to individual differences suggests utility in precision medicine

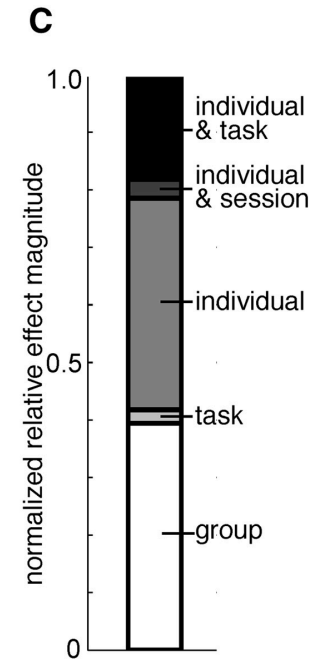
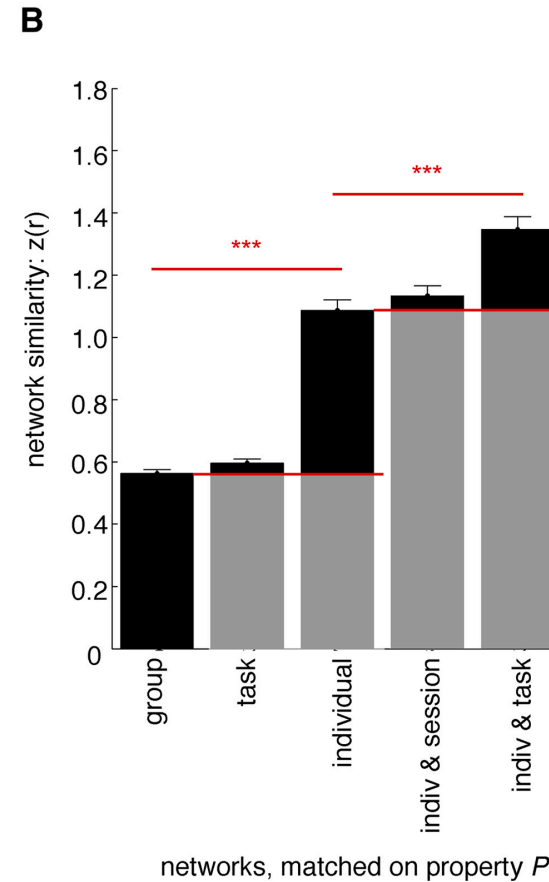
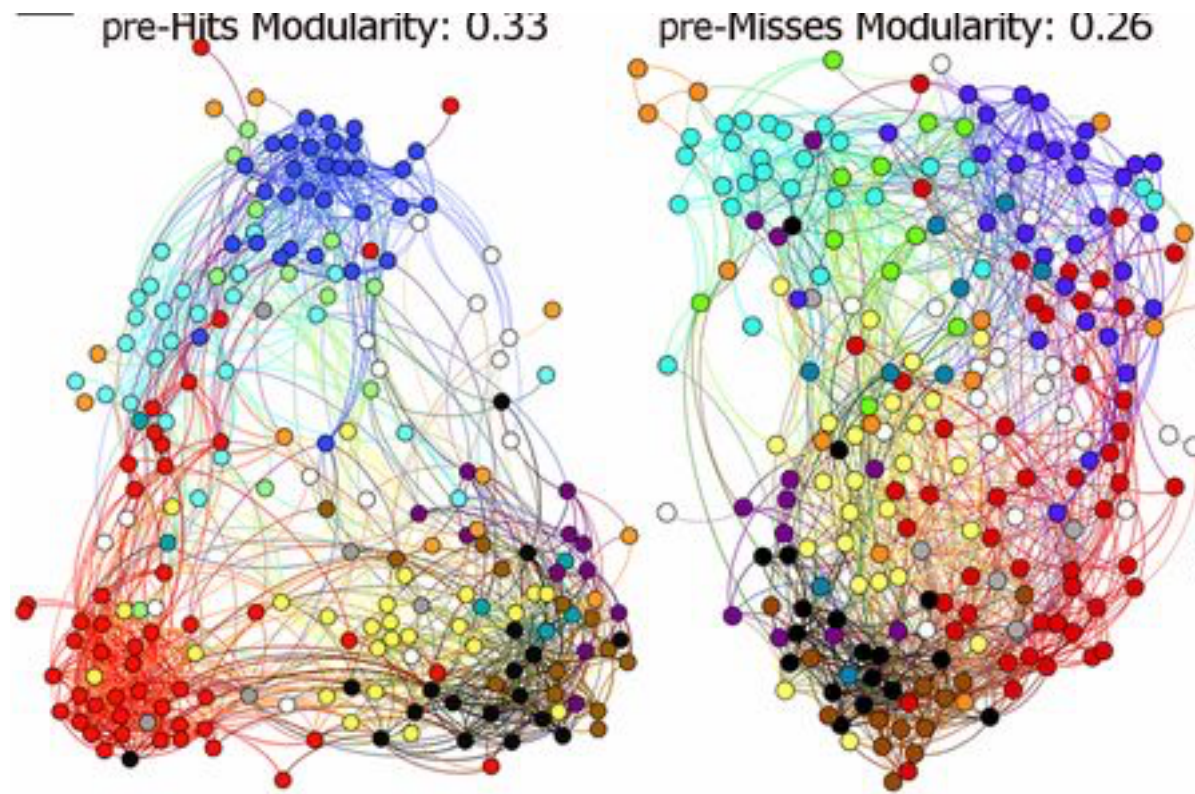


Figure from Gratton 2018

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5912345/>

FC gives us access to network analyses



Graph Theory Terms:

- Topology
- Modularity
- Order
- Small-worldness
- Hubs
- Rich Clubs
- Clustering Coefficient
- Characteristic Path Length
- Network/Global Efficiency

Figure from Sadaghiani, 2015

<https://www.pnas.org/content/112/27/8463>

For more on graph theory, see Boccaletti, 2006

<https://doi.org/10.1016/j.physrep.2005.10.009>

For graph theory in MRI, see Bullmore, 2009

<https://www.nature.com/articles/nrn2575>

And Rubinov, 2010

<https://doi.org/10.1016/j.neuroimage.2009.10.003>

And talks by Dani Bassett

EX: <https://youtu.be/O9GPZ-csR60>

FC predicts behavior & traits

Tone Detection Task

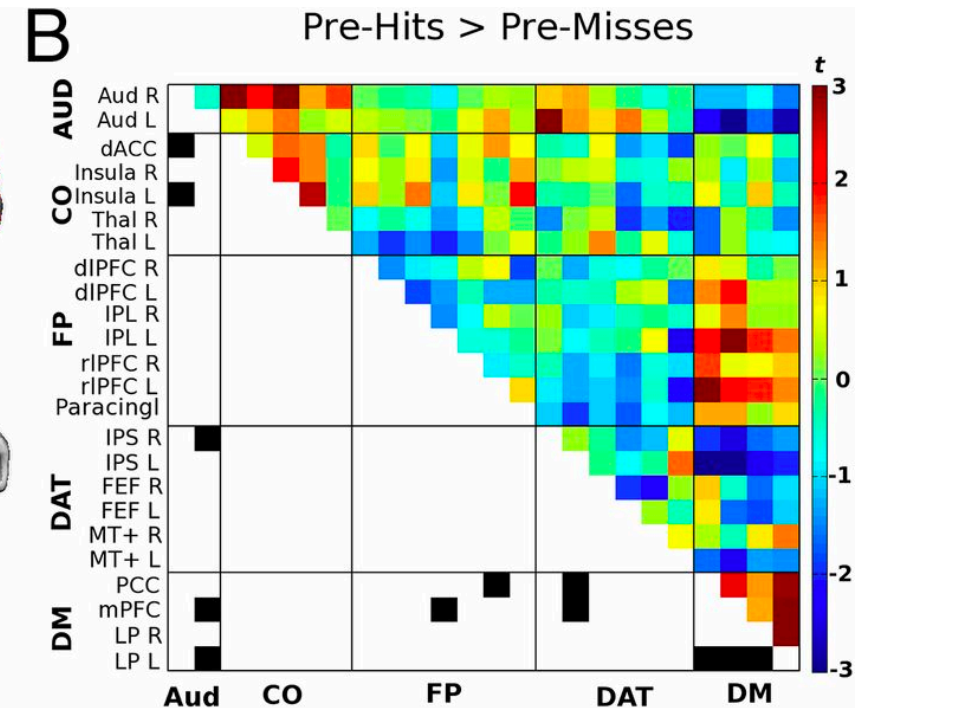
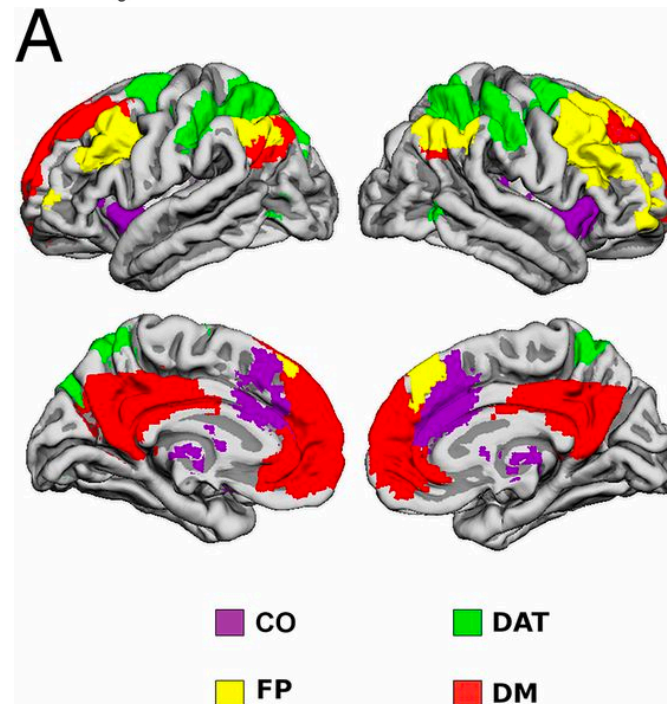
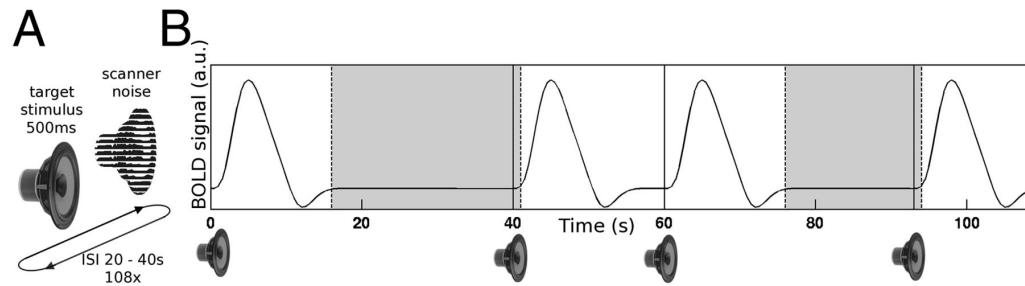
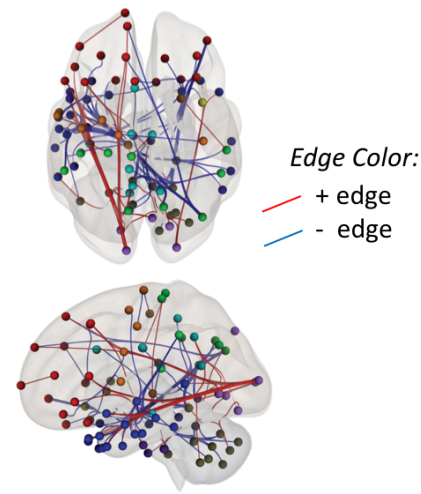


