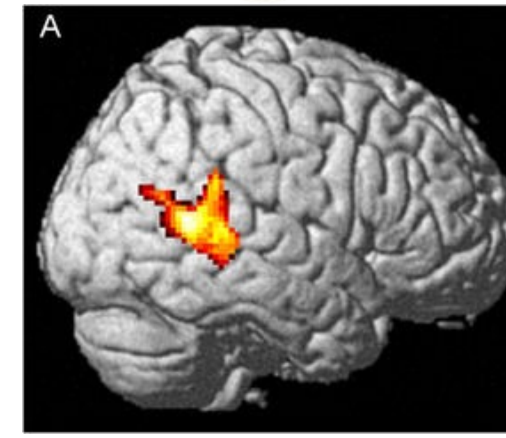
Lecture 20 Review: Theory of Mind: Thinking about Other People's Thoughts



I. Intro: Inferring mental states to understand people

Sally-Anne false belief task as classic test:

3 year olds don't pass, 5 year olds do

develops late in HF ASD (impaired in FB not FP).

II. Do we have special mind/ brain mechanisms for mentalizing?

- ✔ fMRI: false belief vs false photo YES! rTPJ selective for ToM
- ✔ specificity (not just anything social, or even bodily sensations)
- ✔ generality: nonverbal pixar movies

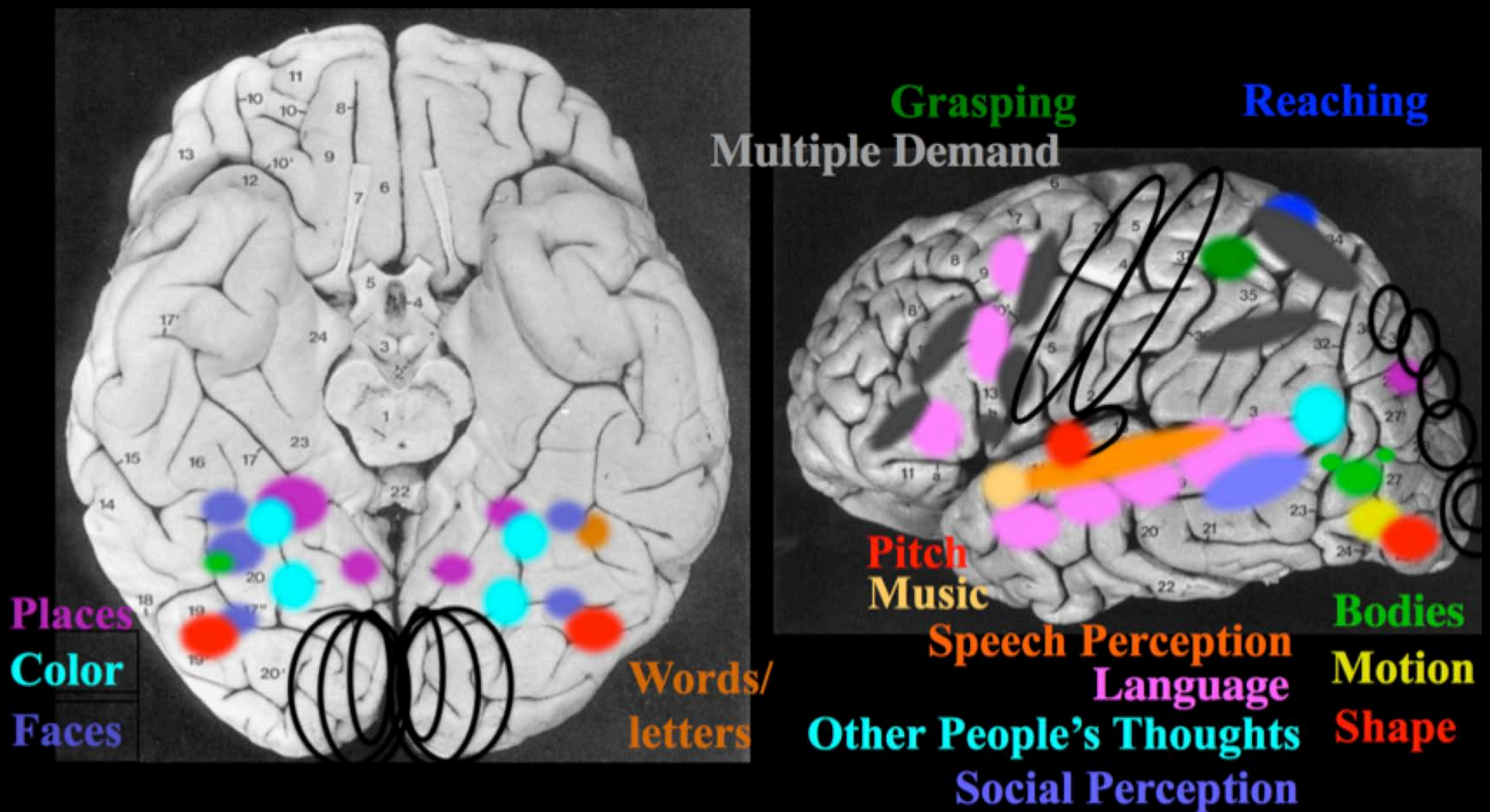
III. Moral Reasoning as a Test Case of ToM

- ✔ less weight to beliefs in ASD (less forgivenss for accidtl harm)
- ✔ TMS to rTPJ disrupts moral judgement
- ✔ MVPA: TPJ distinguishes between intentional vs accidental

But not in ASD!

Many other facets of social perception and cogniton

The Focus of this Course So Far



- Many regions of the human brain conduct distinctive, often highly specific mental functions.
- The field has invested considerable effort to identify these regions and understand what information is processed and represented in each.
- Considerable progress has been made.
- But of course *none of these regions acts alone*.
- To understand these regions, and how they implement cognition, we need to know *how they are connected with each other and the rest of the brain*.

That means looking at not only the cortex, but the white matter!...

Reminder:

Cortex, the outer surface of the brain, or grey matter, is where the cell bodies and circuits reside that do the information processing in the brain.

Underneath the cortex is the white matter, which is made up of bundles of myelinated axons that carry information from one cortical region to another.

Why Should we Care about White Matter?

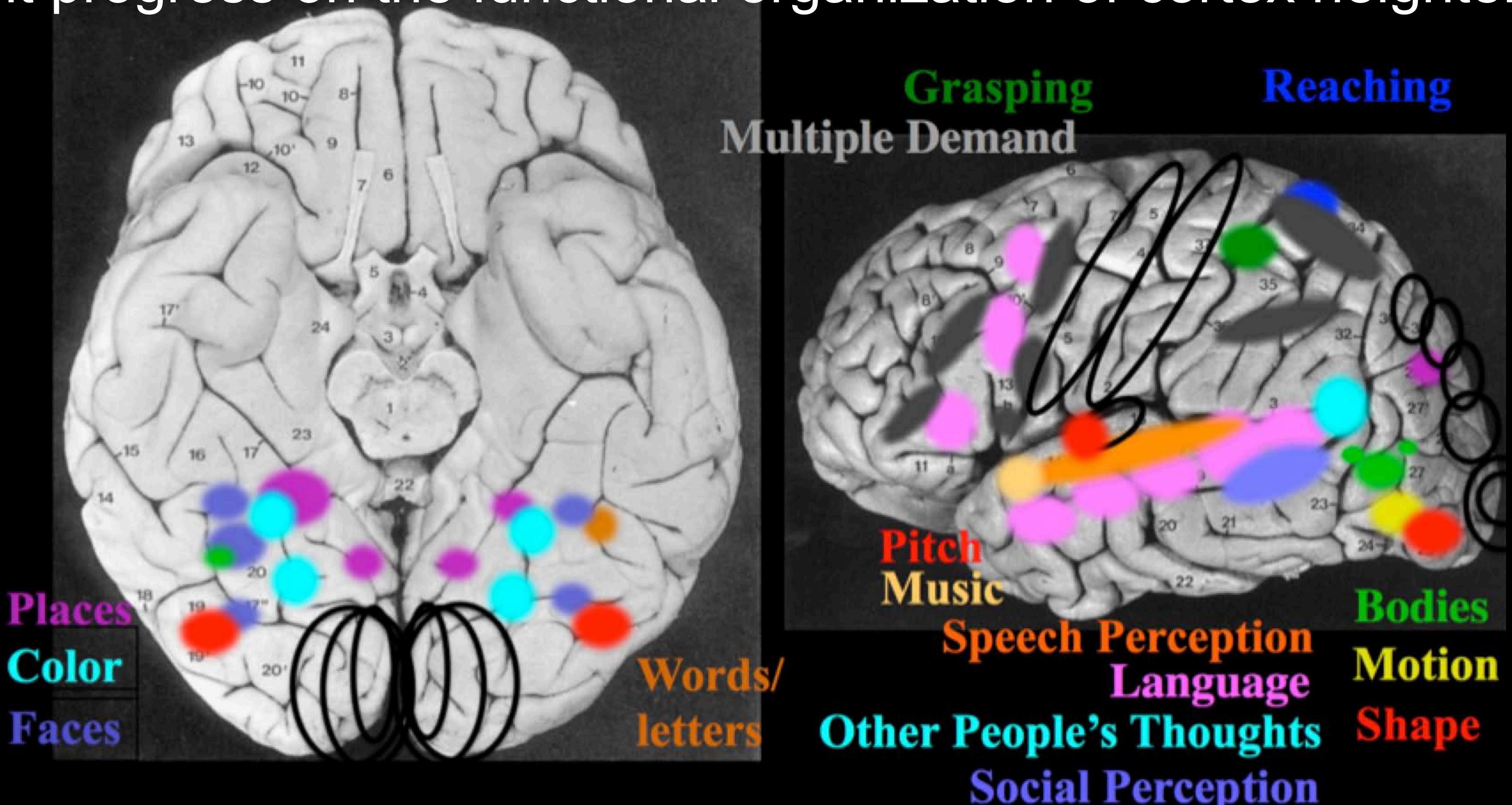
I. White matter makes up 45% of the human brain.

Myelinated fibers from one human brain, laid out end to end, circle the globe > 3x

Only 10% of mouse brain.

2. Can't understand cortex w/out knowing its connections.

Recent progress on the functional organization of cortex heightens the stakes:



a) To understand each functional ROI, we need to know its inputs and outputs.

"… connectivity patterns define functional networks. The inputs to a brain region determine the information available to it, whereas its outputs dictate the influence that that brain region can have over other areas. Therefore, simply by knowing the pattern of inputs and outputs of a brain region we can begin to make inferences about its likely functional specialization." Johansen-Berg & Rushworth (2009)

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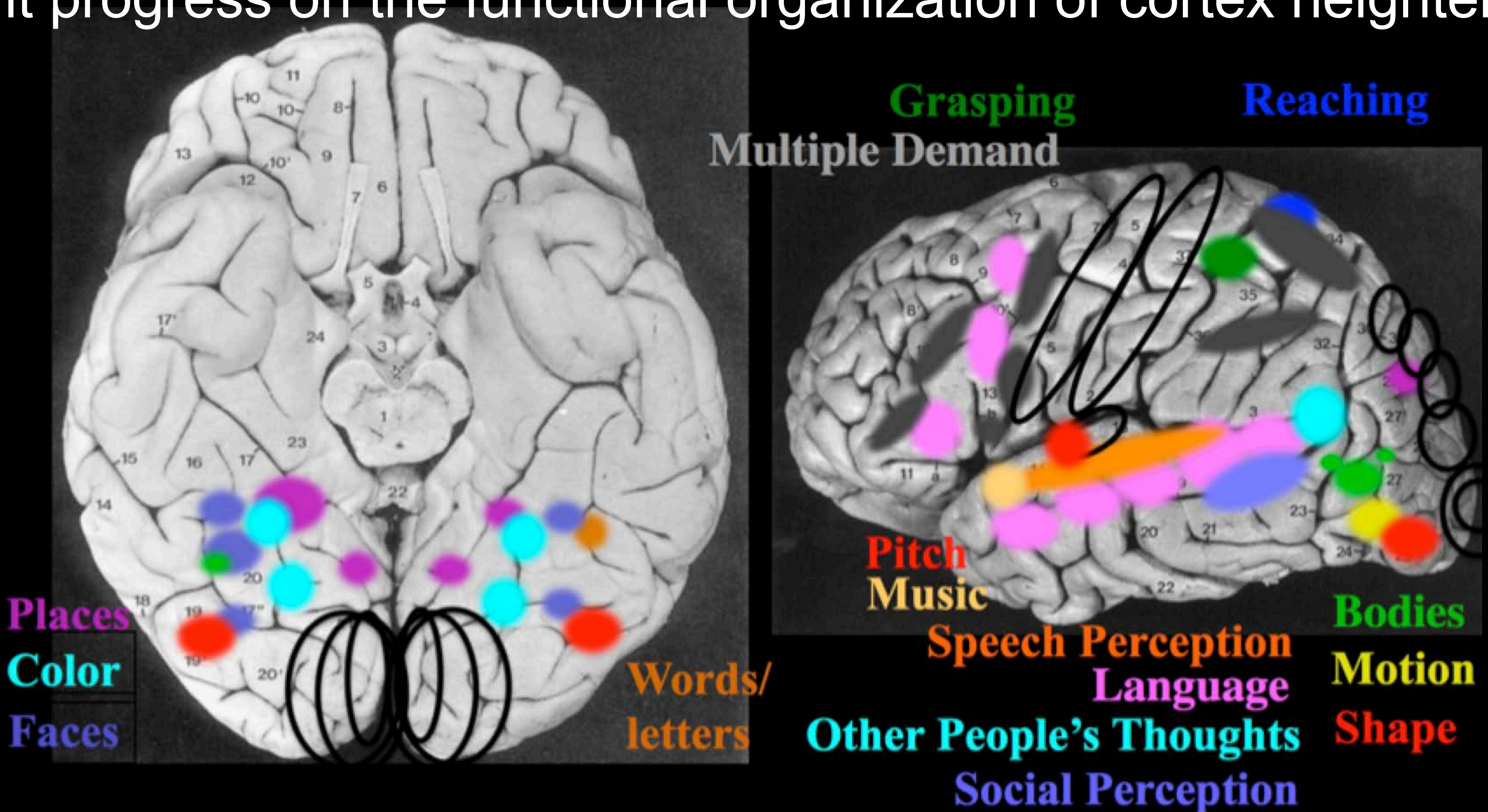

a) To understand each functional ROI, we need to know its inputs and outputs.

b) The connections of each region are a core part of its identity/distinctiveness part of the definition of a cortical area (Felleman & Van Essen, 1991)

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3. The specific connections of each region may serve as a "fingerprint" of that region across species, enabling us to discover interspecies homologies.

