What actually is "connectivity"?

Stephen J. Gotts
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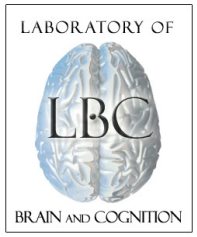

"Connectivity" in the context of MRI/FMRI studies

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It's a label that stands in for a set of (pretty complicated) measures that index anatomical and physiological proxies for actual synaptic connections

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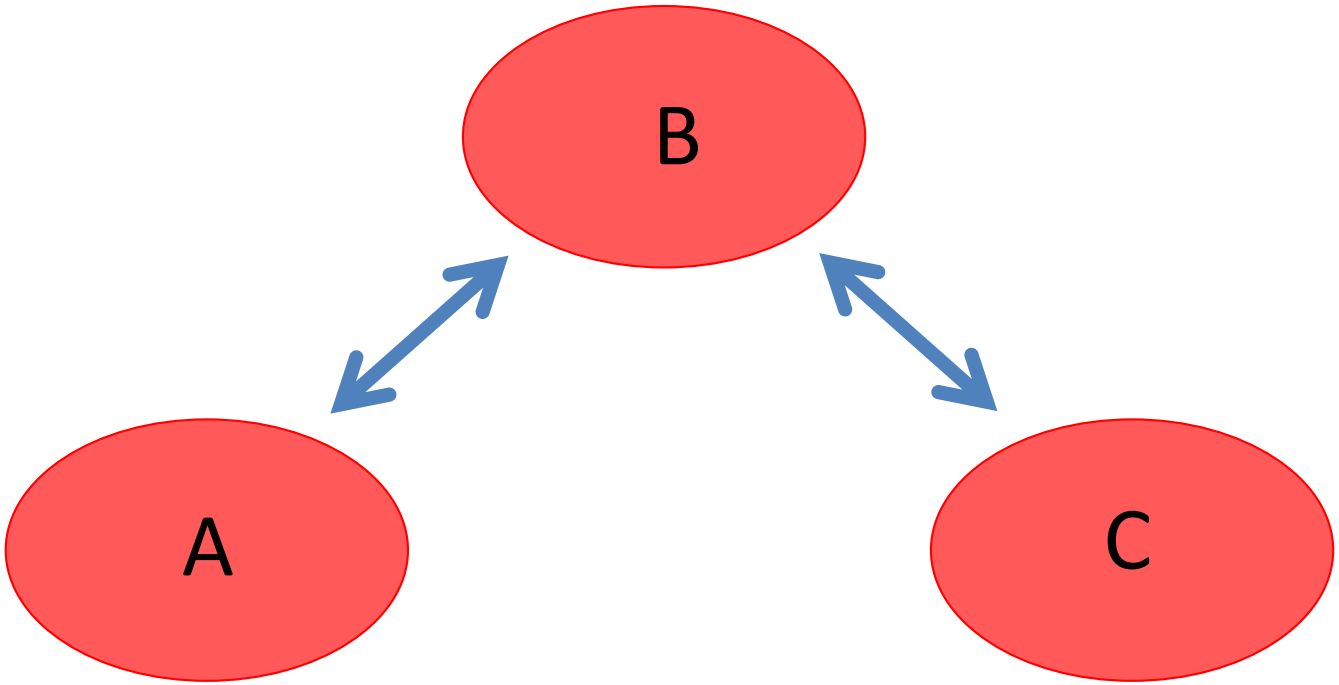
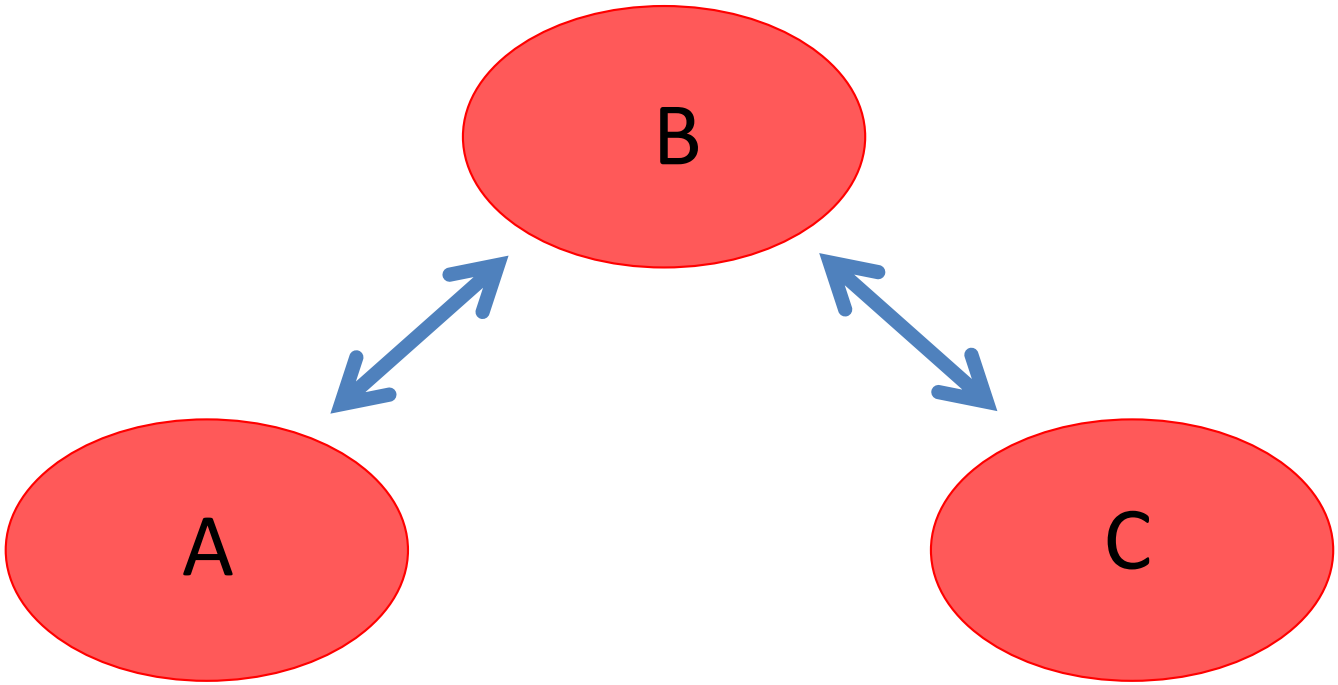
For physiological measures, "connectivity" is constrained by anatomical connections but is not a mirror image of them (due to polysynaptic and network-level interactions)