Figure from Sadaghiani 2015

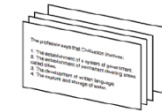
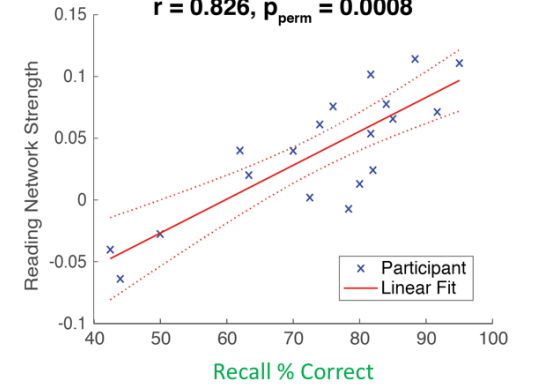
<https://www.pnas.org/content/112/27/8463>

Reading Network



FC in Reading Network Predicts Subject's Recall (LOO Cross-Validated)

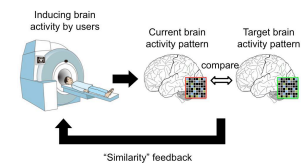
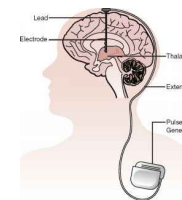
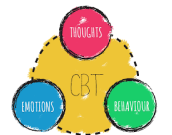
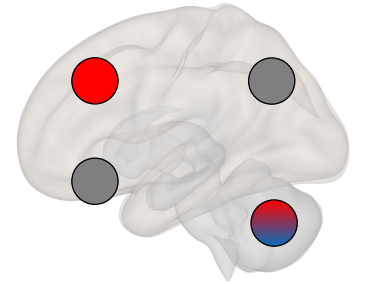
$r = 0.826$, $p_{\text{perm}} = 0.0008$



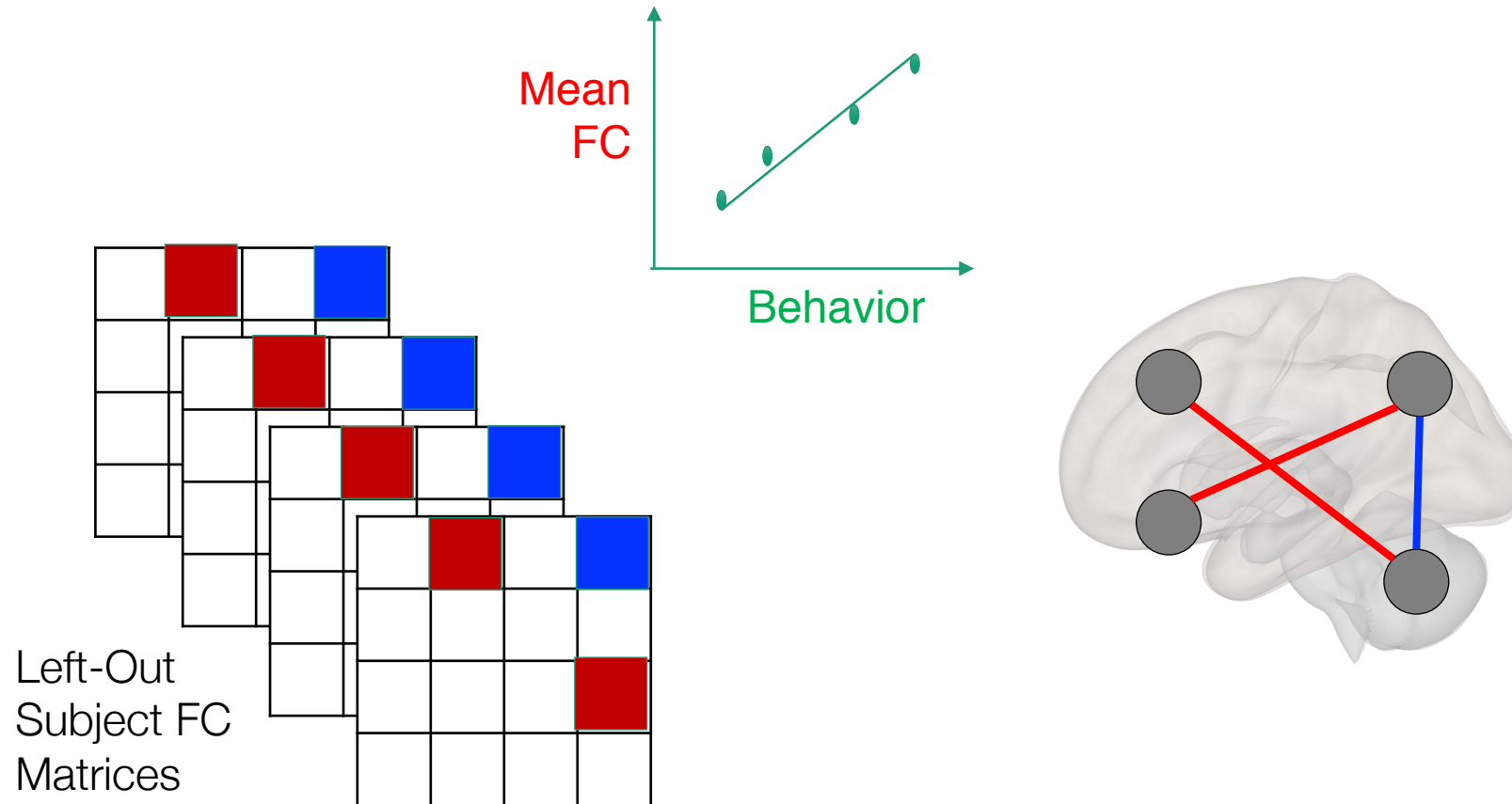
How do we use FC?