Relevant for a) establishing relevance of animal models
b) understanding brain evolution

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4. The specific connections of each region may play a causal role in its development. (rewired ferrets, VWFA study).

5. Disruptions of white matter key to clinical disorders

Devel disorders like dyslexia, autism, devel prosopagnosia, amusia, etc.

Aging: greatest decline with age is white matter

10% decrease in WM fibers per decade from 20 to 80, ugh

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5. Disruptions of white matter key to clinical disorders

6. Changing connections may mediate learning/plasticity.

7. Structural connections provide a major constraint in circuit design and likely too in brain design.

To minimize wiring costs (metabolic, signal delay, devel), place connected neurons nearby >> cortical maps and multiple areas

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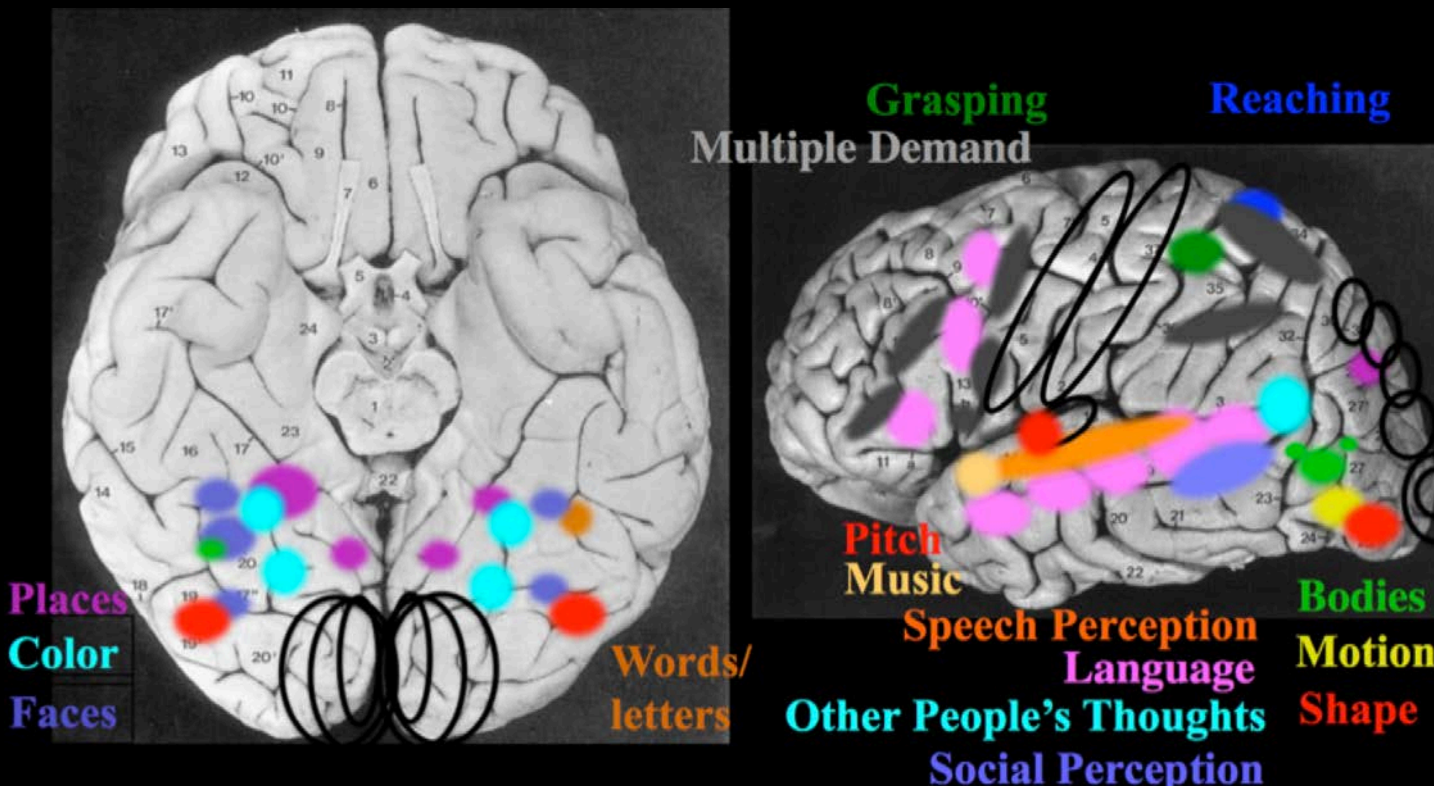
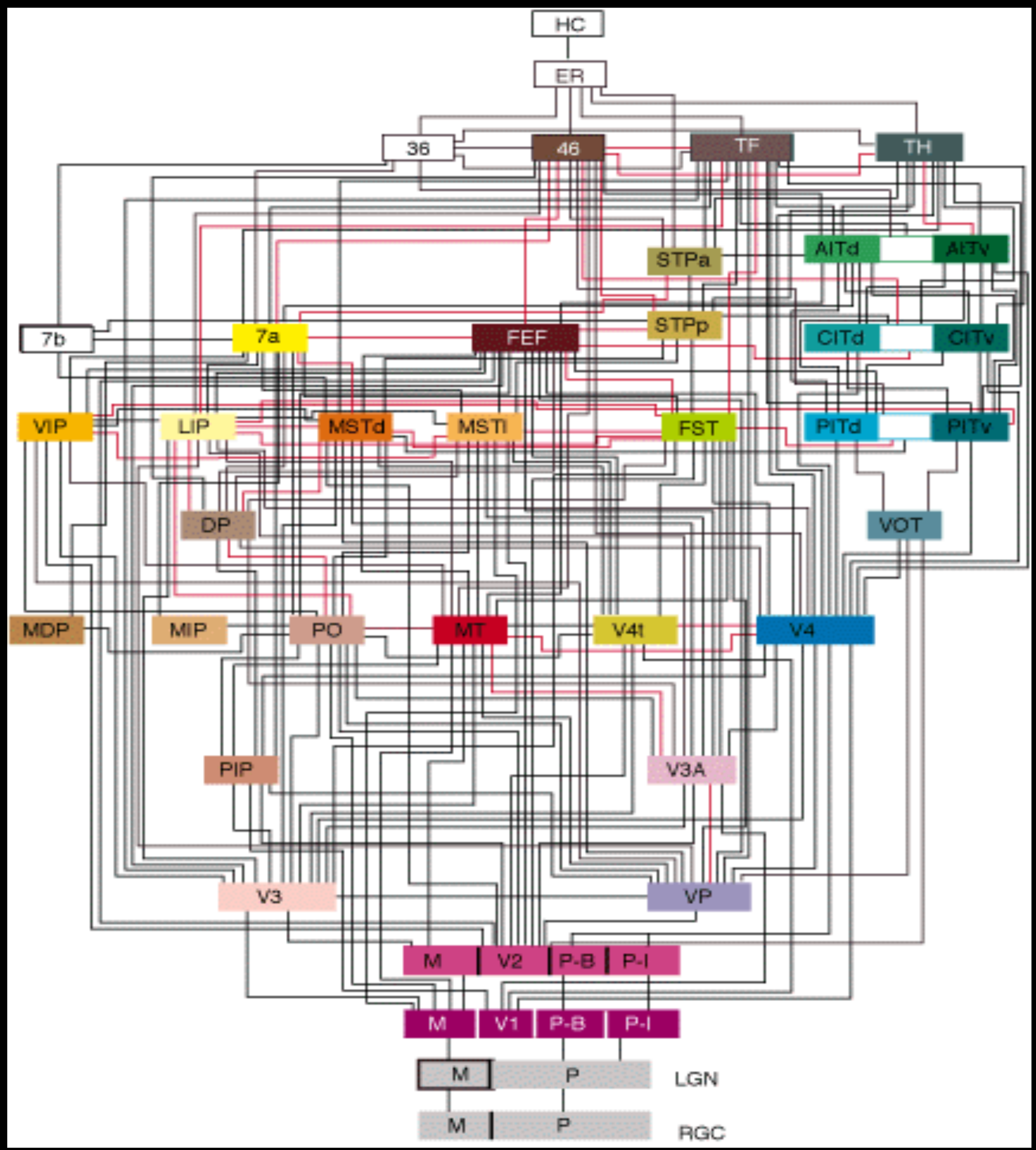
7. Structural connections provide a major constraint in circuit design and likely too in brain design.

8. Cool new methods, e.g. CLARITY & EM reconstruction

What do we know about the connectivity of these Regions?



Connectivity of Regions in Macaque Brain

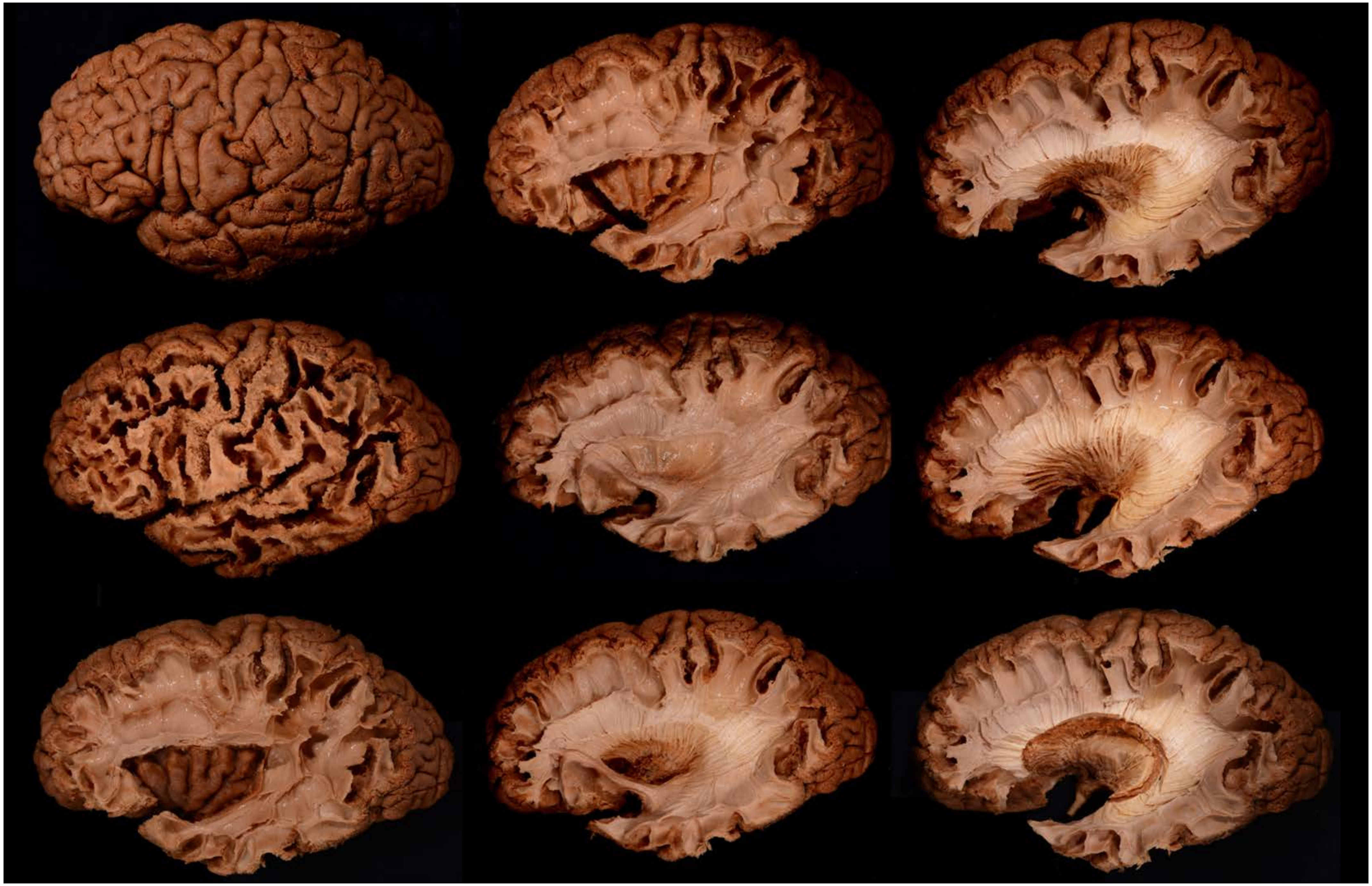


Don't we already know the connections of each of these regions, from this:

No! That is for macaque brains, where you can do tracer studies.
We cannot do those in humans.
With humans we have only 3 methods, none of them great:

- gross dissection (post mortem)
- diffusion tractography (MRI in vivo)
- resting functional MRI (in vivo)

White Matter
visible with gross dissection



What if we don't want to wait until people die?