B
A
C



A and C will often appear "connected" also

"Connectivity" in the context of MRI/FMRI studies

Examples:

"Connectivity" in the context of MRI/FMRI studies

Examples:

Structural Connectivity

- DTI

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Functional Connectivity

- correlation(/regression) using BOLD EPI
- either in resting-state or task-based studies

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Effective Connectivity

- weight parameters within a causal model

Overview of Talk

Overview of Talk

Basic role of connectivity in brain functioning

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Spontaneous versus stimulus/task-driven activity across multiple levels of observation

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Connectivity measured with fMRI

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Connectivity measured with fMRI

How do we know that we're measuring what we want to?

Basic Role of Brain Connectivity in Function

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Basic point:
Function comes from neurons, neurons activate each other via synaptic connections

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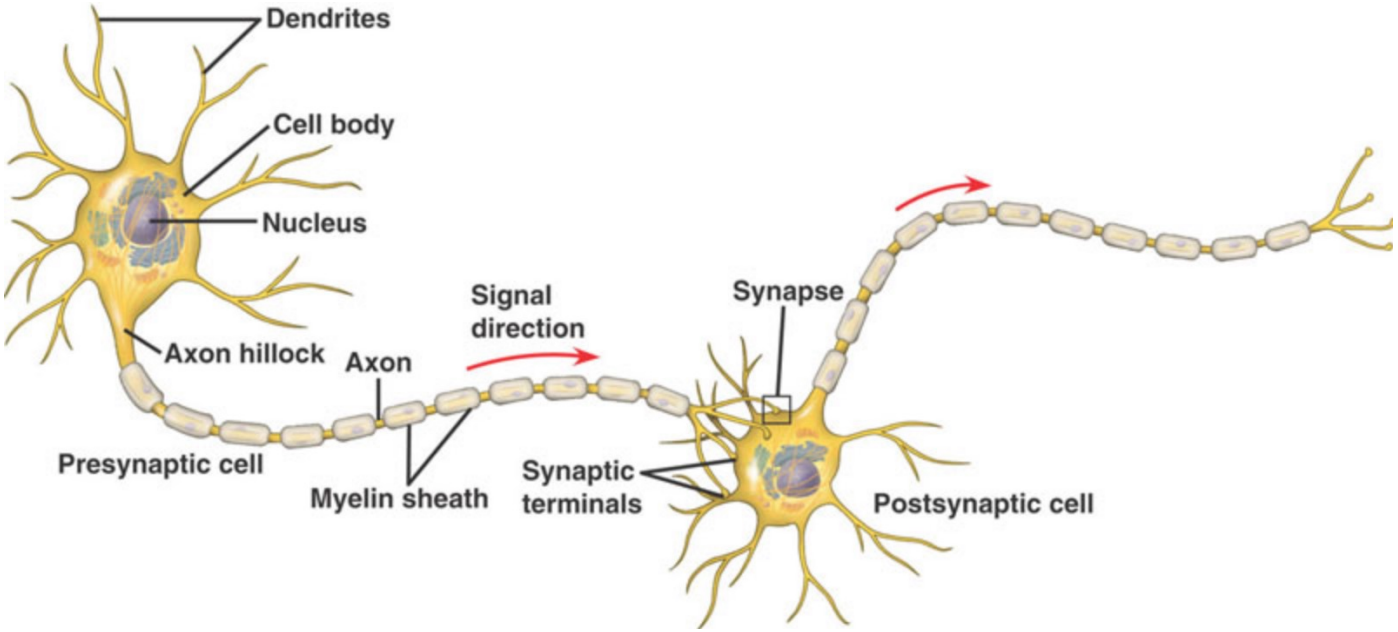