Predicting Traits & Behavior from FC

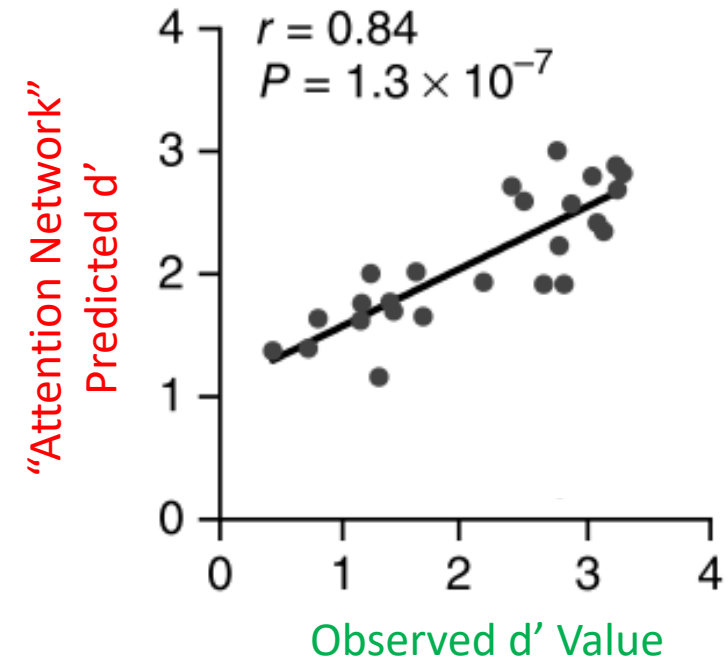
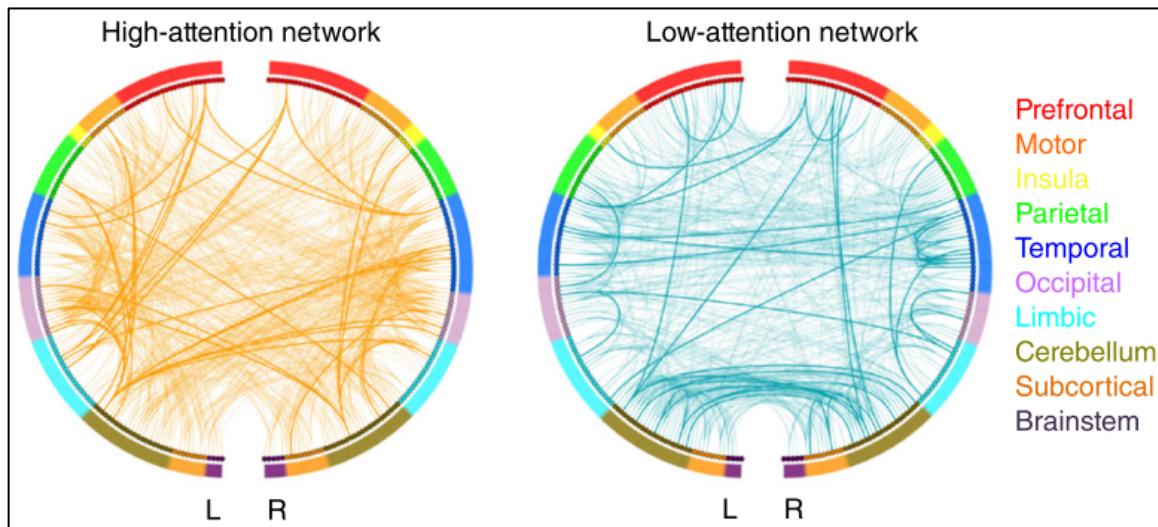
- Shed light on neural processes and **individual differences**
- Make brain-based diagnoses and **predictions**
- Suggest targeted **interventions**
 - Drugs
 - Therapy
 - Brain stimulation
 - Neurofeedback



Predicting Traits & Behavior from Whole-Brain FC



FC Predicts Performance in Sustained Attention



FC Predicts Performance in Reading Recall

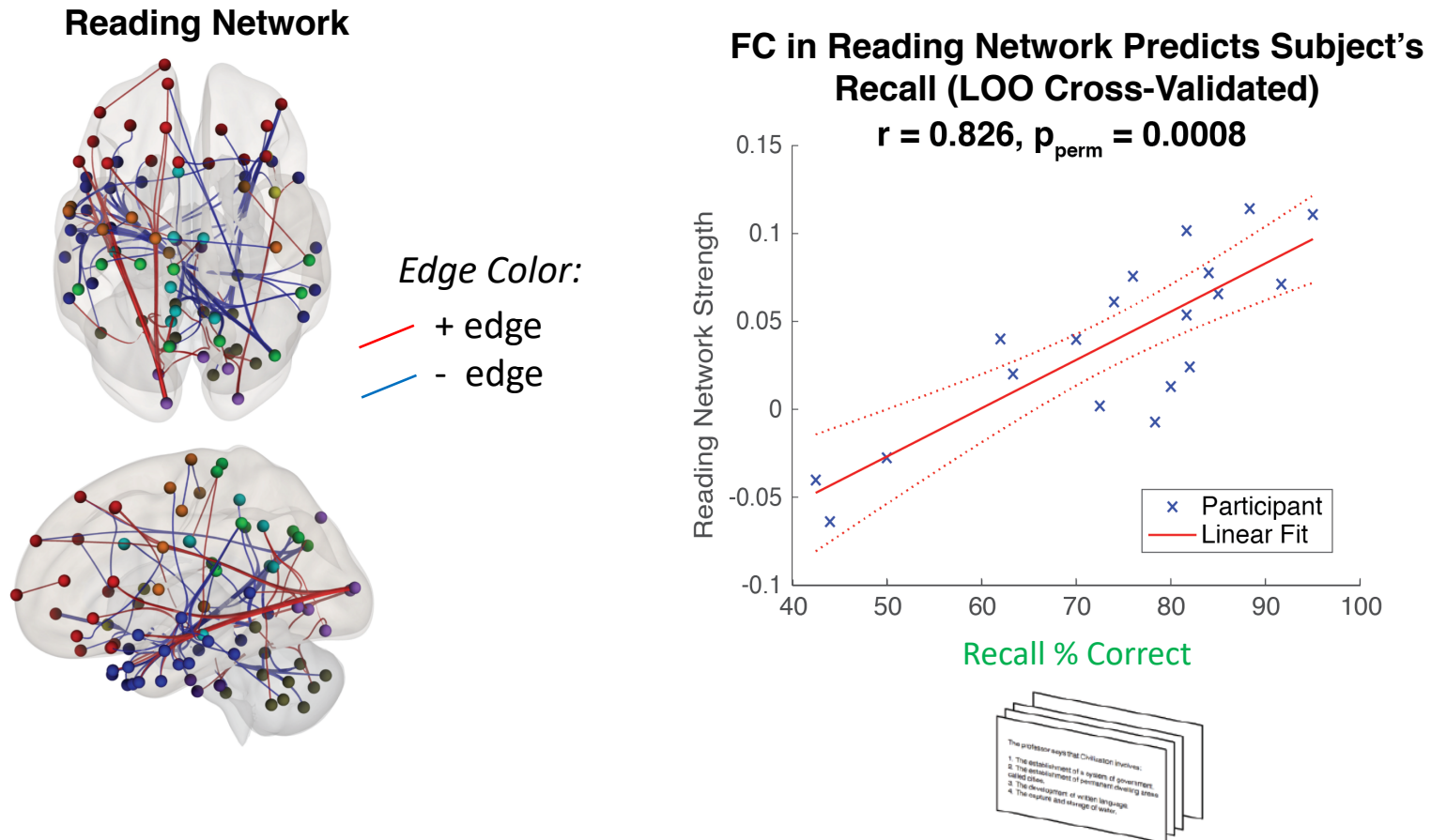


Figure from Jangraw, 2018

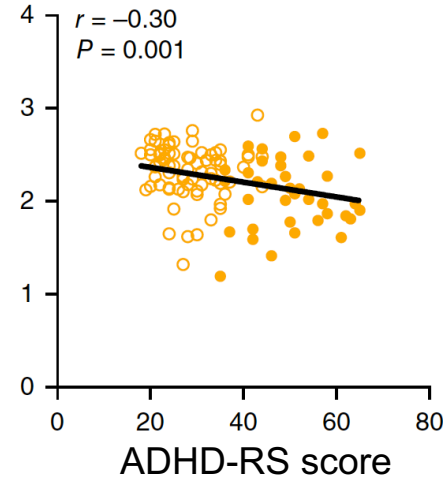
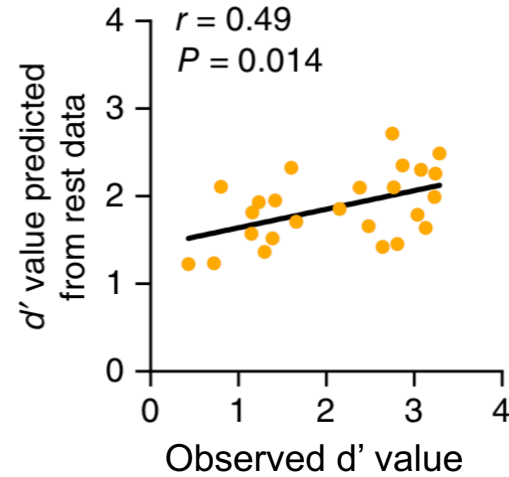
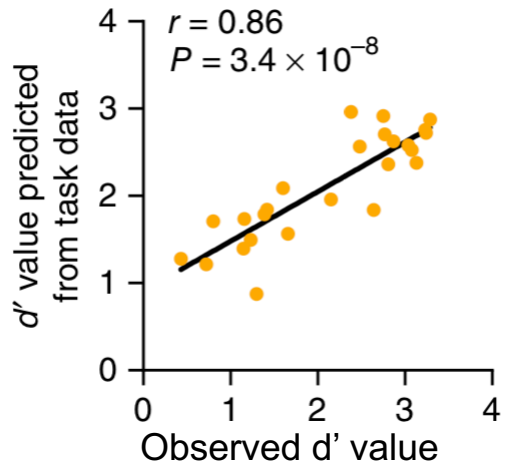
<https://doi.org/10.1016/j.neuroimage.2017.10.019>