Lecture 21: Brain Networks

<u>Outline for Today:</u>

I. Who cares about white matter and why?

II. Diffusion imaging and tractography.

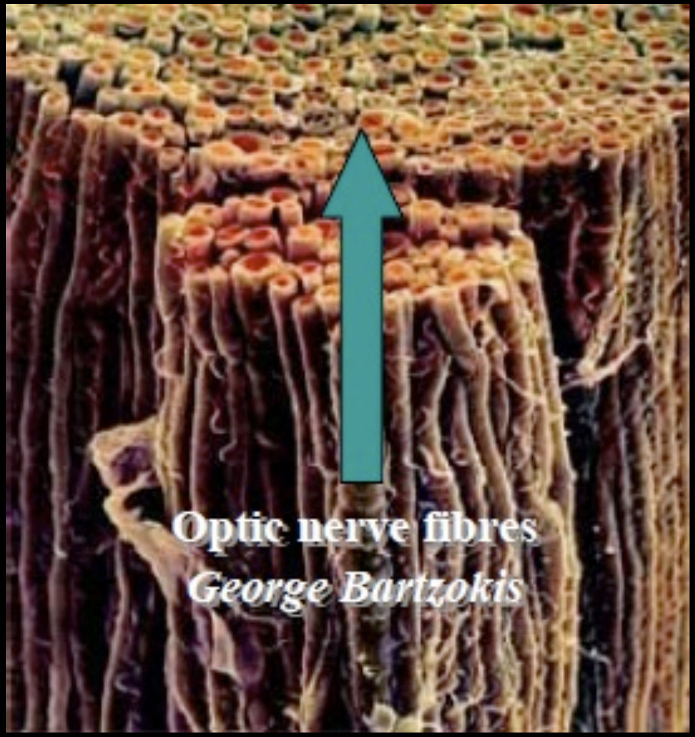
- major white matter tracts in the human brain
  - fractional anisotropy and motion artifacts
- tractography and its challenges
- connectivity fingerprints predict function

III. Resting Functional Correlations

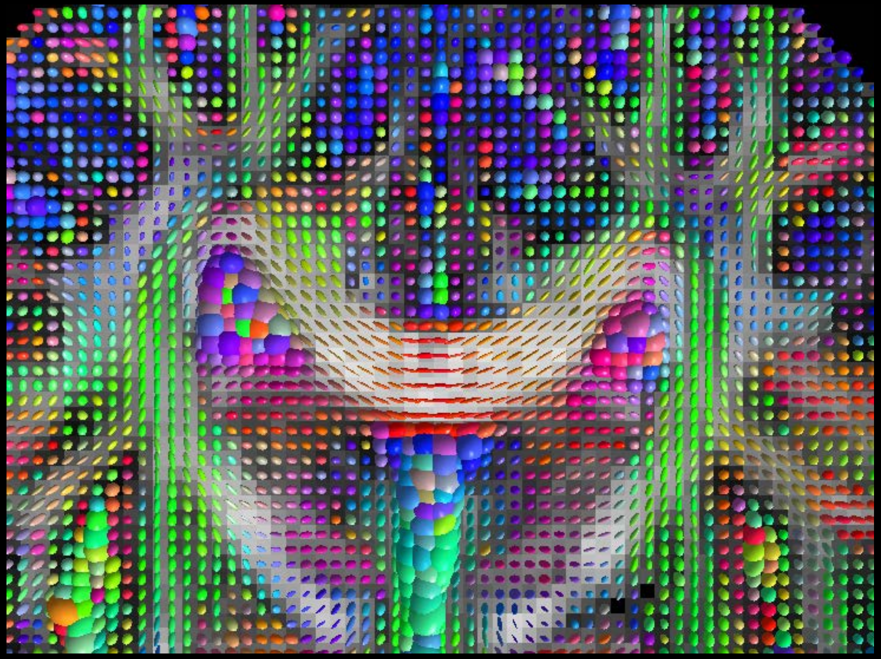
- what they are (correlations between regions)
  - and are not (strong evidence for structural connectivity)
- the “networks” they reveal
  - DMN, fronto-parietal, etc.
  - distinction between language and MD networks (Blank)
  - relation between language & ToM networks (Paunov)

Structural Connectivity from Diffusion Imaging

Principle:
Restricted Diffusion of Water in Axon Bundles

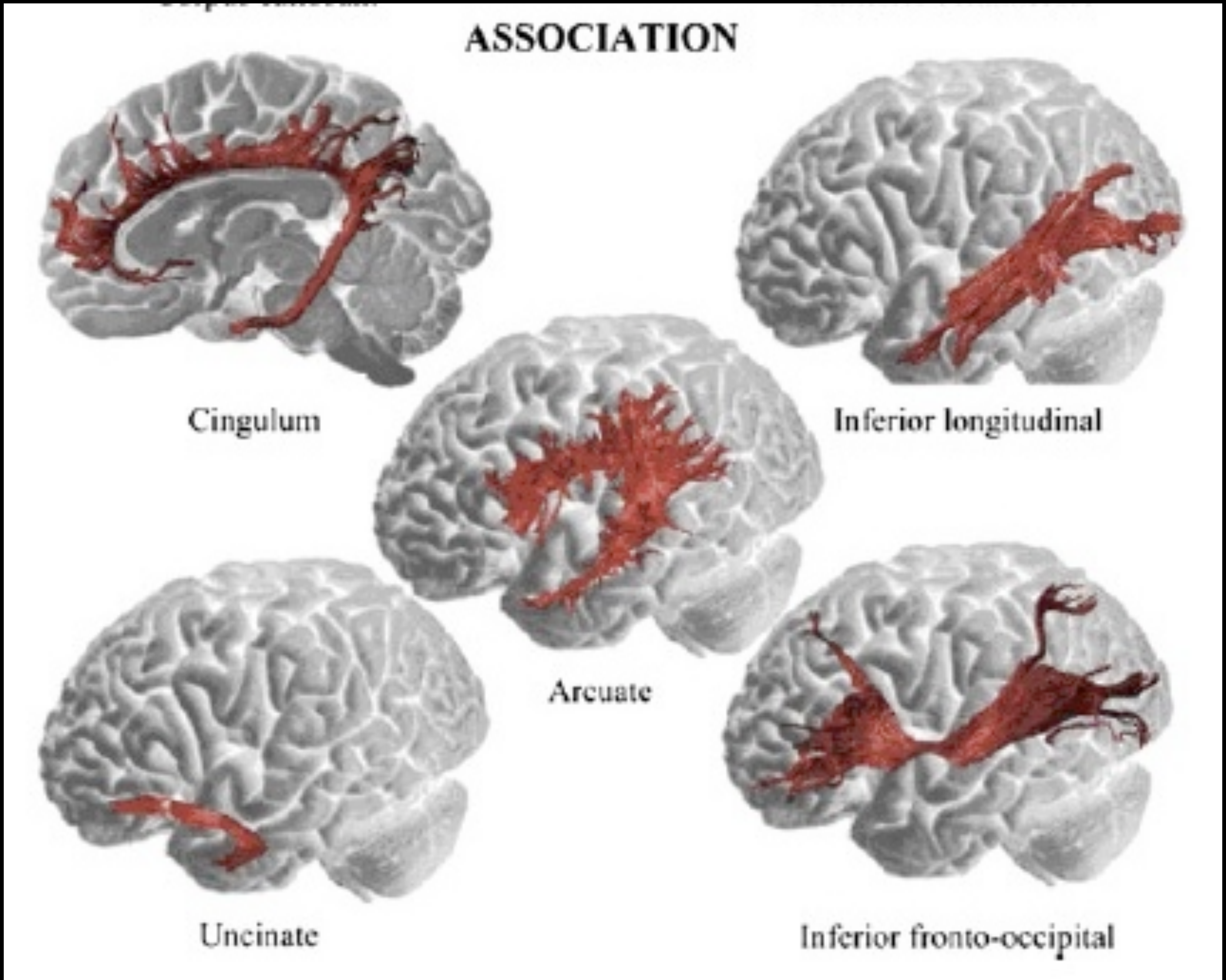


Diffusion MRI discovers orientations of diffusion at each point in brain.



Works well to discover major fiber bundles…

Major Tracts



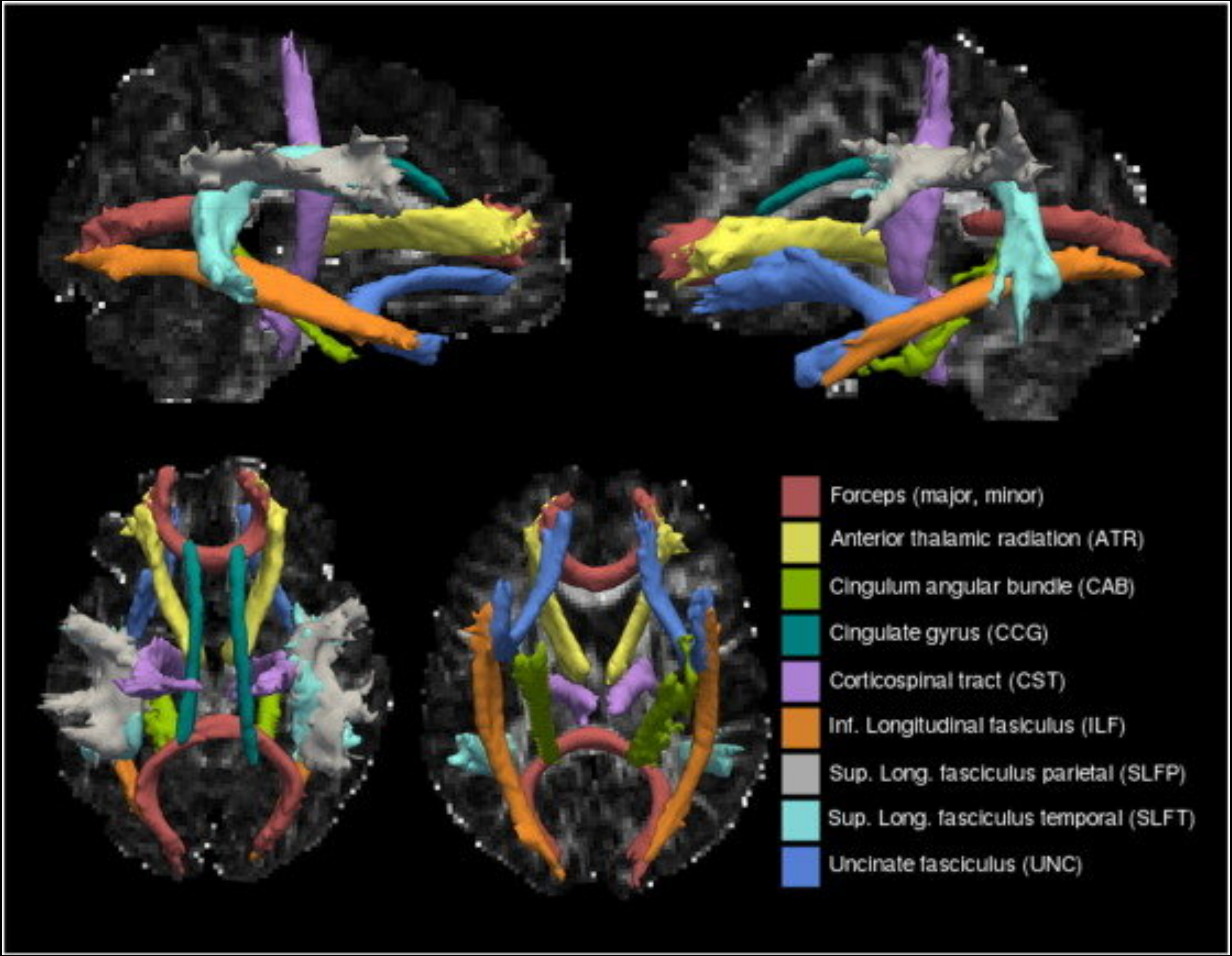
Source: Jones, DK. Cortex 44(8) Sept 2008 pp936 952. https://doi.org/10.1016/j.cortex.2008.05.002

More recent data showing lots of tracts…..

Data from: Catani & Ffytche, 2005; Figure from: Jones, 2008, Cortex

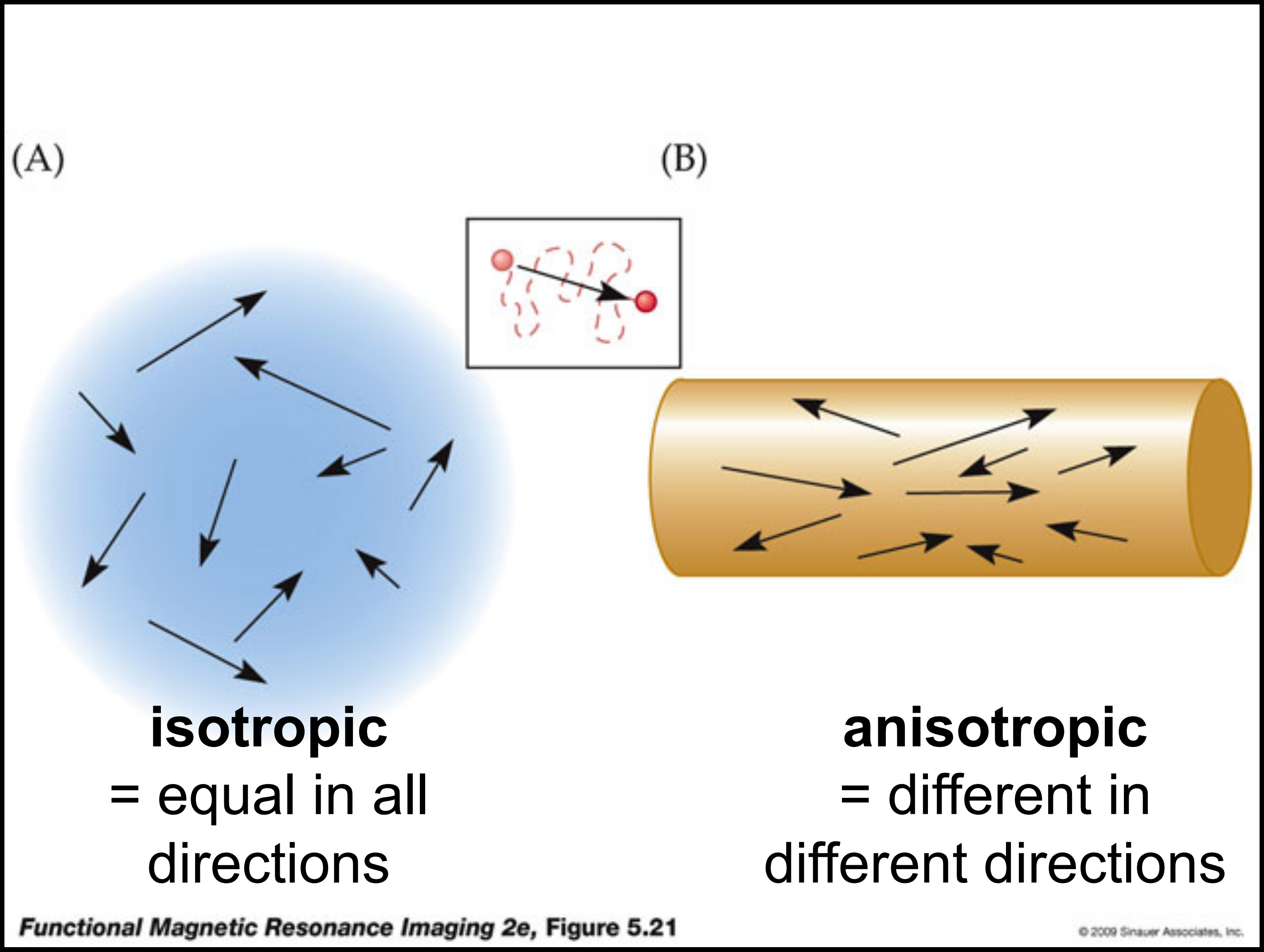
Major Fiber Tracts in the Human Brain

18 of the most prominent fiber tracts, detected with diffusion imaging:



Beyond just *finding* these tracts, with diffusion we can *characterize* them….