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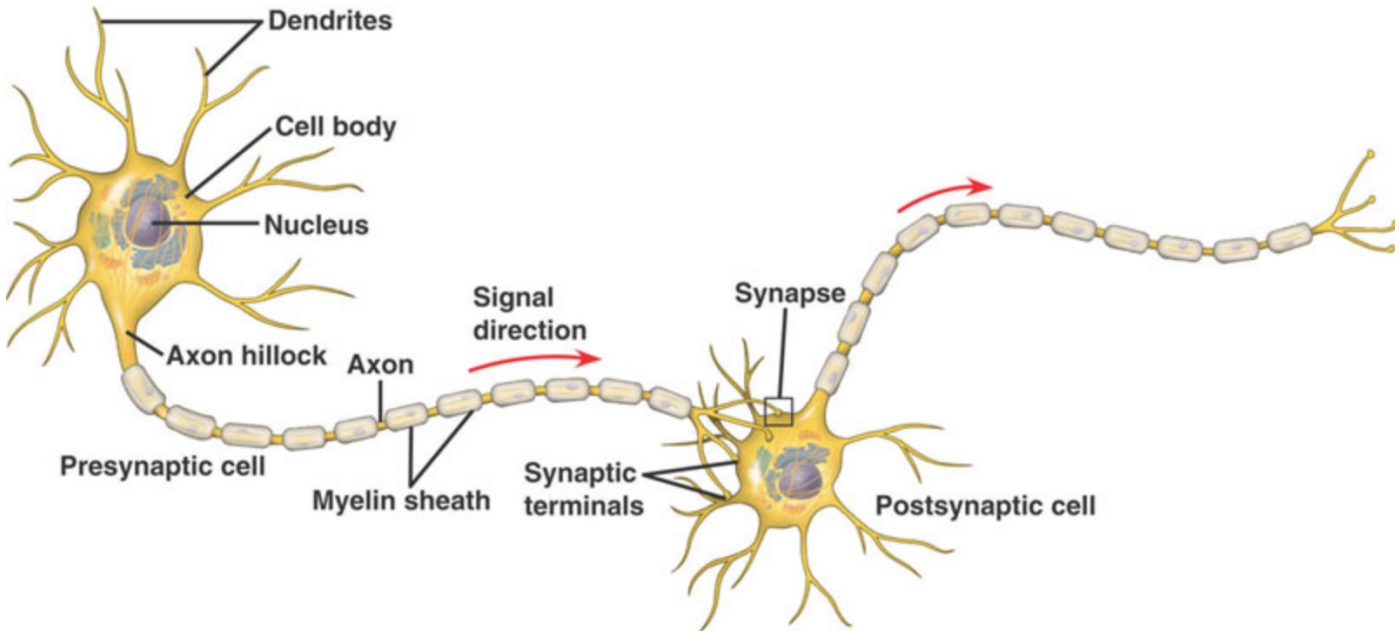

Each cortical neuron has a small (<1 mV) impact on any other, which means that *they must work together*

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Debate for decades over discrete stages vs interactivity

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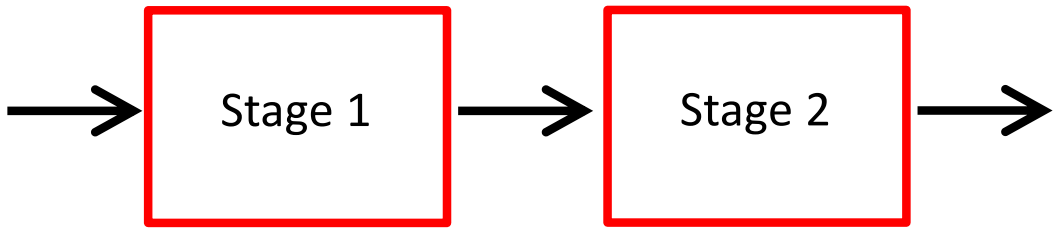

Early Views from Psychology and Cognitive Science: Discrete Stages and Modules (Marr, Fodor, etc.)