FC Predicts Other Behaviors

(slide courtesy of Emily Finn, 2019 fMRI course)

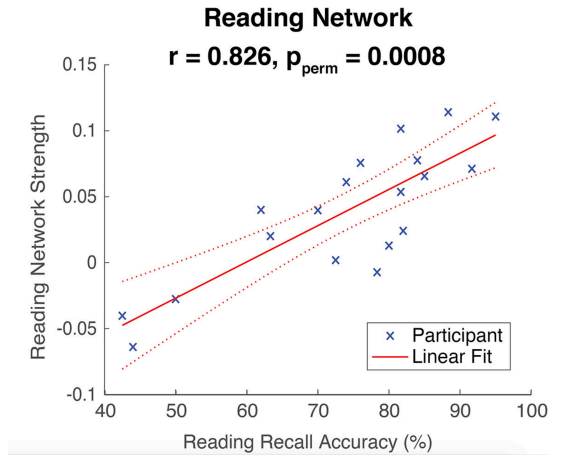
Sustained attention & ADHD symptoms

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



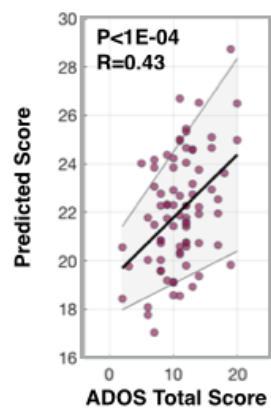
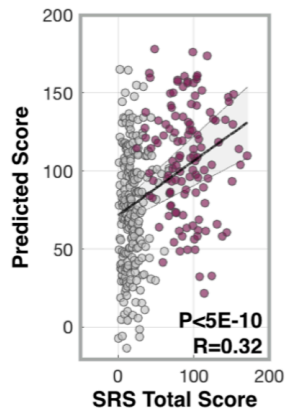
Reading ability

Jangraw et al.,
NeuroImage
(2017)



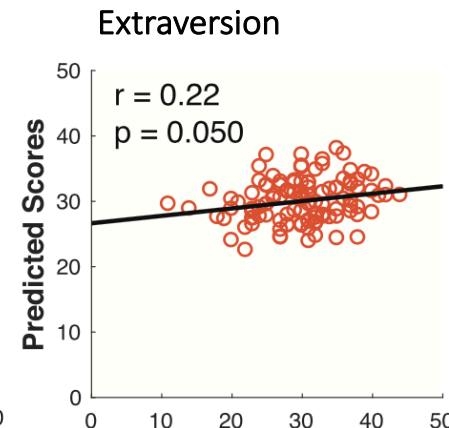
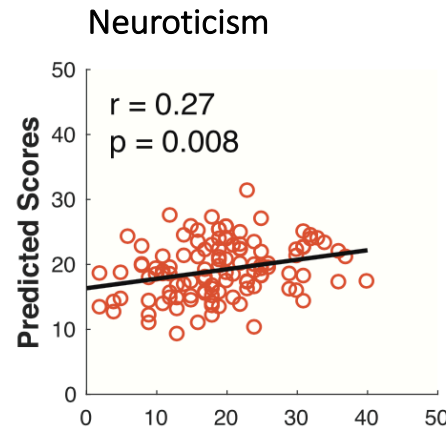
Autism symptoms

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



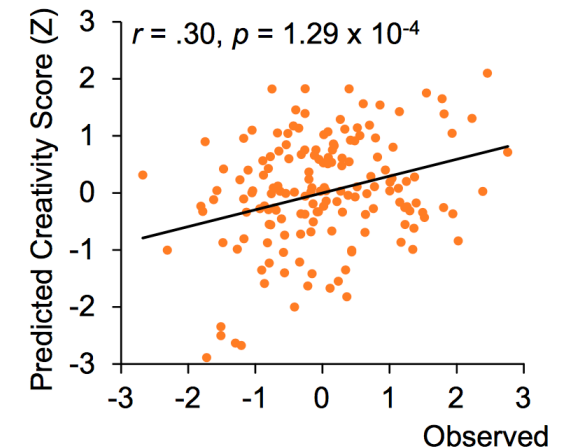
Personality traits

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



Creativity

Beatty et al.,
PNAS (2018)



rs-FC Predicts Response to Therapy in Obsessive Compulsive Disorder (OCD)