Isotropic vs. Anisotropic Diffusion



With diffusion imaging, we can measure the *degree of anisotropy,*
i.e. the "factional anisotropy" (FA), within a tract,
to see how this tract may differ across age, clinical groups, experience, etc.
Example…

The Arcuate Fasciculus in Dyslexia

Christadoulou et al., 2017

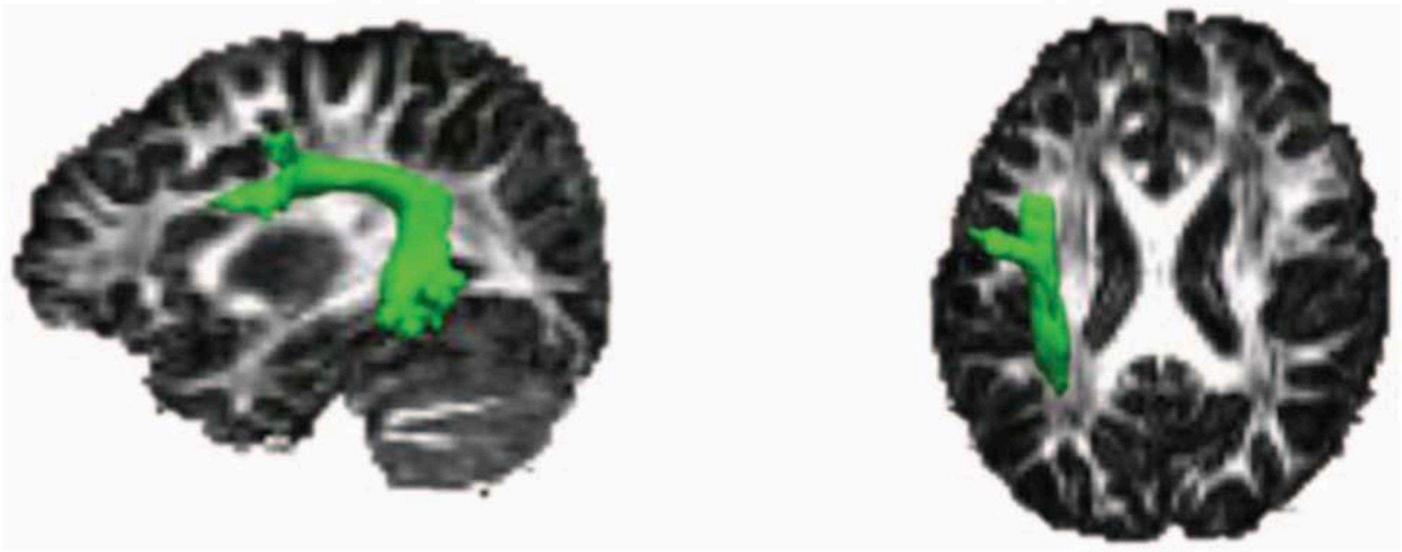


Figure 1. Sample TRACULA reconstruction of the left arcuate fasciculus from probabilistic tractography in sagittal (left) and axial (right) views.

Measured fractional anisotropy (FA) of AF in
- typically reading children (6-9 yo)
- children with reading disability equated on age

and nonverbal cognitive abilities.

Interesting. But:,
- this is just correlational
- not totally clear what FA means
  - (or that high FA is always "good")
- and FA is highly susceptible to artifact
  - for example…

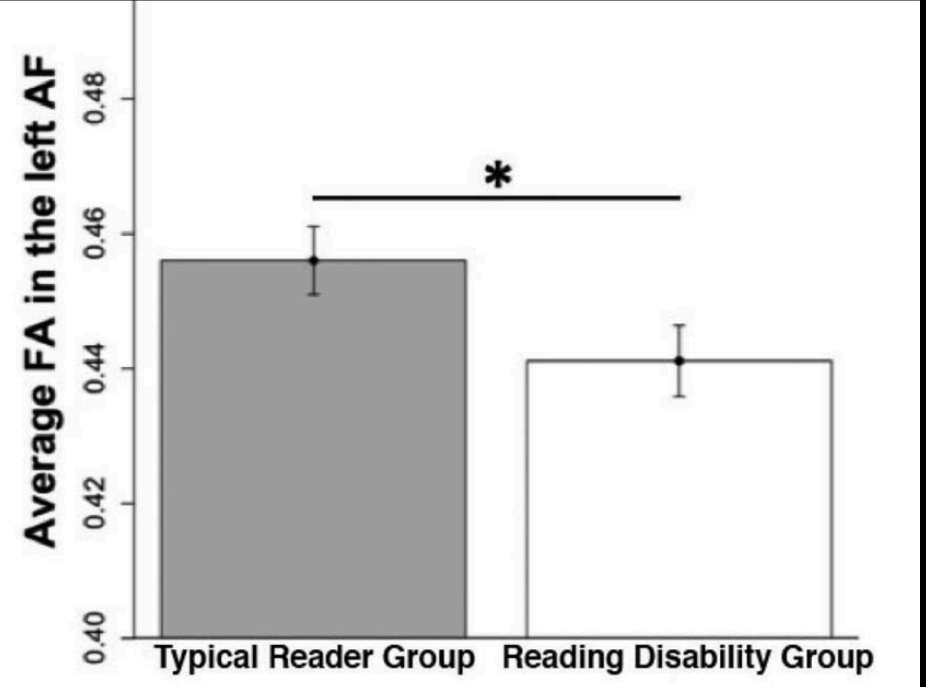


Figure 2. Relative to the typical reading group, the reading disability group had reduced fractional anisotropy (FA) in the left accurate fasciculus (AF). * $p < .05$ (Wilcoxon–Mann–Whitney *U* test); error bars represent standard error.

Overall Lower Integrity (FA) of Major Tracts in Autism? Found in most studies, but…

Koldewyn et al., *PNAS*, 2014

Tract	A	B
f major	↓*	↓
f minor	↓*	↓
L ATR	↑	↑
R ATR	↑	↑
L CAB	↓*	↑
R CAB	↓	↓
L CCG	↓	↓
R CCG	↓	↓
L CST	↓	↓
R CST	↓	↓
L ILF	↓*	↓
R ILF	↓*	↓*
L SLFP	↑	↑
R SLFP	↑	↑
L SLFT	↓	↓
R SLFT	↓	↓
L Unc	↑	↑
R Unc	↓	↑

A: Standard Analysis:
exclude only scans with visible artifacts; control for age, IQ, and sex

Replicate the usual pattern:
- Lower FA in ASD
  for most tracts,
  many of these significant

But kids with ASD might move more than TD kids!
  Possible major artifacts

B. More stringent analysis:
  Select the subset of ASD subjects matched to TDs in head motion/image quality

The usual pattern disappears:
Now only one tract shows significantly lower FA in ASD.

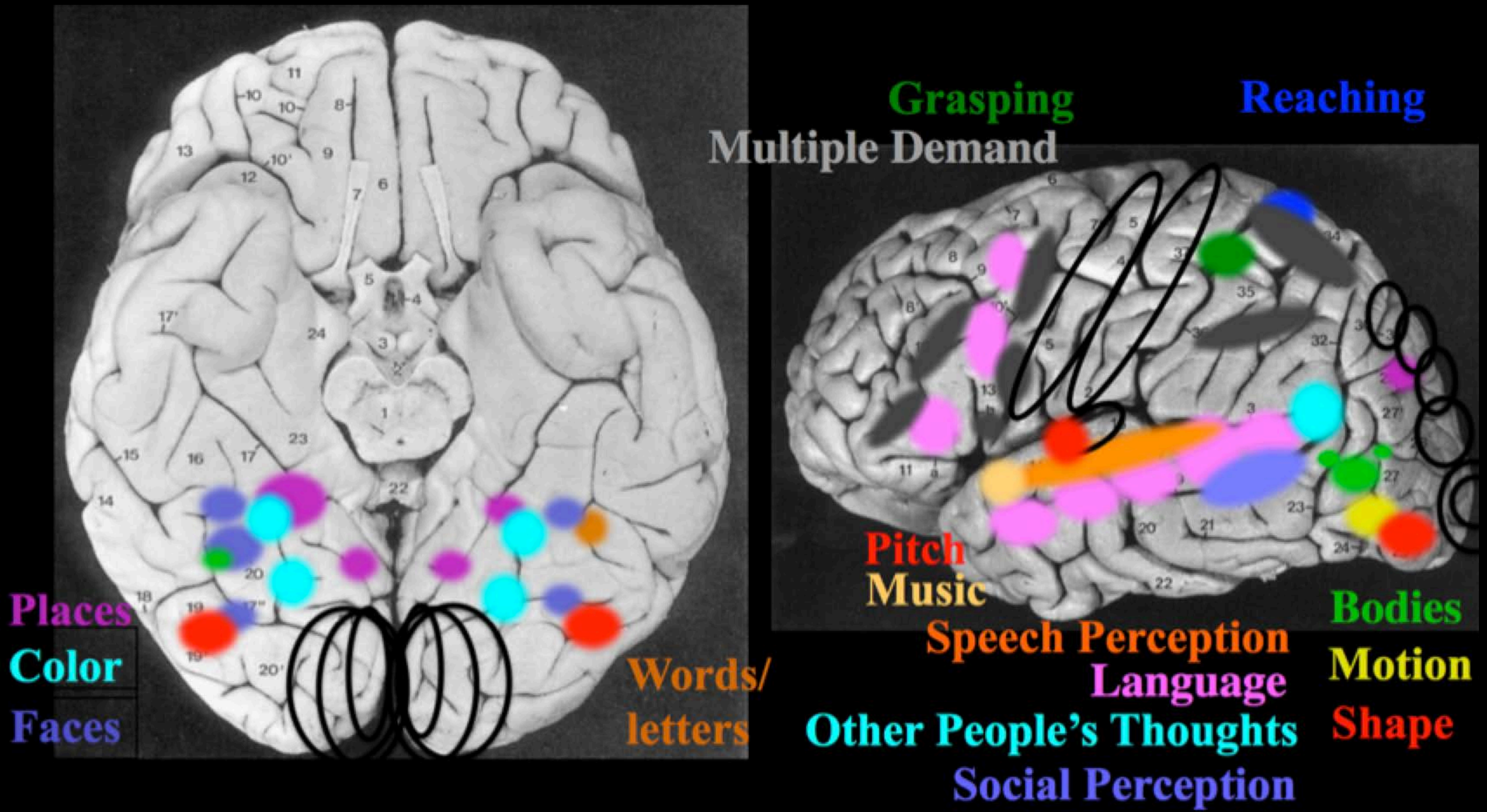
Bottom Line:
Beware of differences in motion between groups!

Now compare the
More artifactual > less artifactual scan *in the same TD subjs*
Replicate the "autism" phenotype of overall lower FA!

Source: K Koldewyn, et al. PNAS February 4, 2014 111 (5) 1981 1986; https://doi.org/10.1073/pnas.1324037111

Fiber Tracts and FA are Nice, But Really What we Need to Know is...

What are the connections of these regions to each other, and to the rest of the brain?

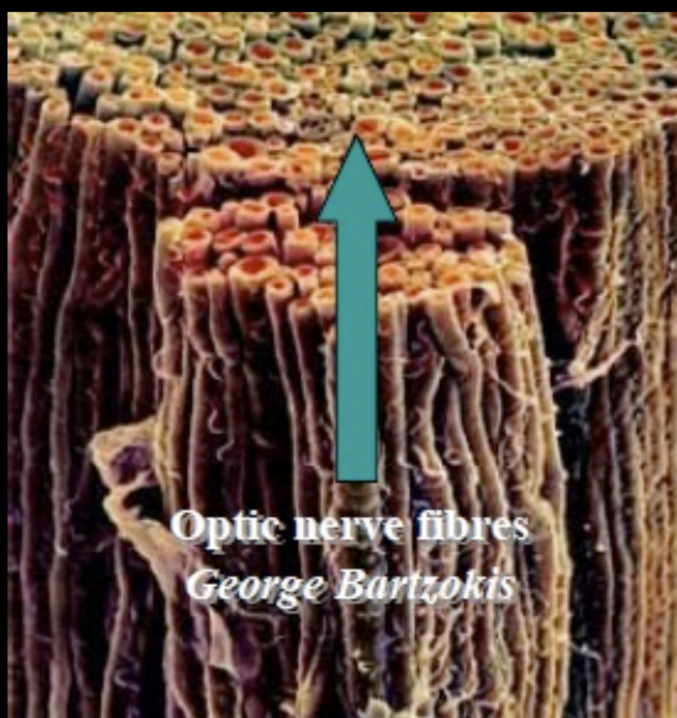


To figure that out we need to study not just white matter, but how white matter fibers come in and out of grey matter.