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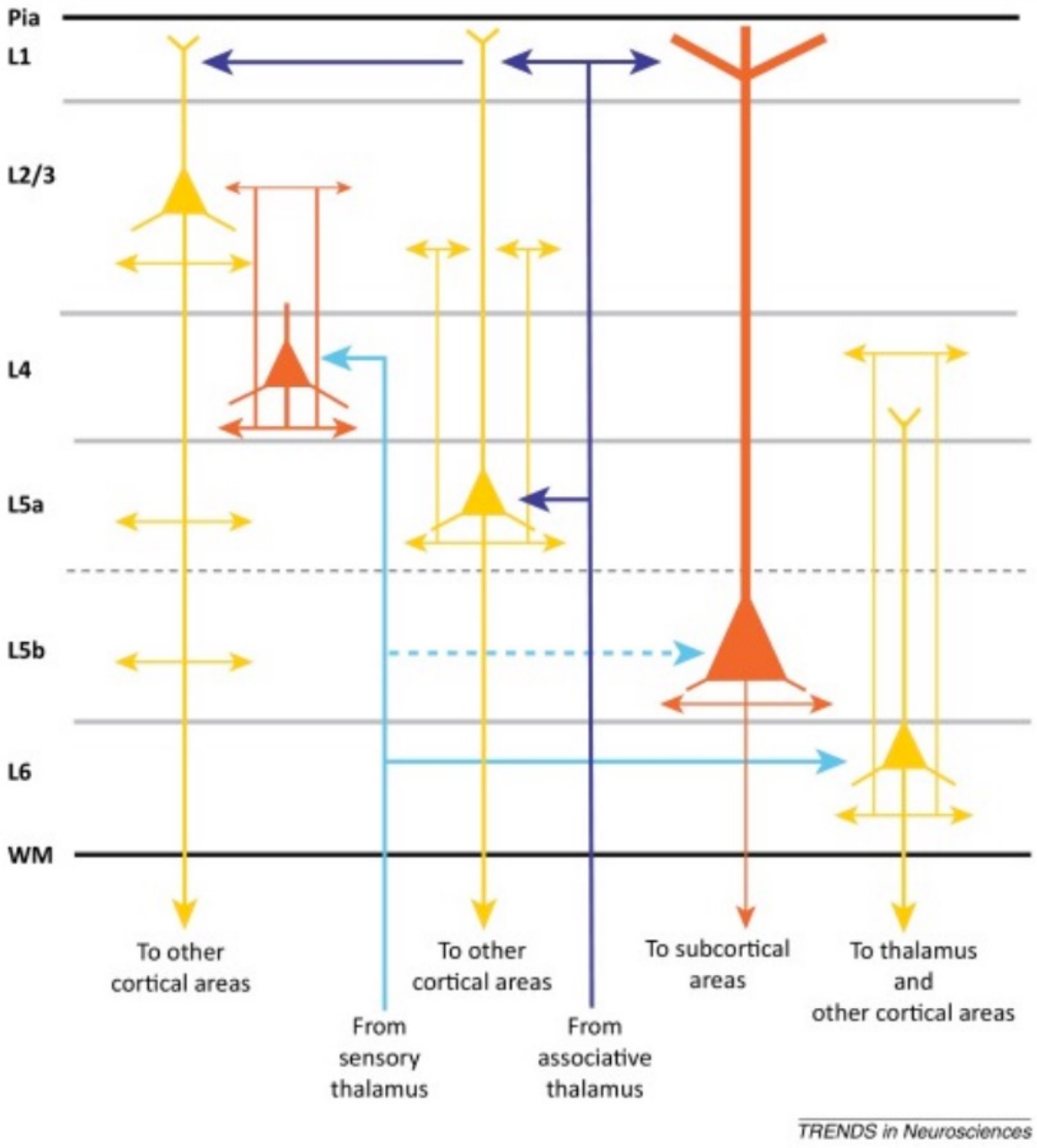
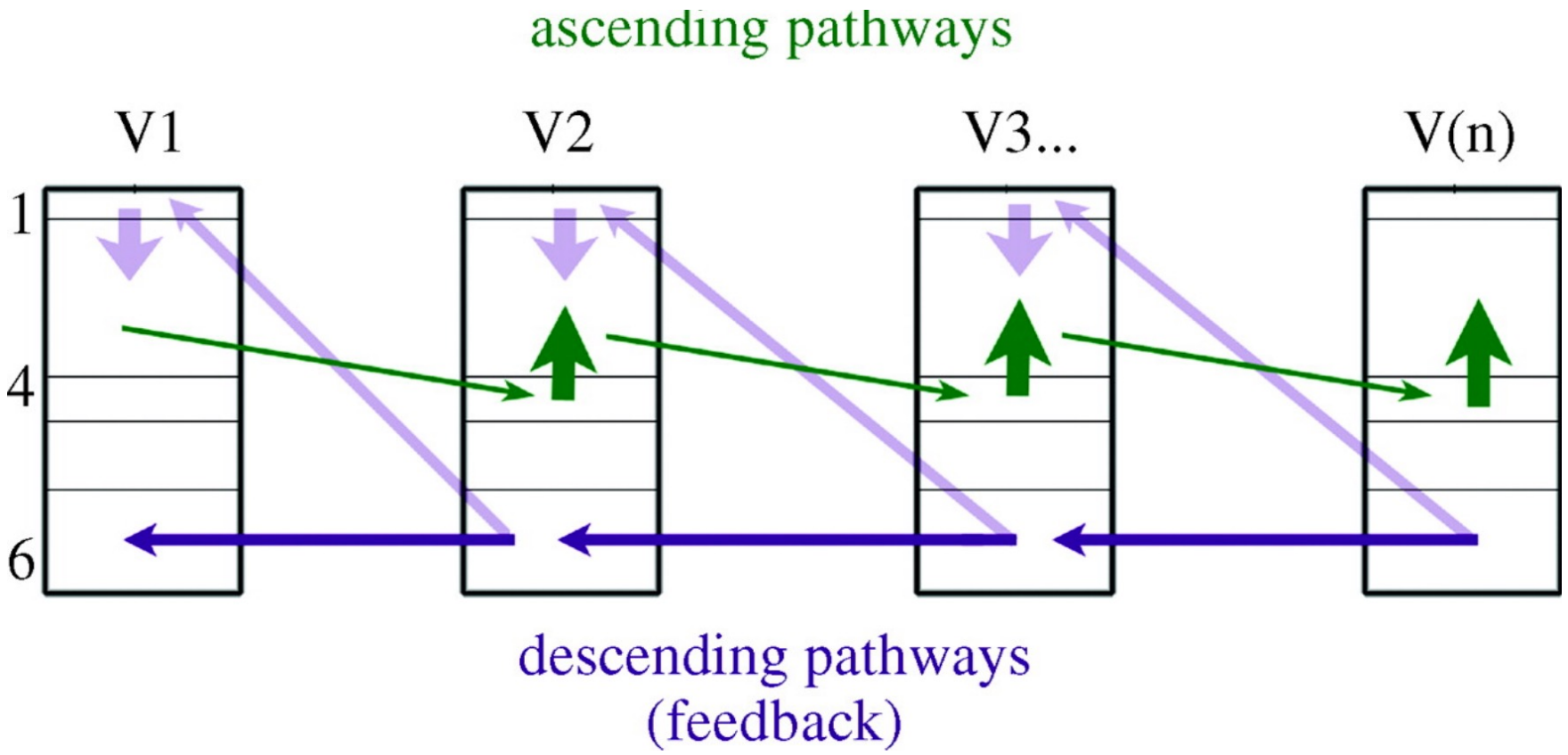
Throughout cortex, many synaptic interactions are effectively bi-directional (e.g. V1<->V2, with Thalamus, etc.)