Predicts effect of CBT in OCD
Better than pre-treatment clinical scores

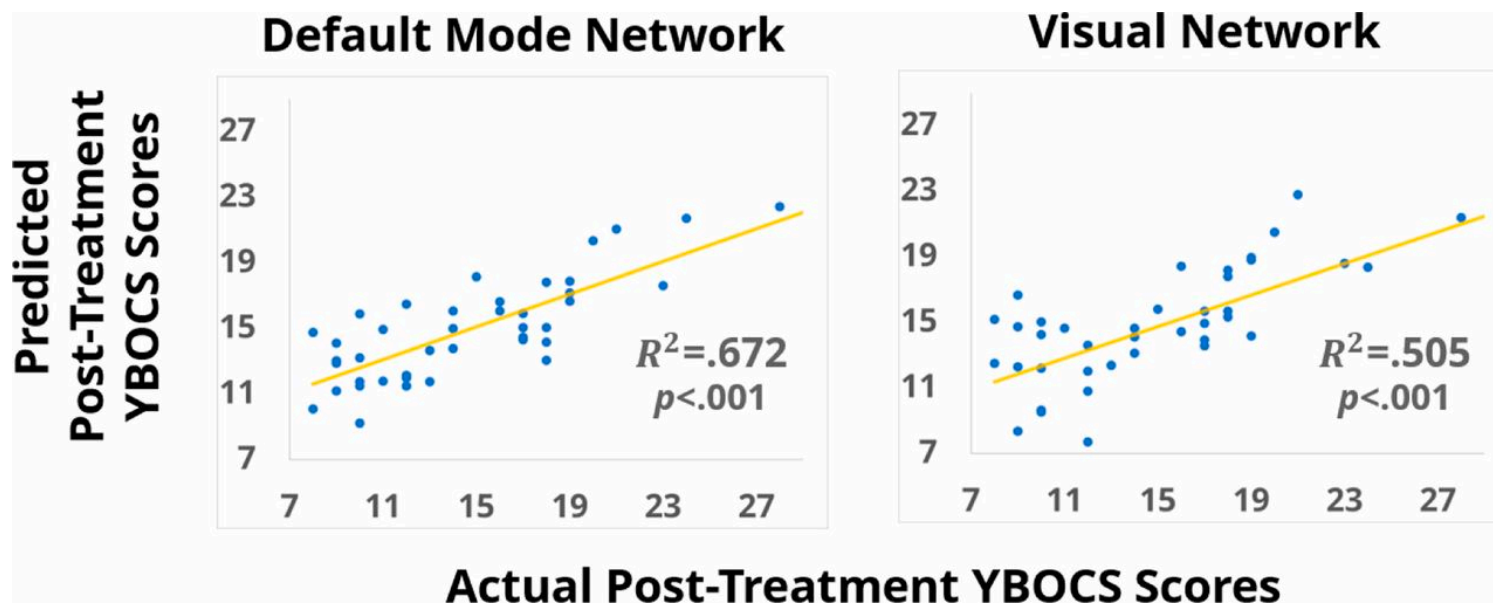


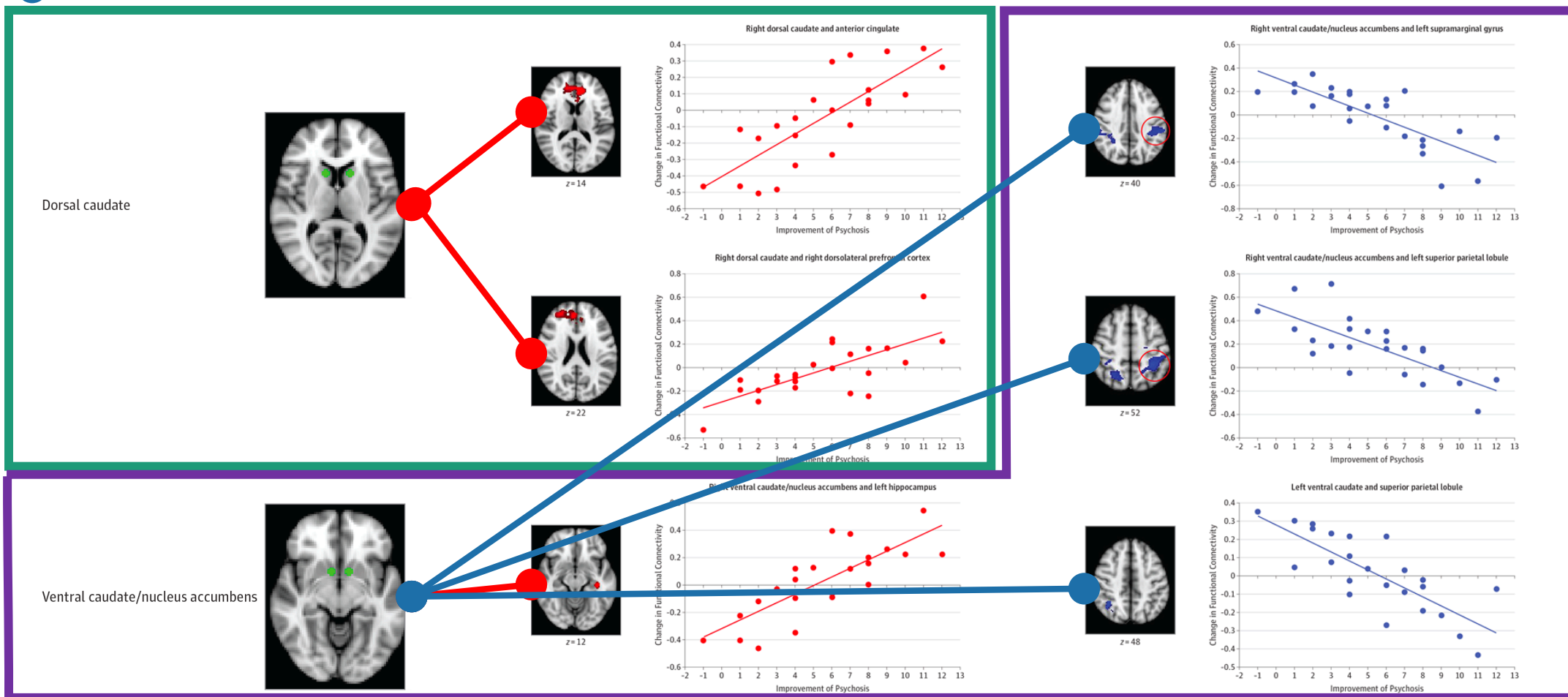
Figure from Reggente 2018

<https://www.pnas.org/content/115/9/2222>

rs-FC Predicts Response to Treatment in Major Depressive Disorder (MDD)

1. Associations between response to **antidepressant medications** and increased functional connectivity between frontal and limbic brain regions, possibly resulting in greater inhibitory control over neural circuits that process emotions
2. connectivity of visual recognition circuits in studies that compared **treatment resistant** and treatment sensitive patients
3. **response to TMS** was consistently predicted by subcallosal cortex connectivity
4. hyperconnectivity of the default mode network and hypoconnectivity of the cognitive control network differentiated **treatment-resistant** from treatment-sensitive MDD patients.

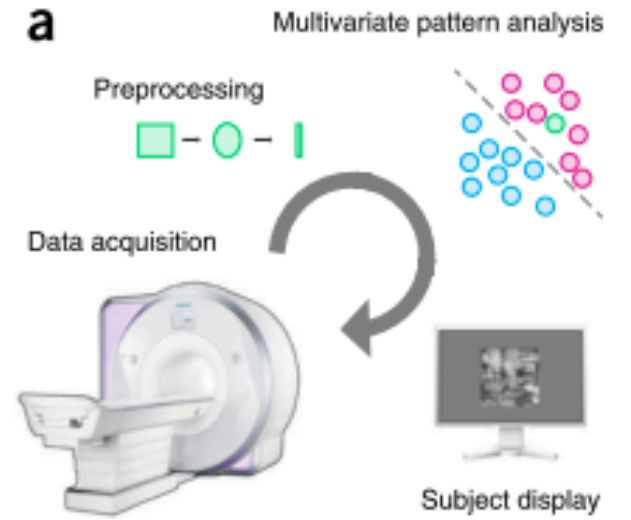
rs-FC Predicts Response to Antipsychotics in Schizophrenia



Figures from Sarpal 2015

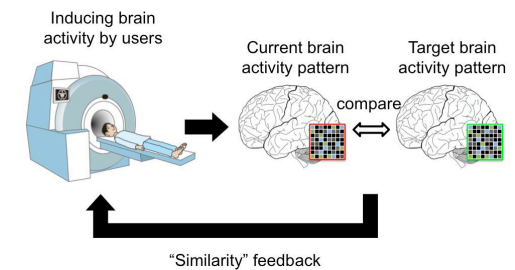
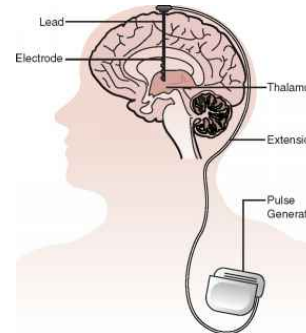
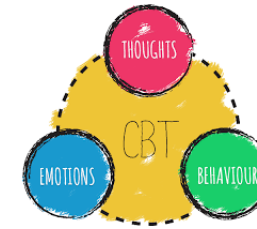
<https://jamanetwork.com/journals/jamapsychiatry/article-abstract/1922090>

How Might FC be Used in the Future?