To do this, we perform *tractography*…

Diffusion Tractography

Principle:
Restricted Diffusion of Water in Axon Bundles



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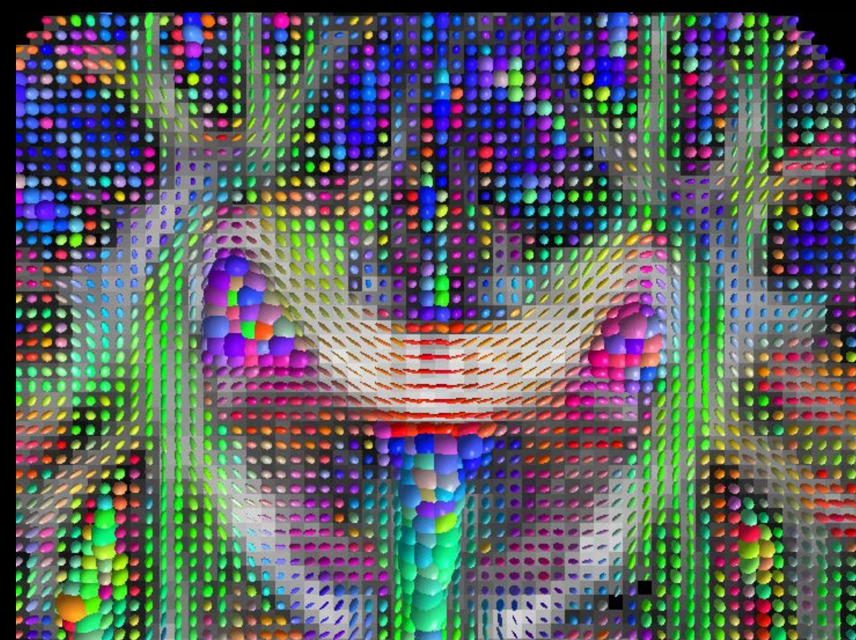


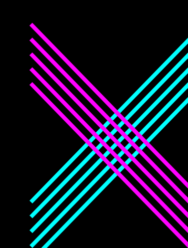
Tractography follows these vectors to reconstruct structural connections.

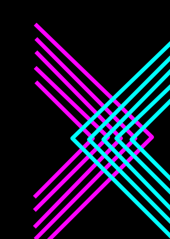
The best method for discovering structural connectivity in humans.

- e.g. start in the FFA, where can you go?

But this method is highly fallible, especially in

- the entrance and exit ramps on and off the "highways" (tracts)
  - i.e. from grey to white matter and vice versa
- cannot distinguish "crossing" versus "kissing" fibers





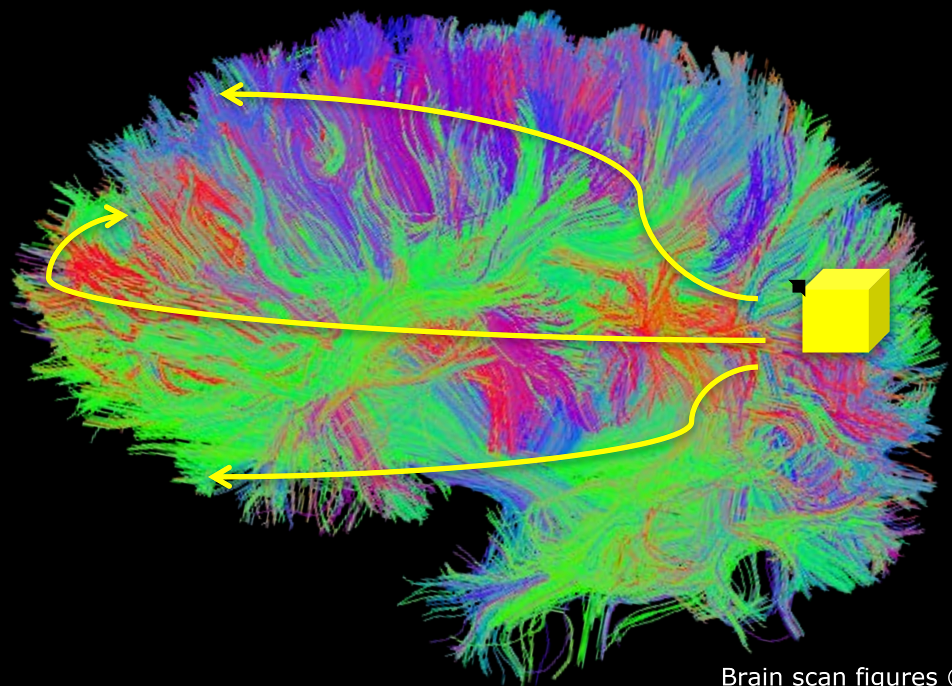
But, better than nothing, especially for finding "connectivity fingerprints"….

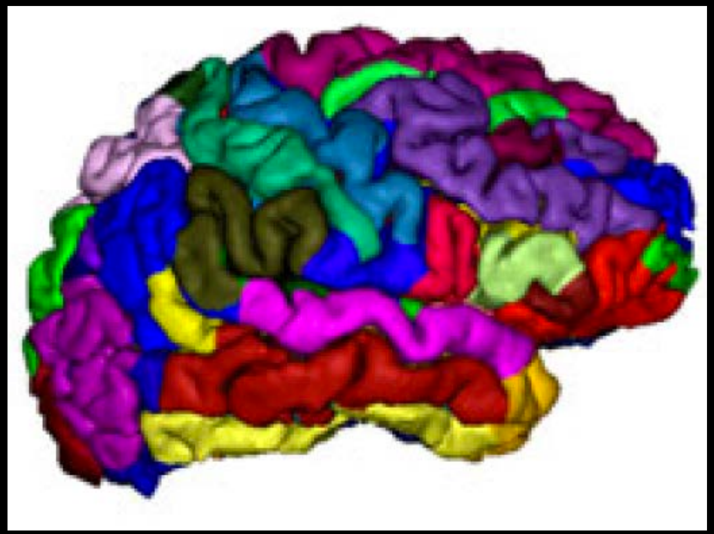
Review: Connectivity Fingerprints Predict Function

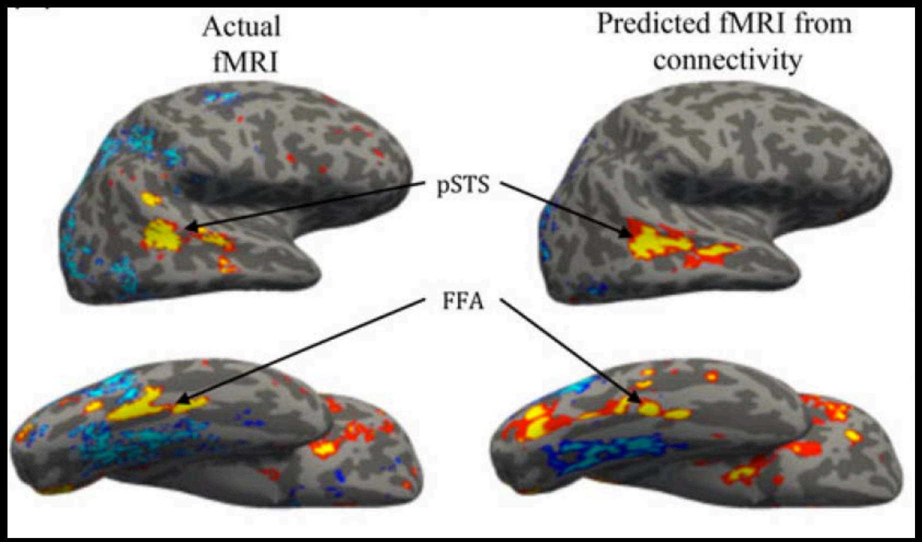
For each voxel:
Find its connectivity:

To each of a set of anatomical regions:

Saygin et al (2012): we can predict the function of a voxel from its CF:





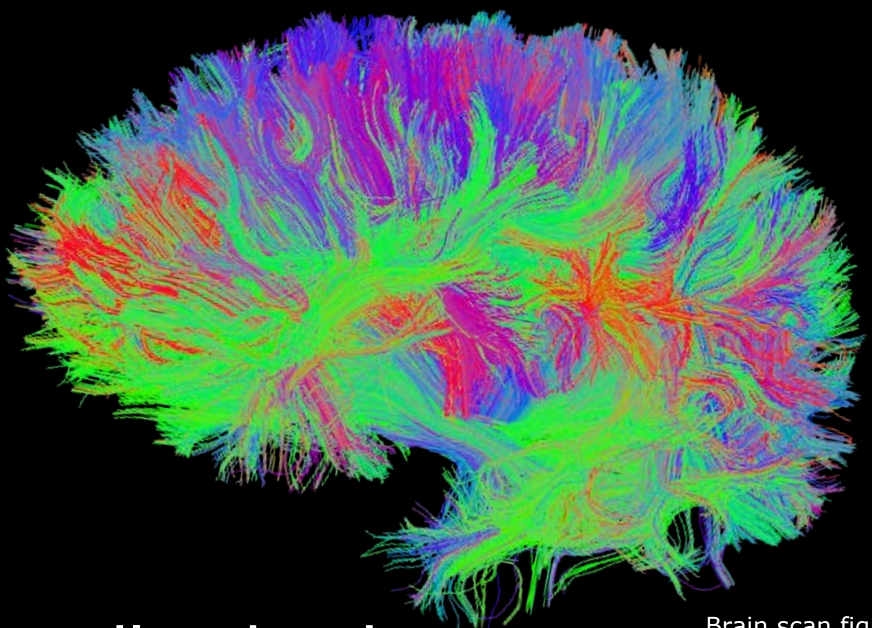


This is the "connectivity fingerprint" of that voxel.

Recall that connectivity and function go together
- indeed, connectivity is a defining property of a cortical area.
- so this helps validate the FFA as an area (sort of)

Can also use this method to ask what counts as the "same" area
- across sighted and blind subjs
- across species

Summary on What Diffusion Imaging tells us about Structural Connectivity



Can find major fiber bundles in vivo.

Can characterize their FA, etc.

    though not totally clear what these measures mean

Can find approx. "connectivity fingerprint" of a cortical area;

    good enough to predict function.

BUT: cannot very accurately determine the actual structural connections of a particular cortical area.

Which is a serious drag.

So, let's consider the other method people have used to look at this….

Lecture 21: Brain Networks

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III. Resting Functional Correlations

- what they are (correlations between regions)
  and are not (strong evidence for structural connectivity)
- the "networks" they reveal
  - DMN, fronto-parietal, etc.
  - distinction between language and MD networks (Blank)
  - relation between language & ToM networks

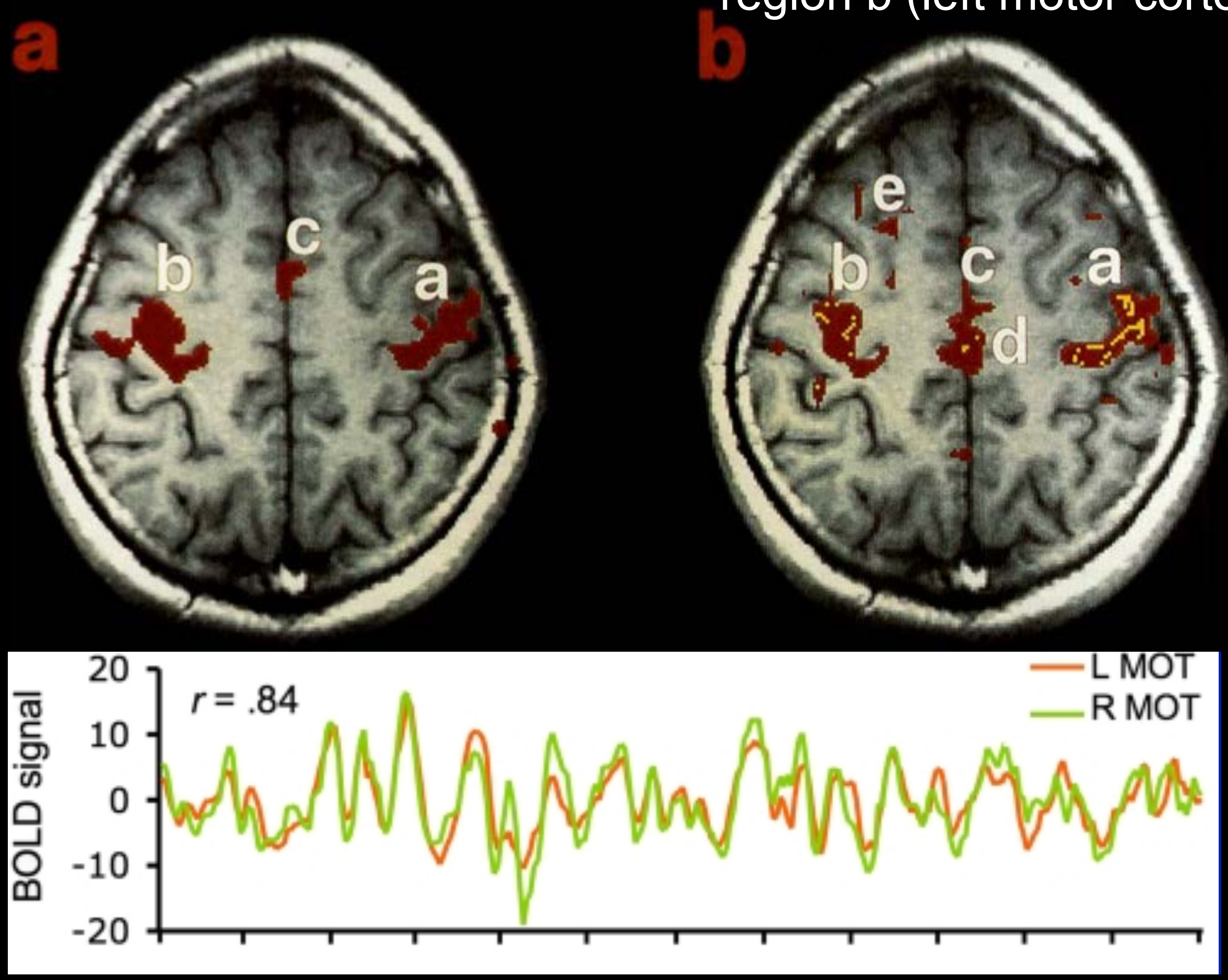
This story starts with a surprising and mysterious discovery….