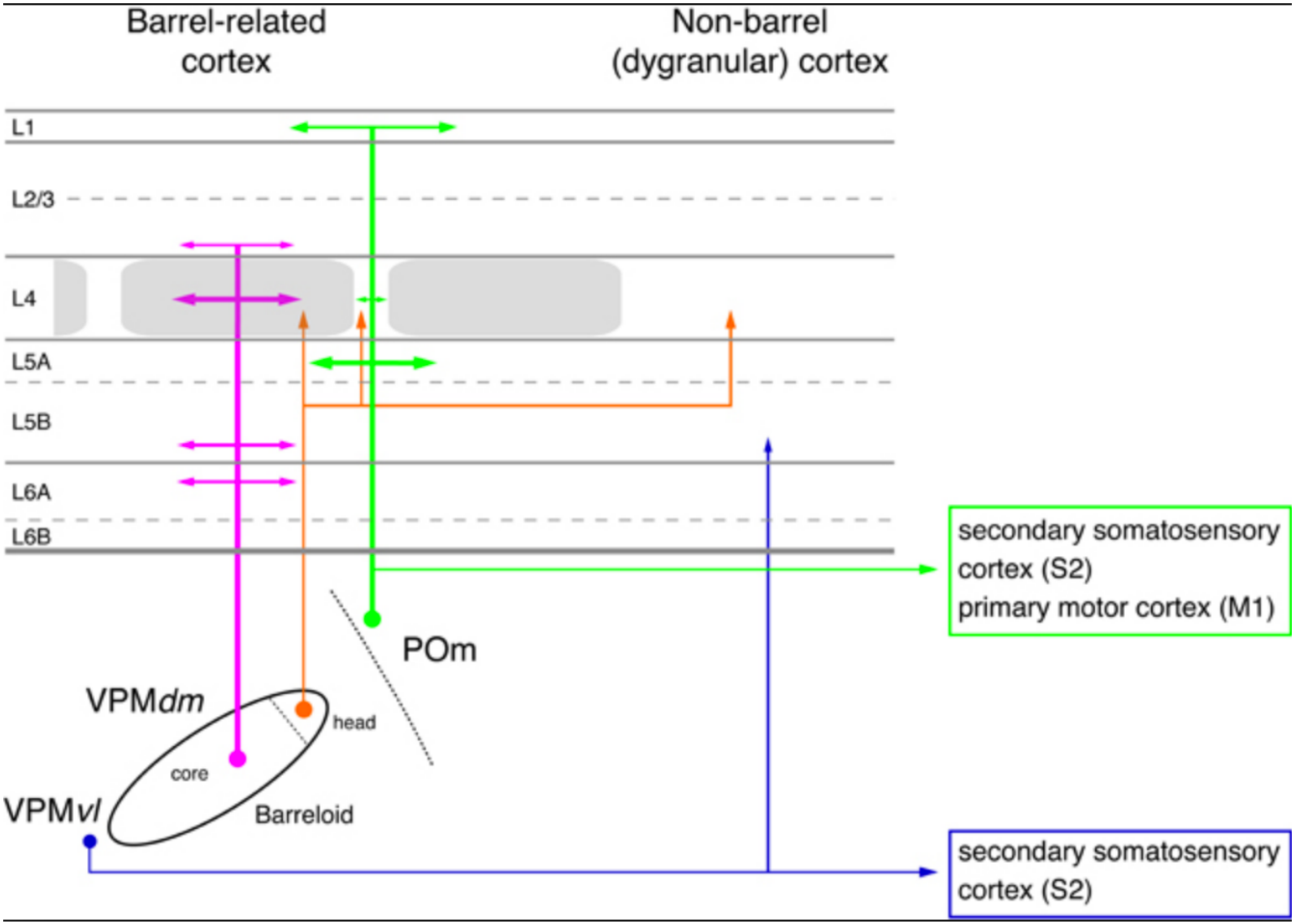


Allene et al. (2015). Trends in Neurosciences 38, 524-34.

Cartoon of Laminar Structure in the Early Visual System



Cartoon of Laminar Structure in the Rat Somatosensory System (Barrel Cortex)



Transition in thinking within the domain of language:

Poeppel et al. (2012). J Neurosci 32, 14125-31.

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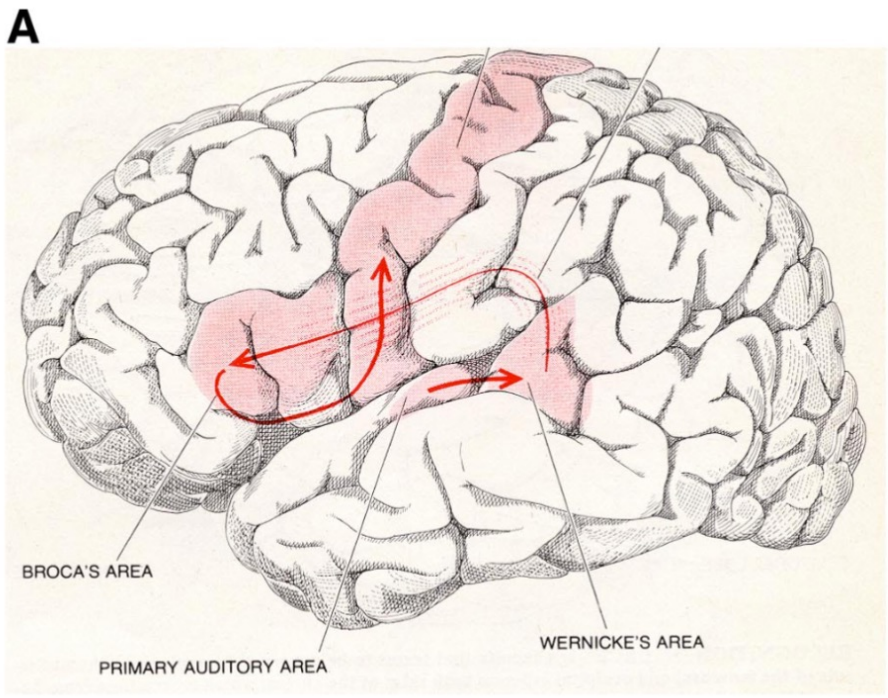