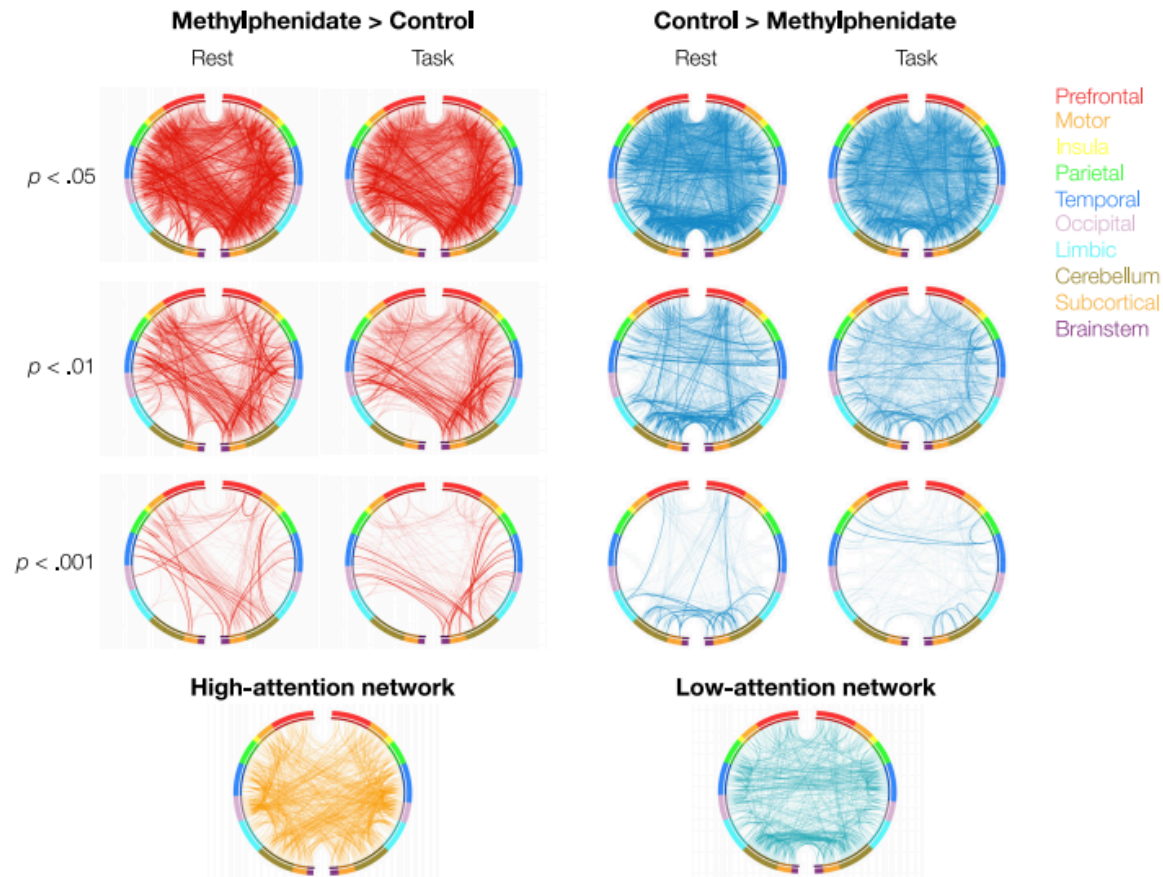


Targeted Interventions to Improve Performance

- Drugs
- Therapy
- Brain stimulation
- Neurofeedback



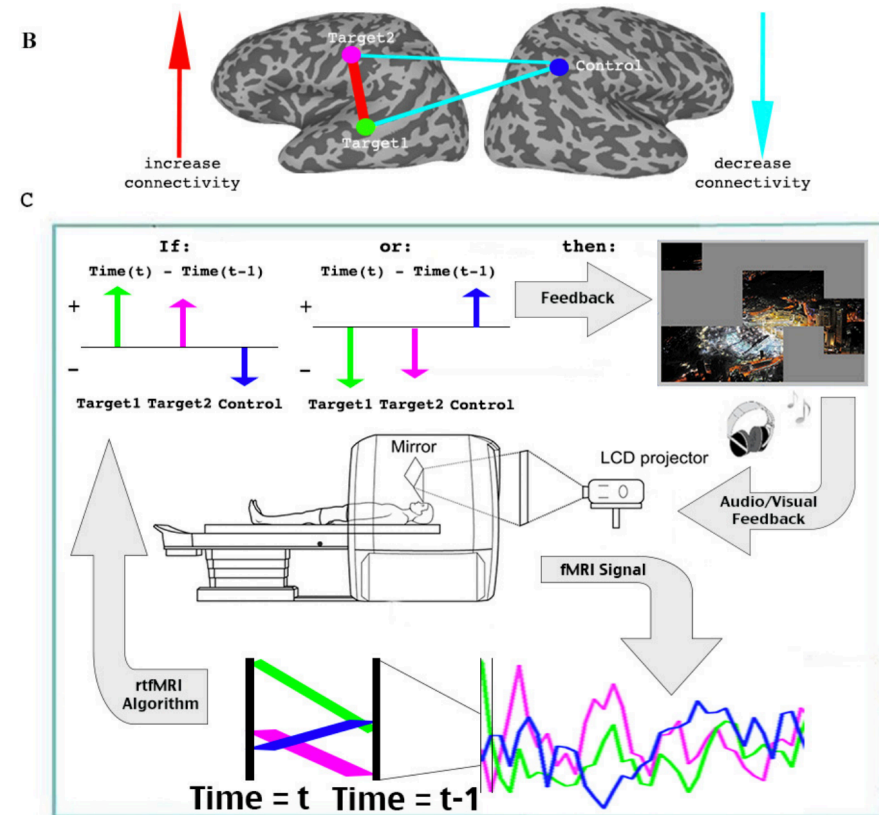
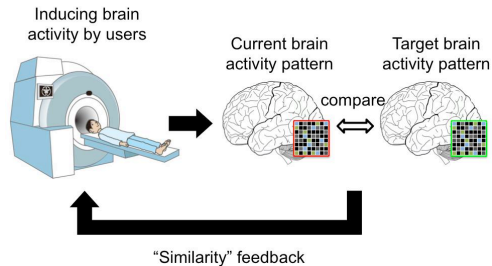
“Attention Network” Functional Connectivity Influenced by Methylphenidate (Ritalin)

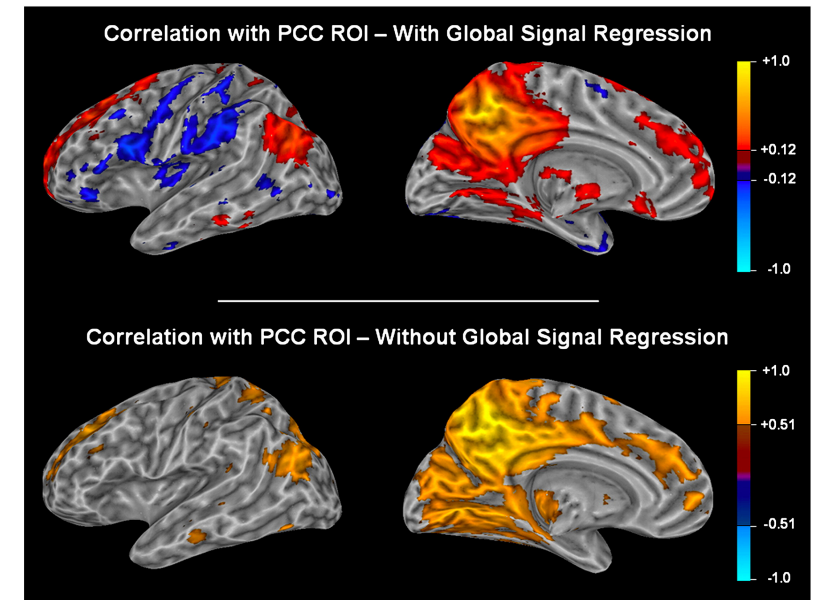


Rosenberg, Monica D., et al. "Methylphenidate Modulates Functional Network Connectivity to Enhance Attention." *Journal of Neuroscience* 36.37 (2016): 9547-9557.

FC patterns and Neurofeedback in Autism

- FC between pair of regions correlated with Autism symptoms
- Neurofeedback based rewards on upregulating this FC edge.





What controversies surround FC?

Does rsFC originate from neural activity?

- Simultaneous neural and hemodynamic recordings in rats suggest that yes, rsFC has neural origins.

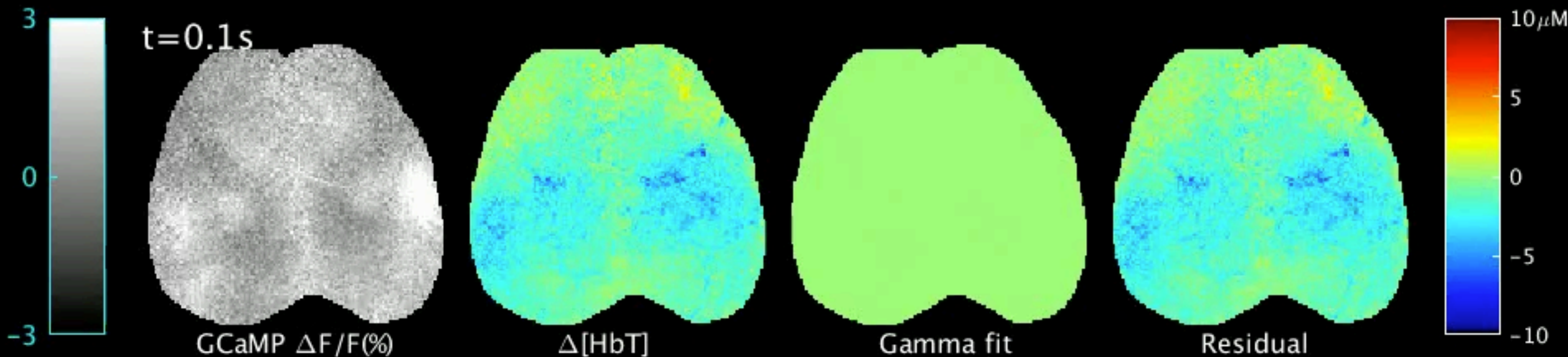
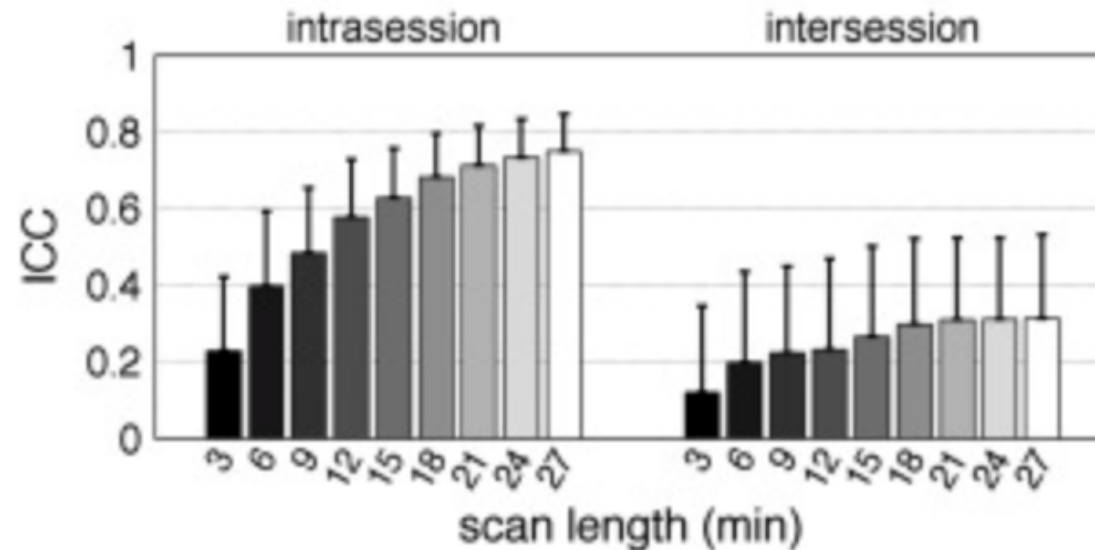


Figure from Hillman, 2016

<https://www.pnas.org/content/113/52/E8463.short>

How long should we scan?

- Longer scans increase FC reliability
 - Many people choose ~10min



Top figure from Birn, 2013

<https://doi.org/10.1016/j.neuroimage.2013.05.099>

What should the subject be doing?