Resting Functional MRI Correlations

Biswal et al., 1995

Activations of Motor Cortex from bilateral finger tapping

Voxels correlated at rest with a pixel in the middle of region b (left motor cortex)

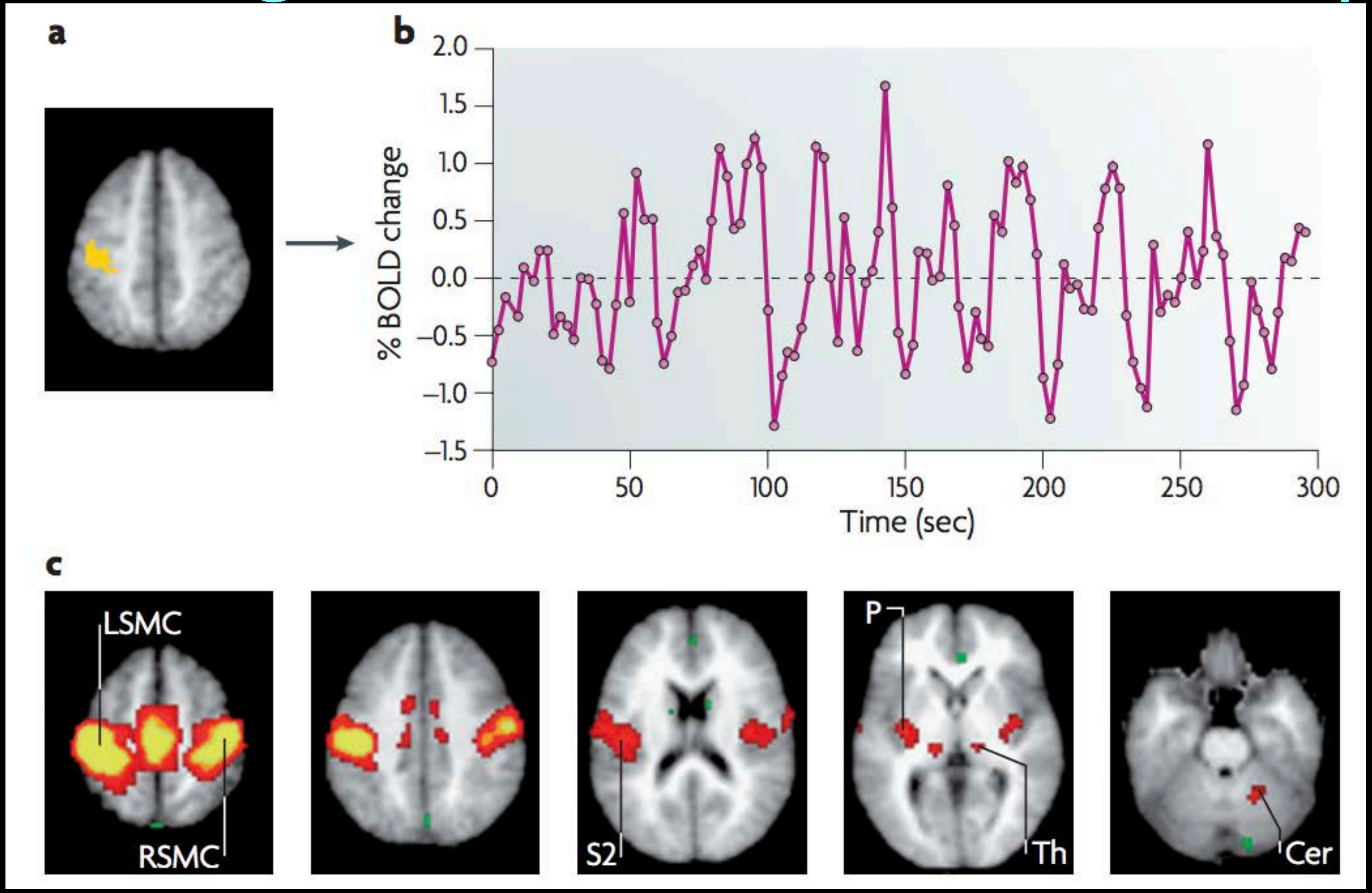


Source: B Biswal, et al. Magnetic Resonance in Medicine 34(4) p. 537 541. https://doi.org/10.1002/mrm.1910340409

So: At "rest", some far-away cortical regions have highly correlated time courses.
Does this imply structural connectivity between those correlated regions?
Not always (could be common input). But it can be pretty informative…..

Generating an rsfMRI Correlation Map

a | Seed region in the left somatosensory/ motor cortex (LSMC) is shown in yellow.



b | Time course of spontaneous fMRI signal during resting fixation and extracted from the seed region.

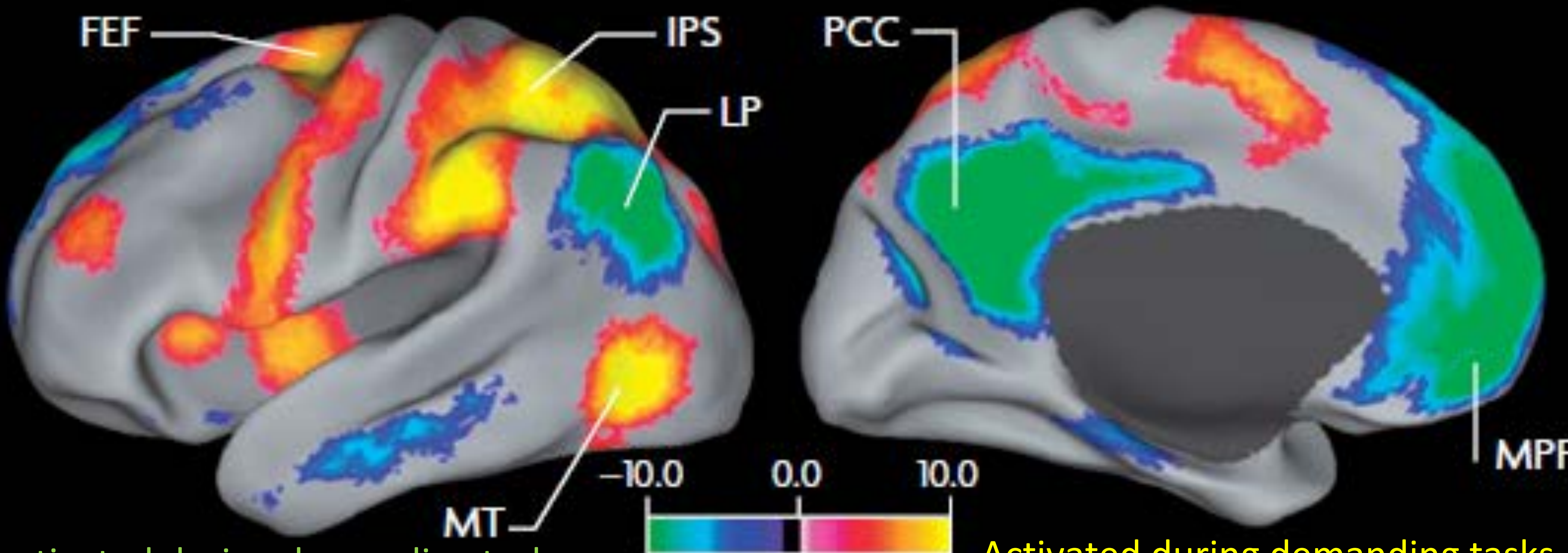
Source: Fox, M., Raichle, M. Nat Rev Neurosci 8, 700 711 (2007). https://doi.org/10.1038/nrn2201. https://doi.org/10.1002/mrm.1910340409

- c | Statistical map showing voxels that are significantly correlated with the extracted time course.

- So, even when you are lying in the scanner "at rest", remote regions of your brain are producing very similar fMRI changes over time.
- Common interpretation: these regions are "part of a network".
- But Important Caveat: despite the common use of thee phrase "resting connectivity", regions correlated at rest are not necessarily directly structurally connected.

Fox & Raichle, 2007, Nat Rev Neurosci

The “Default Mode Network” (DMN)



Deactivated during demanding tasks

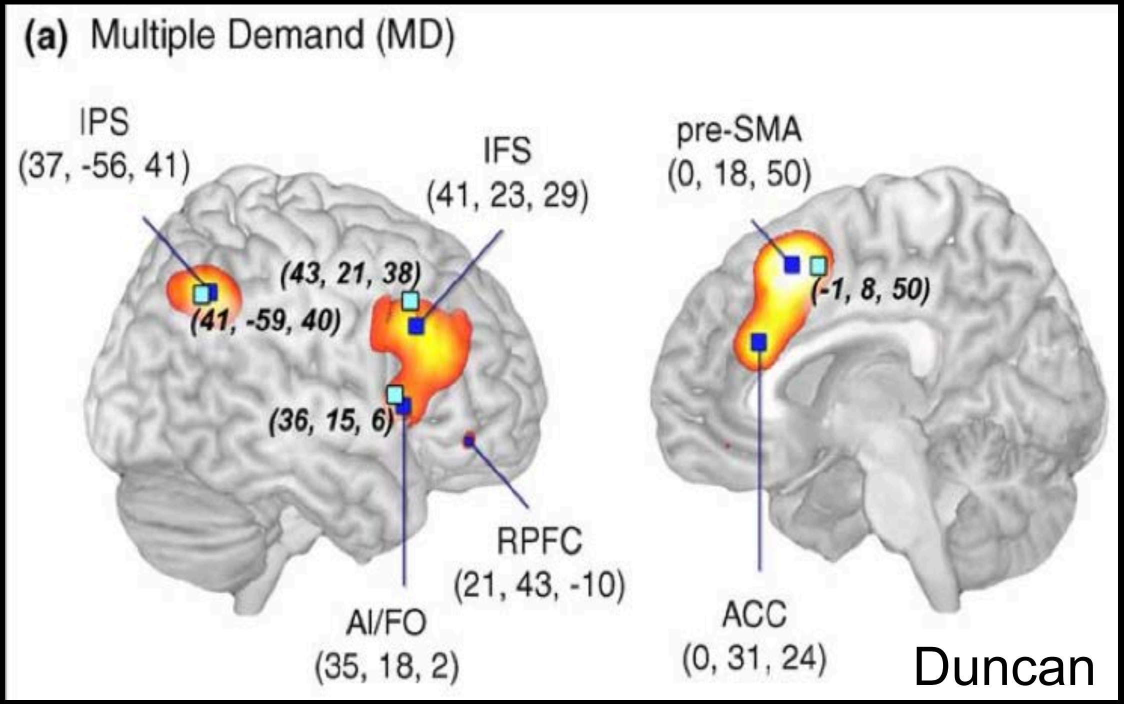
Activated during demanding tasks

The “DMN” was originally defined as a set of regions that tend to be more active at “rest” than during performance of a difficult task.

But then it was discovered that all these regions are also correlated with each other at rest.
Interestingly, the “DMN” overlaps a lot with the social cognition network. (why might that be?)
The “task positive” network responds more during most tasks compared to rest.
These two networks are evident in resting scans:
Areas within a network are correlated with each other at rest, whereas areas between networks are anticorrelated.
The task positive network goes by other names…

Fox & Raichle, 2007, Nat Rev Neurosci

"Multiple Demand" Regions



Source: J. Duncan. *Trends in Cognitive Sciences* April 2010, Vol.14 No.4. https://doi.org/10.1016/j.tics.2010.01.004

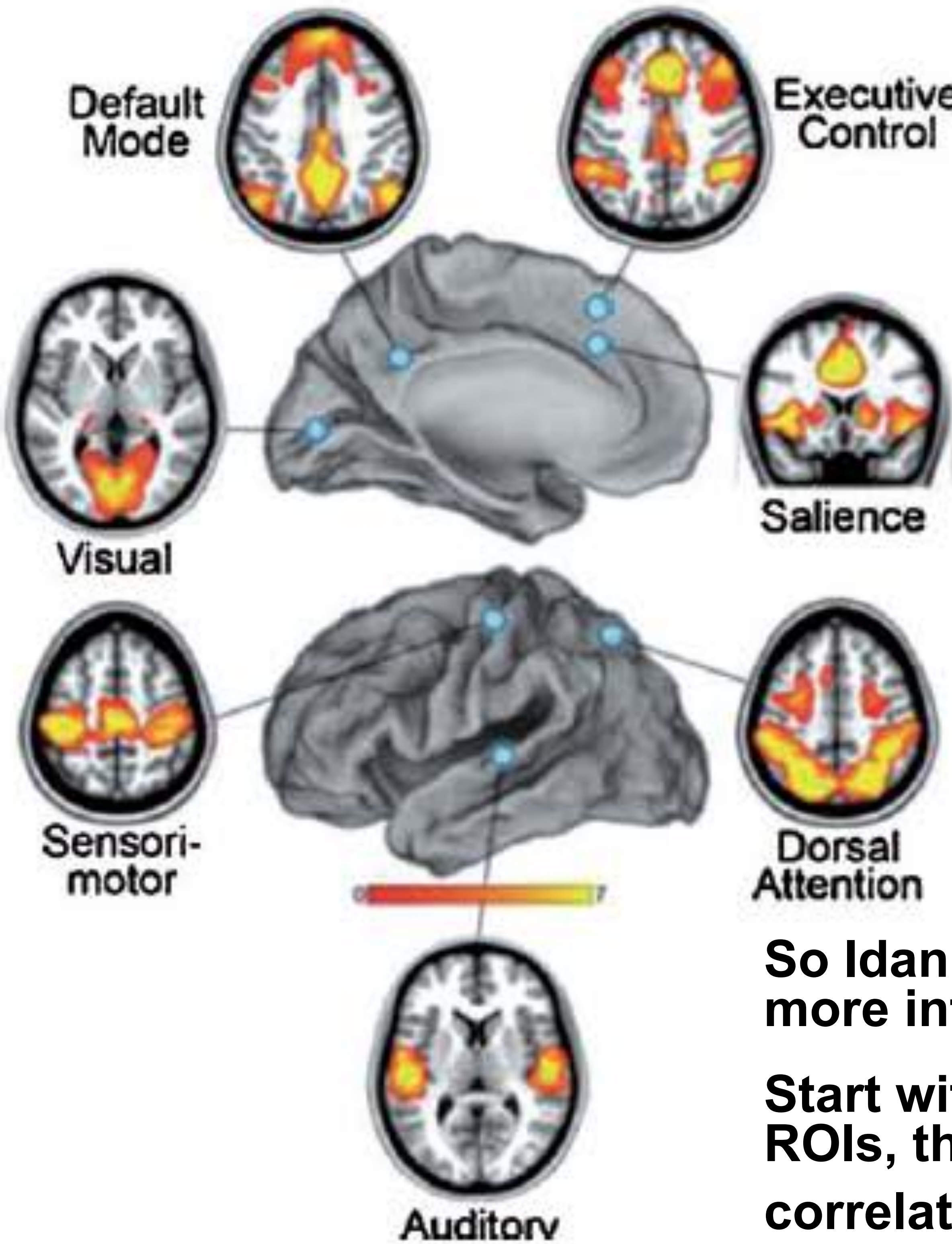
- Engaged in a wide variety of difficult cognitive tasks
  hence "multiple demand" (~= "fronto-parietal network")
- The opposite of all the regions we have studied so far:
  scandalously domain-general
- Related to fluid intelligence:
  activated during fluid intelligence tasks
  causal role in fluid intelligence
    6.5 IQ pts/ 10 cm3 of MD cortex
- Critical for solving novel problems

rsfMRI has revealed other networks…

Multiple Resting State Networks (RSNs)

<u>**The Big Idea Here:**</u>
"Networks" as basic units of brain organization, not just the ROIs we have been talking about.