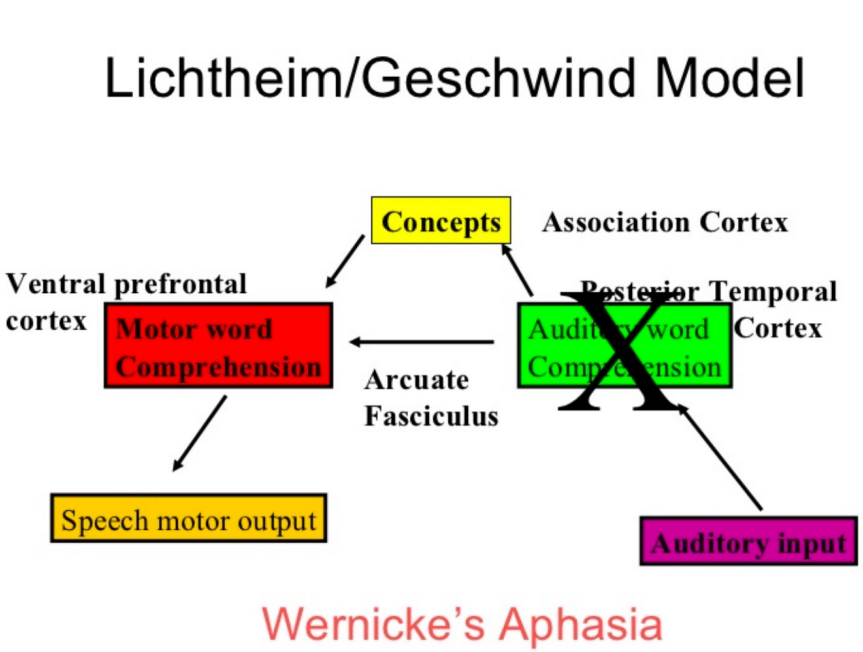

Wernicke's Aphasia

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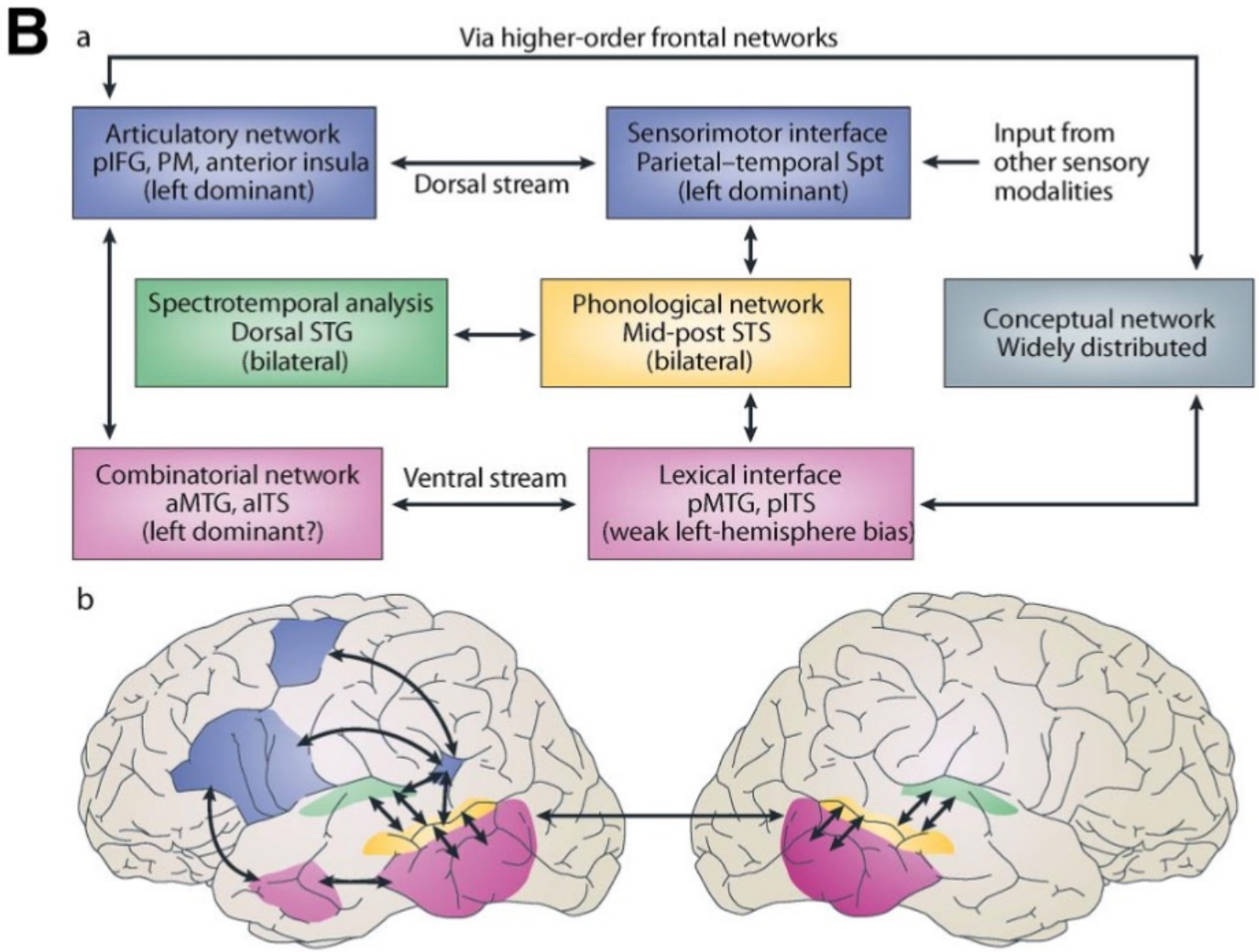