- Rest may not be best for Inter-subject differences

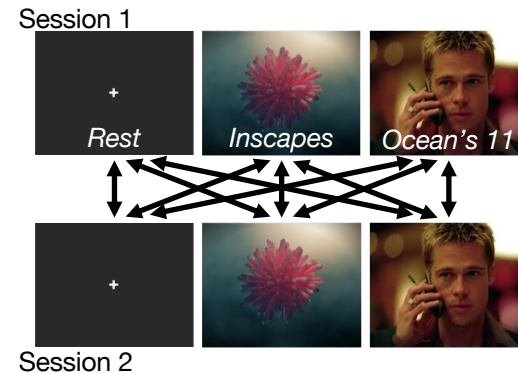
- Engaging movie
- Ambiguous movie
- Task using ability of interest

- But rest scales well

- Everyone's doing it!

- When analyzing task data, should you regress out the task-related activations before analyzing the FC?

- If your question is about underlying state, then maybe so
- For prediction purposes, probably not.



How should we preprocess?

- FC is sensitive to choices affecting SNR
 - **Motion artifacts**
 - Parcel size
 - Parcel location (dropout)
- Removing WM/CSF signal
- Band-Pass Filtering ($\sim 0.01-0.1\text{Hz}$)
- Global Signal Regression
 - Mostly removes global motion artifacts
 - but introduces anticorrelations

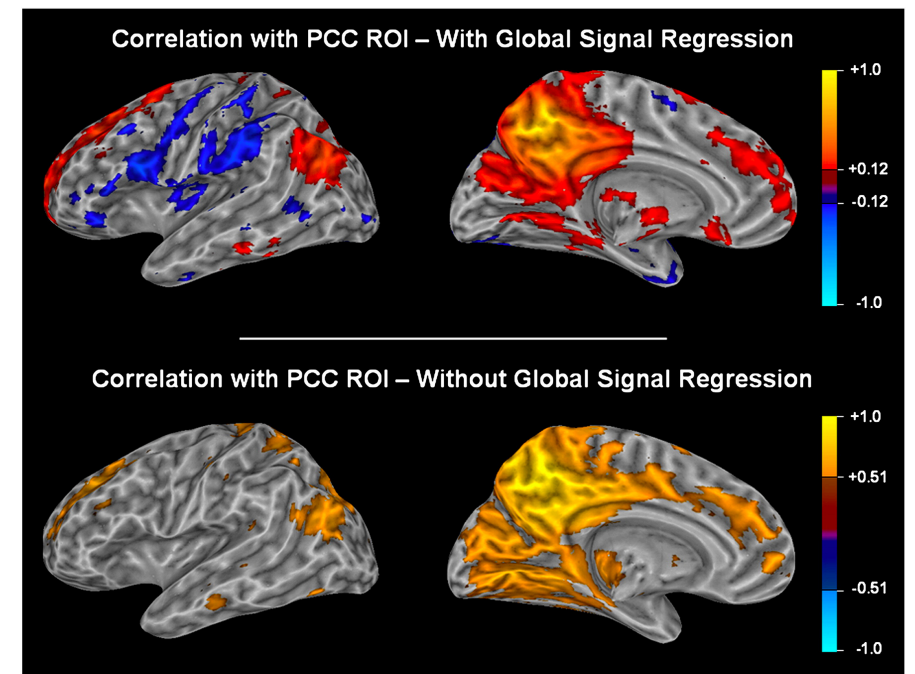


Figure from Murphy, 2009

<https://doi.org/10.1016/j.neuroimage.2008.09.036>

For more info on GSR, see Murphy 2016

<https://doi.org/10.1016/j.neuroimage.2016.11.052>

How should we select ROIs?

- Level of specificity:
 - ROI to all voxels
 - ROI to ROI
 - All parcels to all parcels
- Sharpness of parcel cutoffs:
 - ROIs (hard)
 - Components like ICA (soft)
- Inter-subject alignment:
 - Spatial alignment
 - Hyperalignment (align ROIs responding similarly to independent video)
 - See Haxby, 2011 <https://doi.org/10.1016/j.neuron.2011.08.026> and **figure above**
 - Group ICA (Find subject-level ICs whose time-courses match across subjects)
 - See Calhoun, 2009 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2651152/>

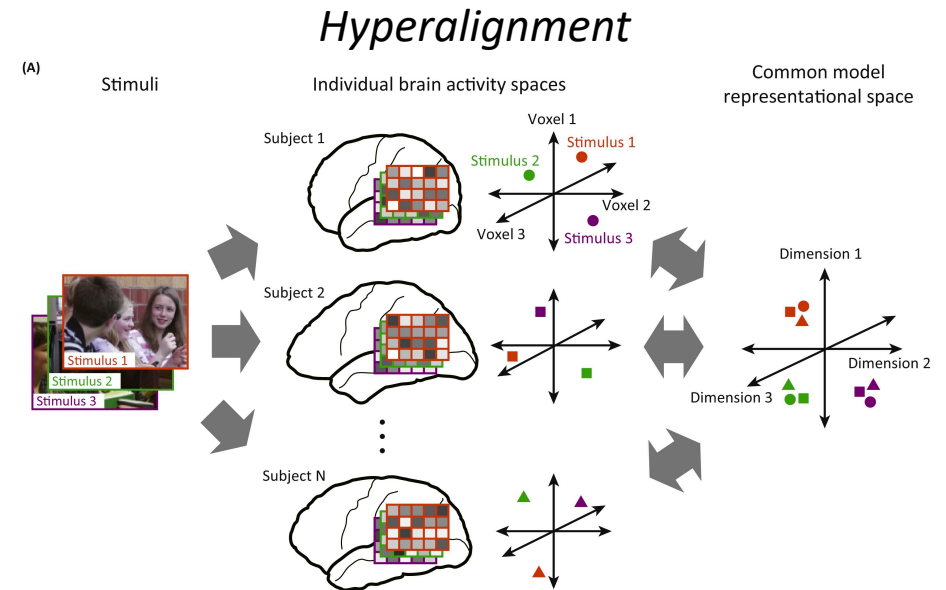


Figure from Haxby, 2011

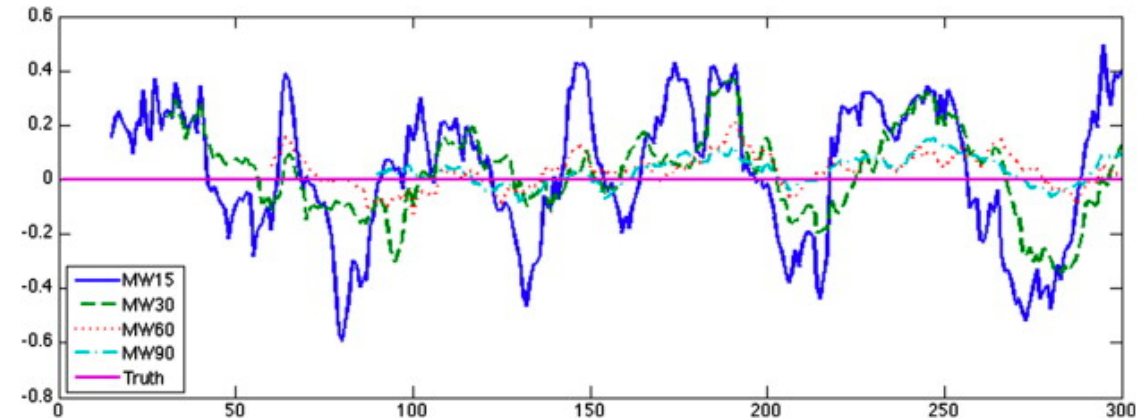
<https://doi.org/10.1016/j.neuron.2011.08.026>

How should we compute FC?

- Pearson correlation
 - Simple, interpretable
- Beta series
 - estimate beta for each trial, then correlate trial betas from different regions (helps compensate for **uneven hemodynamic delays**)
- Partial correlation
 - correlate two regions after the effect of all other regions has been removed (helps protect against **“illusory”, indirect effects**)
- Inverse covariance (precision)
 - Finds and removes conditionally independent pairs to get **sparse representation**

How can we be sure FC is dynamic?

- Static FC can look like dynamics
 - See Lindquist, 2014
<https://doi.org/10.1016/j.neuroimage.2014.06.052>
- Static FC can result in “beat frequencies” that look like dynamics
 - See Leonardi, 2015
<https://doi.org/10.1016/j.neuroimage.2014.09.007>
- Solutions:
 - careful stats testing & controls
 - alternatives to sliding window (wavelets, model-based approaches)



How can we compute dynamic FC?