<u>**Cool. But:**</u>
What can we make of these things, without knowing what these regions *do*?



So Idan Blank tried something more interesting:

Start with relatively-understood ROIs, then ask which are correlated with each other....

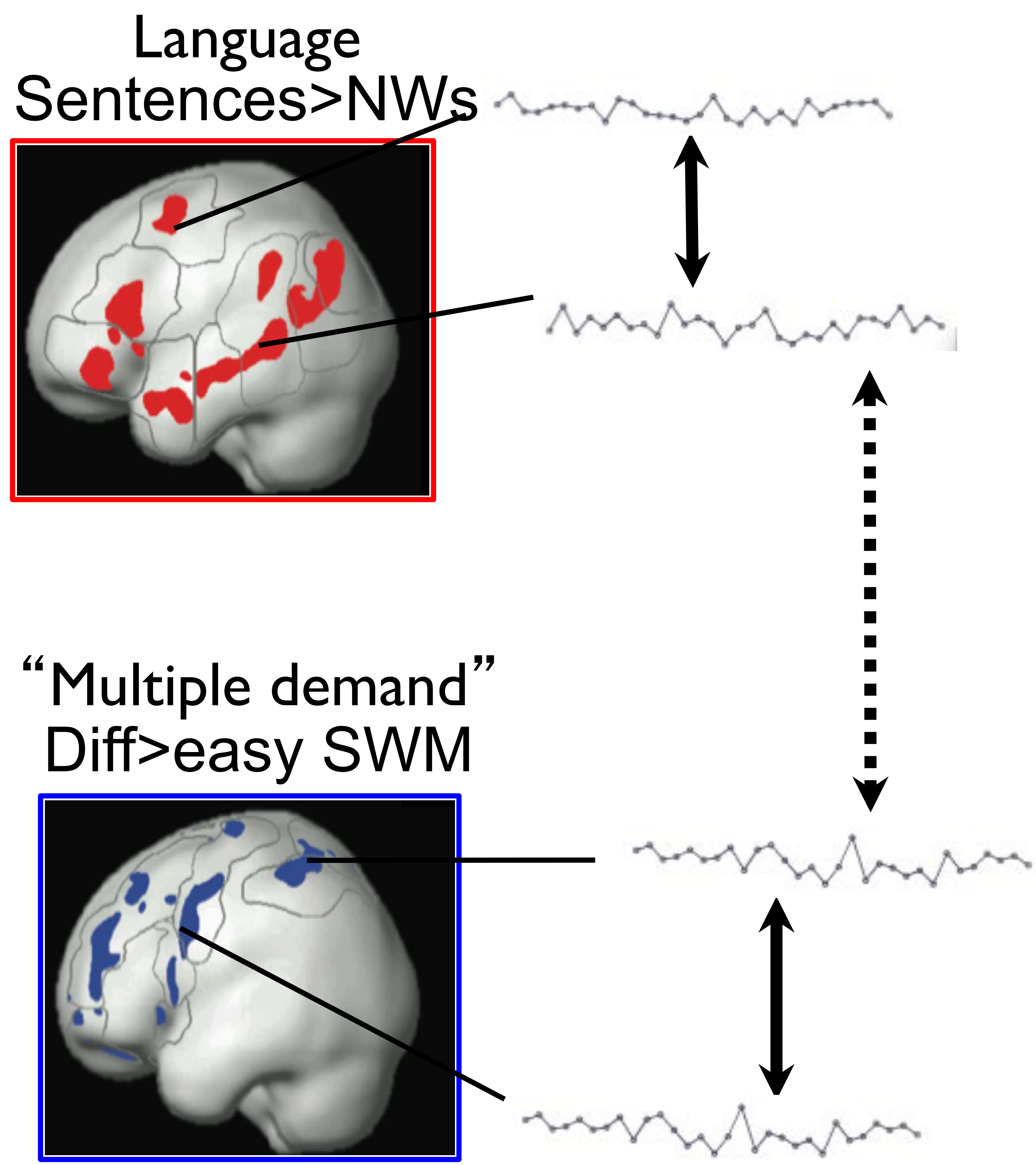
Raichle 2011, 2015

Resting fMRI Correlations across ROIs

1. Define language vs. MD fROIs in each individual.

2. Extract the timecourse at rest from each individually defined fROI.

3. Examine correlations between the timecourses of the regions
   - within each network
   - across networks

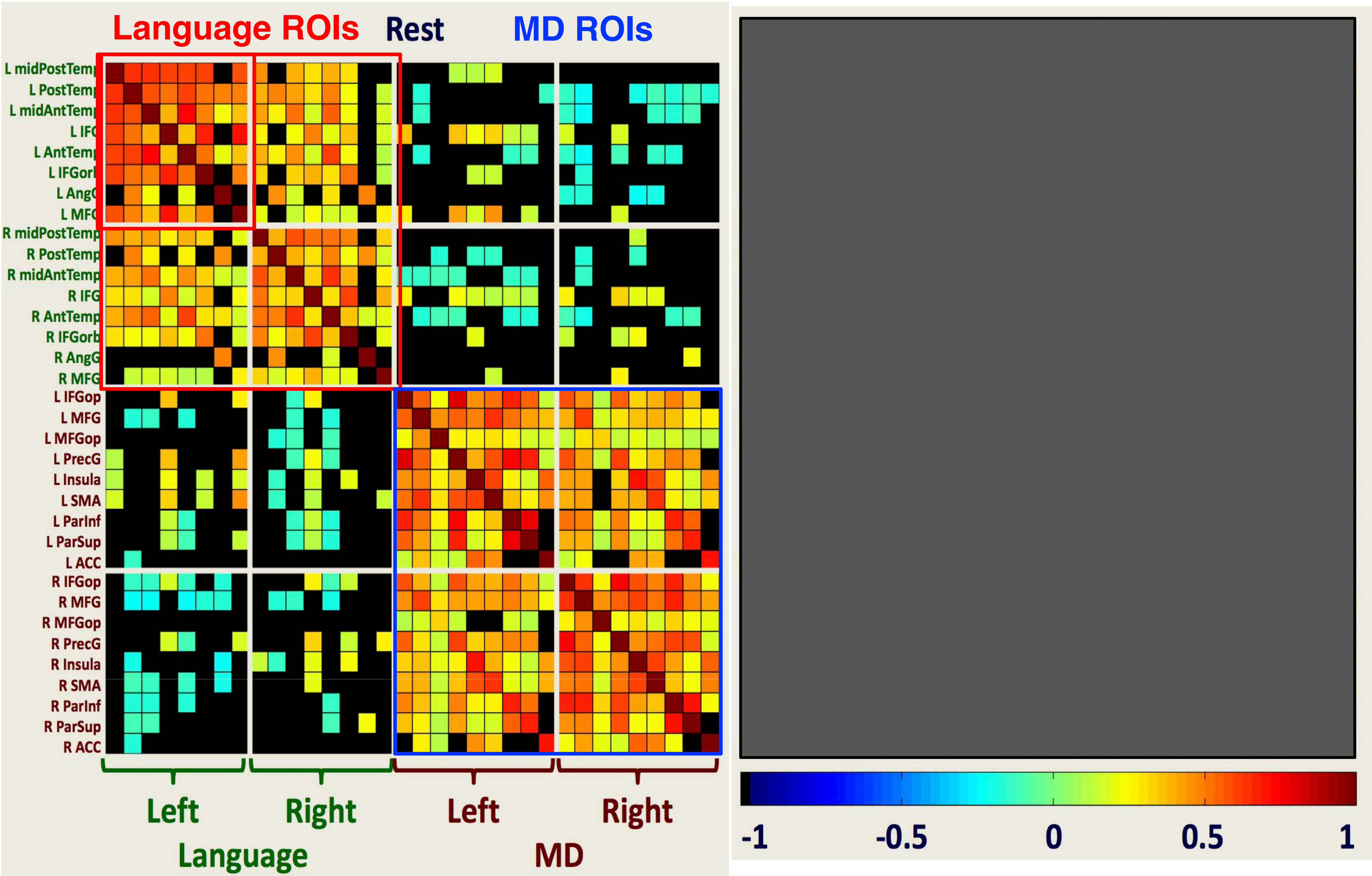


What did he find?

Source: Blank I, Kanwisher N, Fedorenko E. J Neurophysiol. 2014 Sep 1;112(5):1105-18. doi: 10.1152/jn.00884.2013

Correlations across ROIs

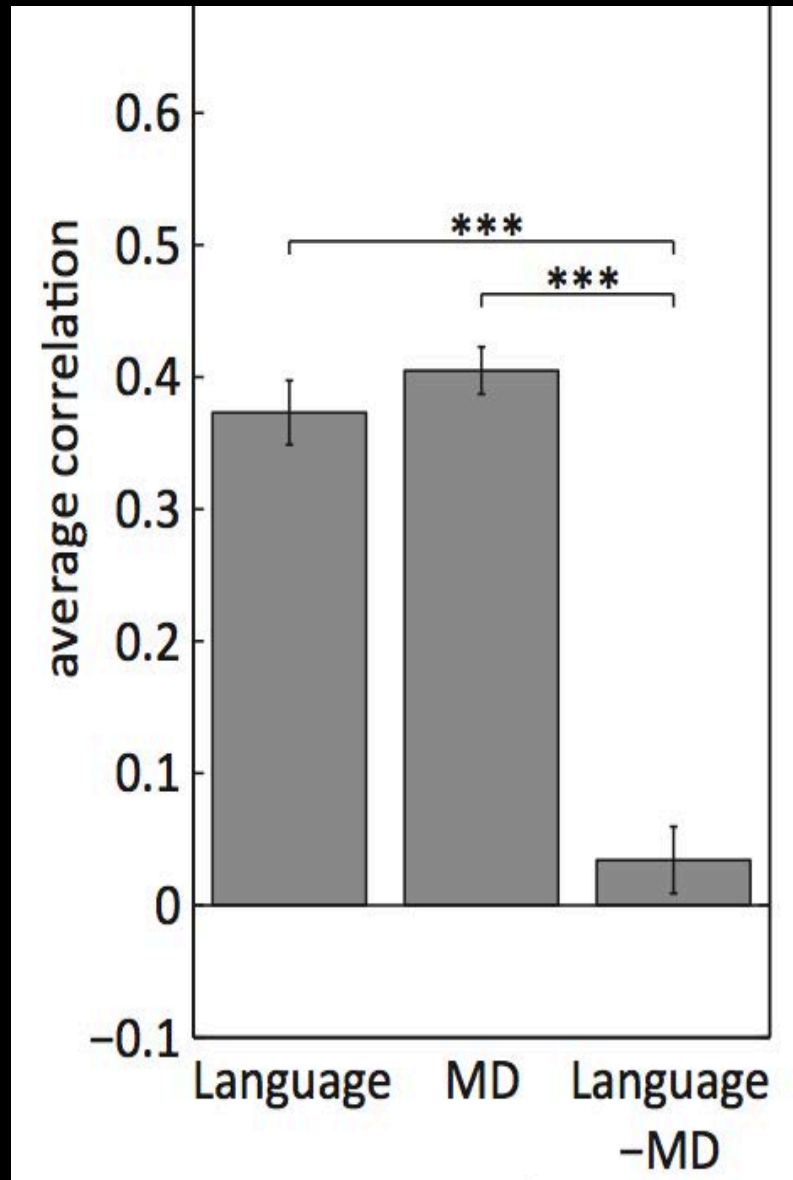
What about during language comprehension?



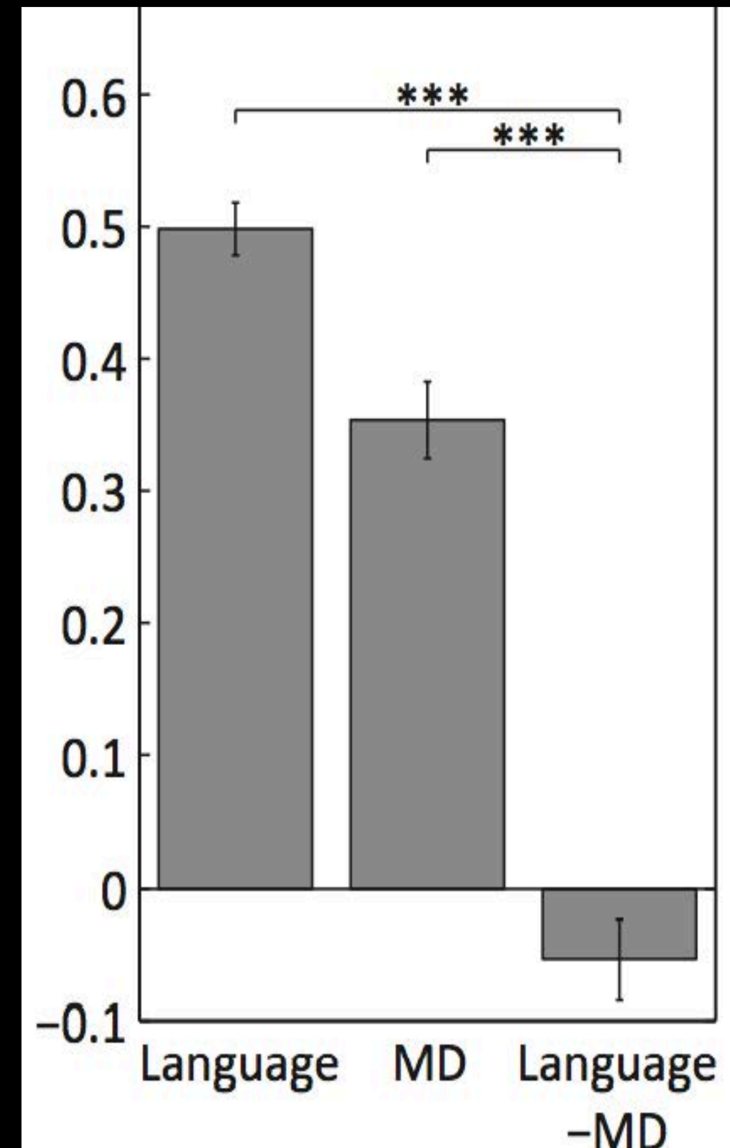
Time courses are correlated within a system, not between

 Source: Blank I, Kanwisher N, Fedorenko E. J Neurophysiol. 2014 Sep 1;112(5):1105-18. doi: 10.1152/jn.00884.2013

“Rest



Story Listening



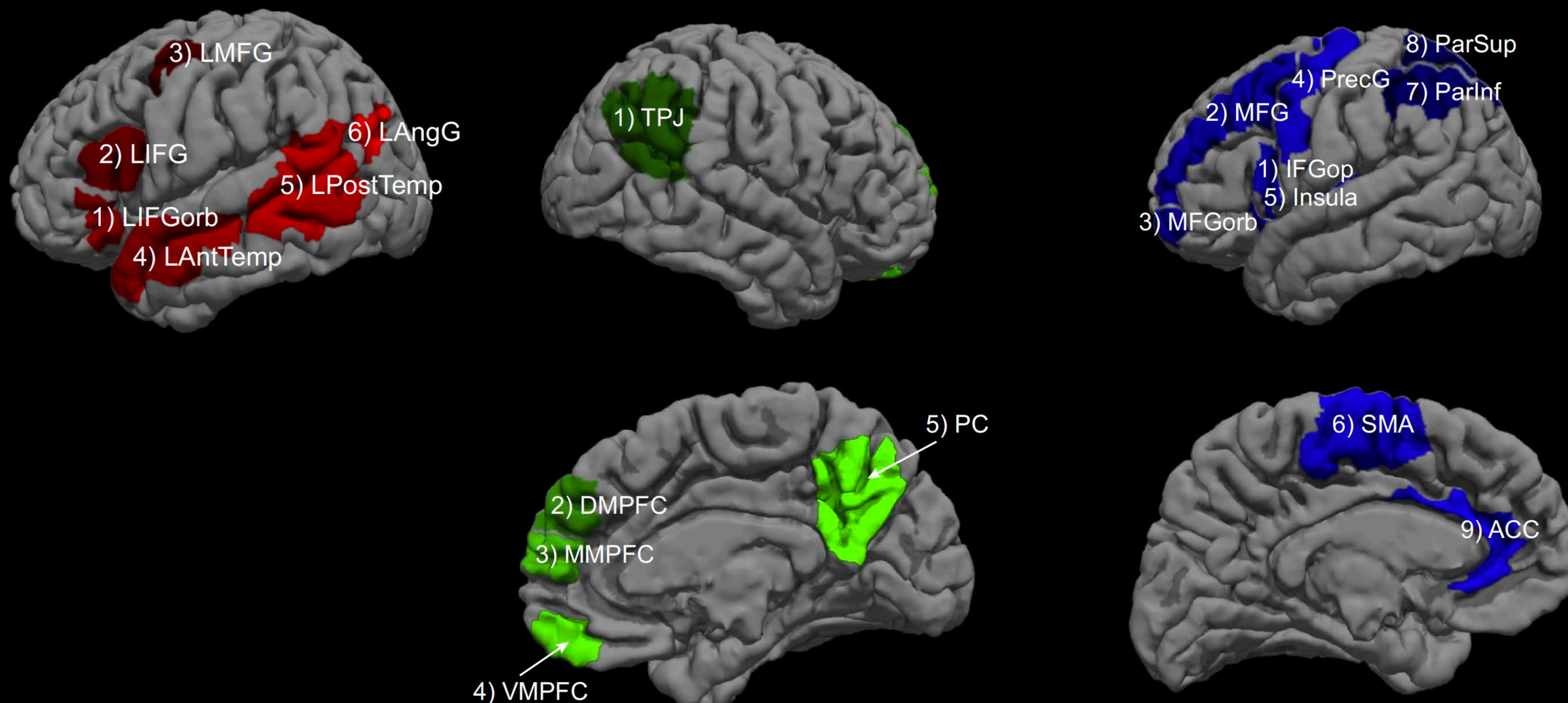
OK, so where are we now? Taking stock…

 Source: Blank I, Kanwisher N, Fedorenko E. J Neurophysiol. 2014 Sep 1;112(5):1105 18. doi: 10.1152/jn.00884.2013

- **The language system is a coherent “thing”,**
- **the “MD” system is a “thing,**
- **these two things are different from each other!**
- **So, resting functional correlations are tightly linked to functional organization discovered from other methods.** ***Time courses are correlated within a system, not between***

Not just Brain *Regions*, but Brain *Networks*

Language Network (S>N)	ToM Network (FB>FP)	Multiple Demand Network (H>E)



Source: AM Paunov, IA Blank, & E Fedorenko. J Neurophysiol. 2019 Apr 1;121(4):1244 1265. doi: 10.1152/jn.00619.2018.

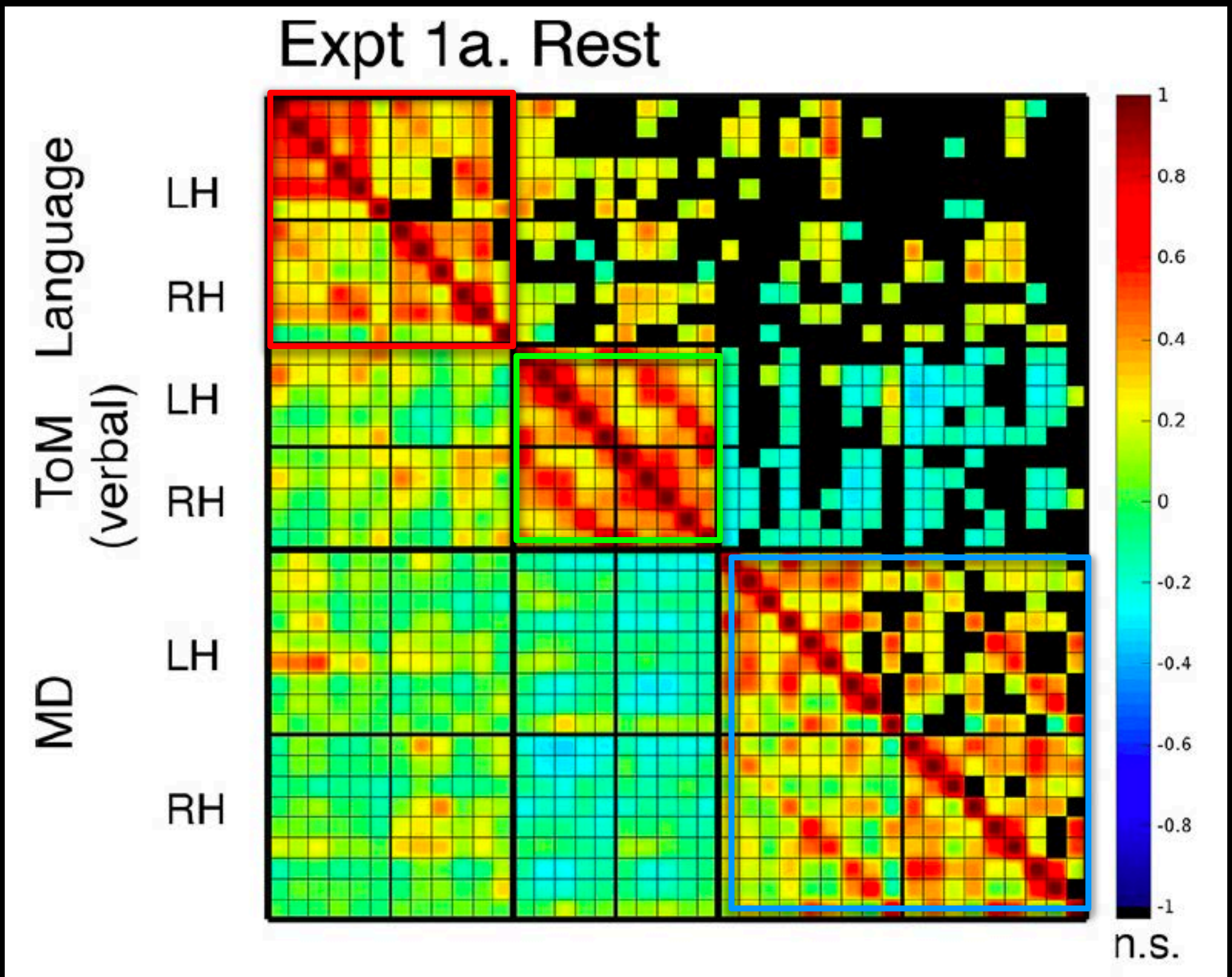
So, rsfMRI shows: The Language and MD systems are two distinct networks.

How do you think the Theory of Mind network fits in?

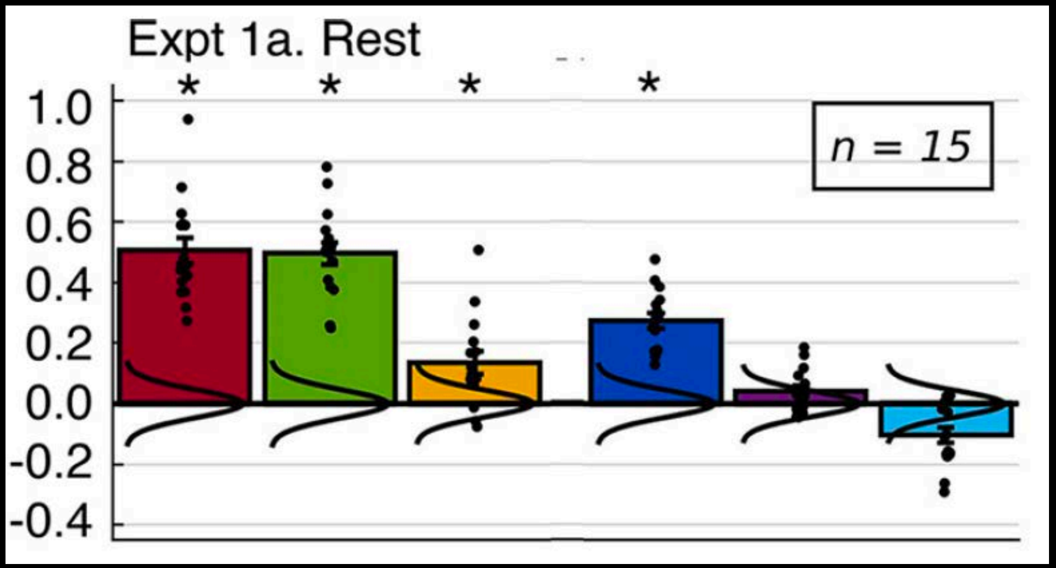
A third completely distinct network, or some linkage to Lang and/or MD?
How would you find out?

Not just Brain Regions, but Brain *Networks*

Language Network (S>N) | ToM Network (FB>FP) | Multiple Demand Network (H>E)



The half-matrix below the diagonal shows all correlations, the half-matrix above the diagonal highlights the significant ones .



- Correlations w/in each network
- Sig correlation btwn
  - Language & ToM

No correlation between
  Lang & MD (as before)
  ToM and MD

Source: AM Paunov, IA Blank, & E Fedorenko. J Neurophysiol. 2019 Apr 1;121(4):1244 1265. doi: 10.1152/jn.00619.2018.

ToM: A third completely distinct network, or some linkage to Lang and/or MD?

Lecture 21: Brain Networks

Summary:

I. Who cares about white matter and why?

A large percent of the brain, plus:
Crucial for understanding how regions interact with each other,
As well as development, evolution, and brain disorders

II. Diffusion imaging and tractography.

Can use to find major white matter tracts in the human brain
Measure properties, e.g. fractional anisotropy
Tractography to obtain connectivity fingerprints
Challenges with determination of actual connectivity

rsfMRI carves out a groups of brain regions that seem to act together, another level of brain organization from ROIs.

III. Resting Functional Correlations

Correlations between regions at rest
Not strong evidence for structural connectivity, but reveals "networks":
- DMN: regions more activated during "rest" correlated w/ each other
- Multiple demand (MD) network:
  - domain-general, engaged in most difficult tasks
- Rs-fMRI shows: language and MD networks not correlated
  - ToM network weakly correlated with lang network, not with MD