- Sliding window
 - Requires lots of data and careful statistical tests
 - Most people don't collect enough data to estimate
- Tapered windows
 - Reduces edge artifacts from large spikes
 - See Allen, 2014 (link below, figure at right)
- Dynamic Conditional Correlation
 - Model-based approach used in finance
 - See Lindquist, 2014 <https://doi.org/10.1016/j.neuroimage.2014.06.052>
- Hidden Markov Models
 - Model brain activity as a dynamic sequence of distinct brain networks
 - See Vidaurre, 2018 <https://doi.org/10.1016/j.neuroimage.2017.06.077>

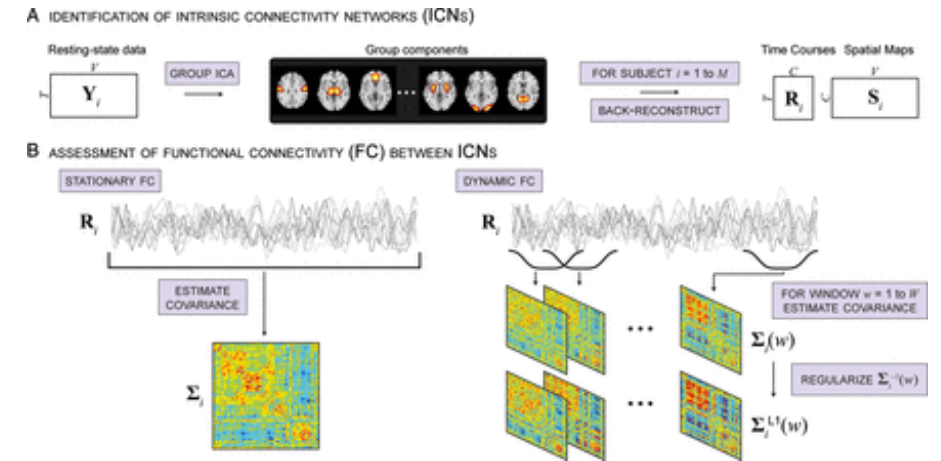
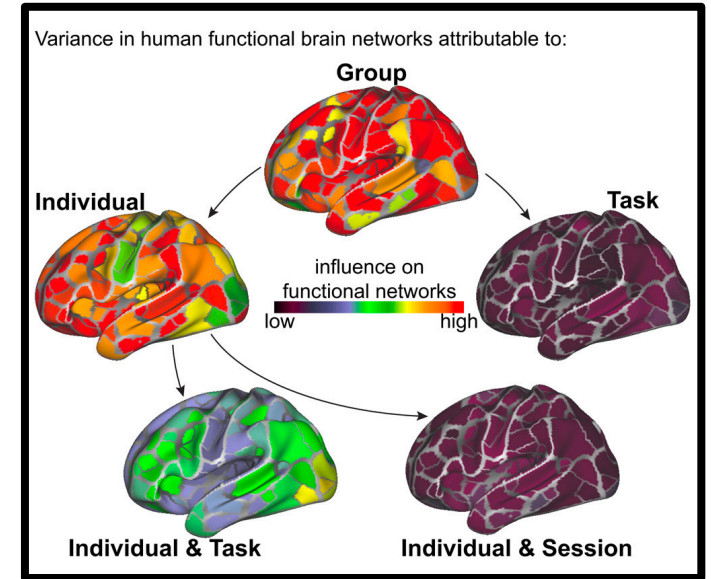


Figure from Allen, 2014

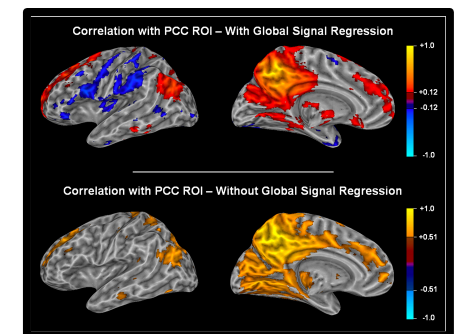
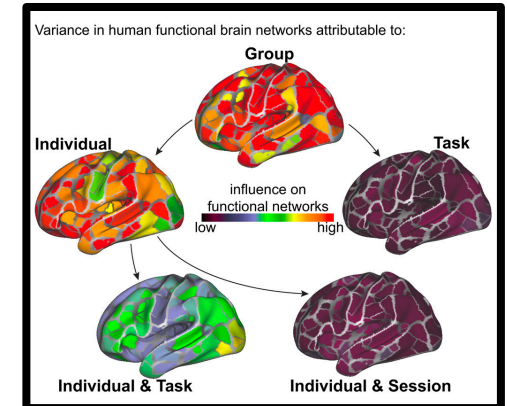
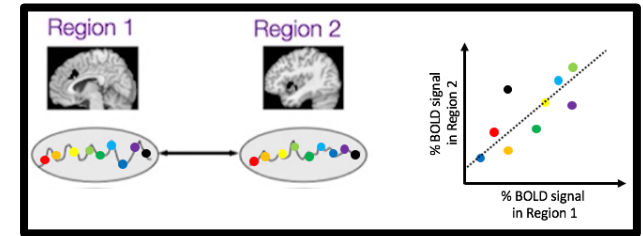
<https://academic.oup.com/cercor/article/24/3/663/394348>

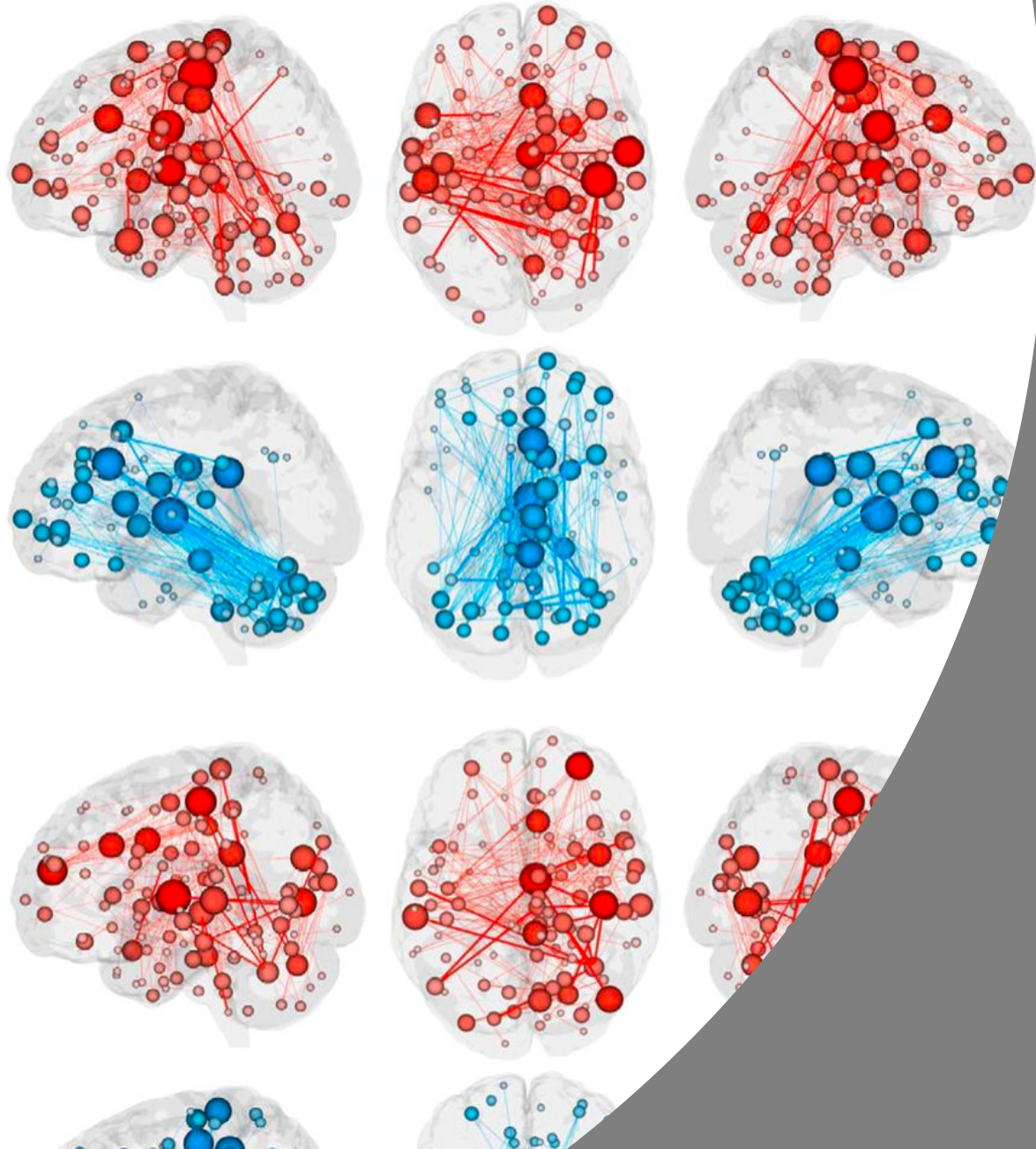


TL;DR: Take-homes

Points to Remember

- FC is an undirected association between fMRI time-series
 - A **correlation**, without direction, directness, or biological basis
- FC is not SC
 - SC can predict **~50% of the variance** in FC
 - Unlike SC, FC is dynamic and can be negative
- FC variability is largely inter-individual variability
 - ~40% group, **~40% individual**, **~20% individual x task**
- This variability can **predict outcomes** and suggest treatments
- Acquisition and **Preprocessing choices matter**
 - Longer scans give more stable estimates
 - Global Signal Regression can make correlations look like anticorrelations
 - Estimating dynamic FC requires big datasets and careful stats





Thanks to:

- Emily Finn
- Joelle Sarlls
- Monica Rosenberg, U Chicago
- Section on Functional Imaging Methods
 - Peter Bandettini
- Emotion and Development Branch
 - Daniel Pine
 - Ellen Leibenluft
 - Argyris Stringaris
- You for your attention!