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Sources of activity fluctuations:

- Spontaneous activity
- Endogenous (i.e. internal, voluntary)
- Exogenous (i.e. stimulus-driven)

Activity (Co-)Fluctuations At Multiple Spatial Scales

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Brain activity (action and synaptic potentials) never stops entirely in the absence of a stimulus.

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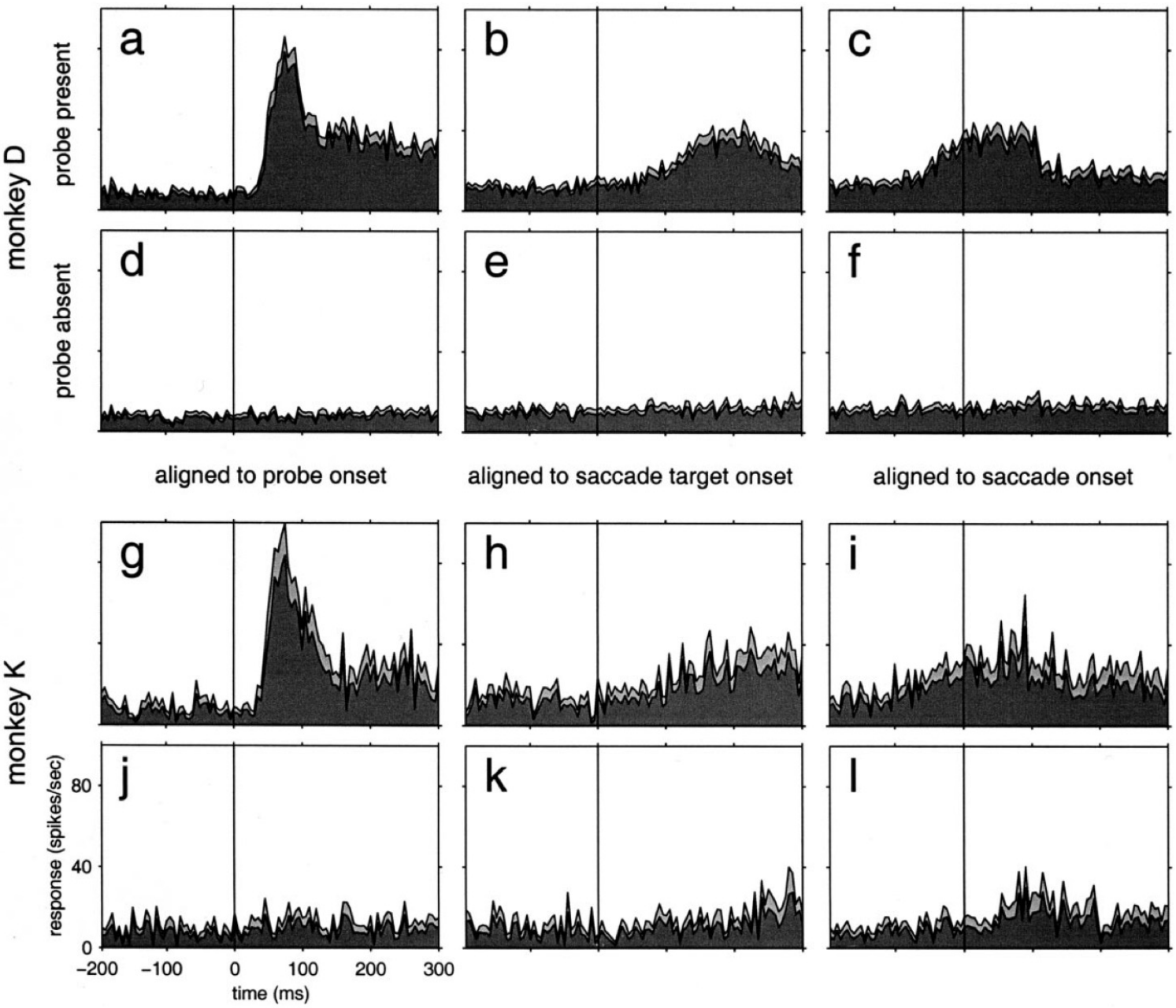
Cells in cortex typically fire at a baseline rate of

~ 1-10 spikes/second (Hz)

Spike recordings in monkey **Extrastriate Visual Cortex (V4)**:
(e.g. Tolias et al., 2001, Neuron)



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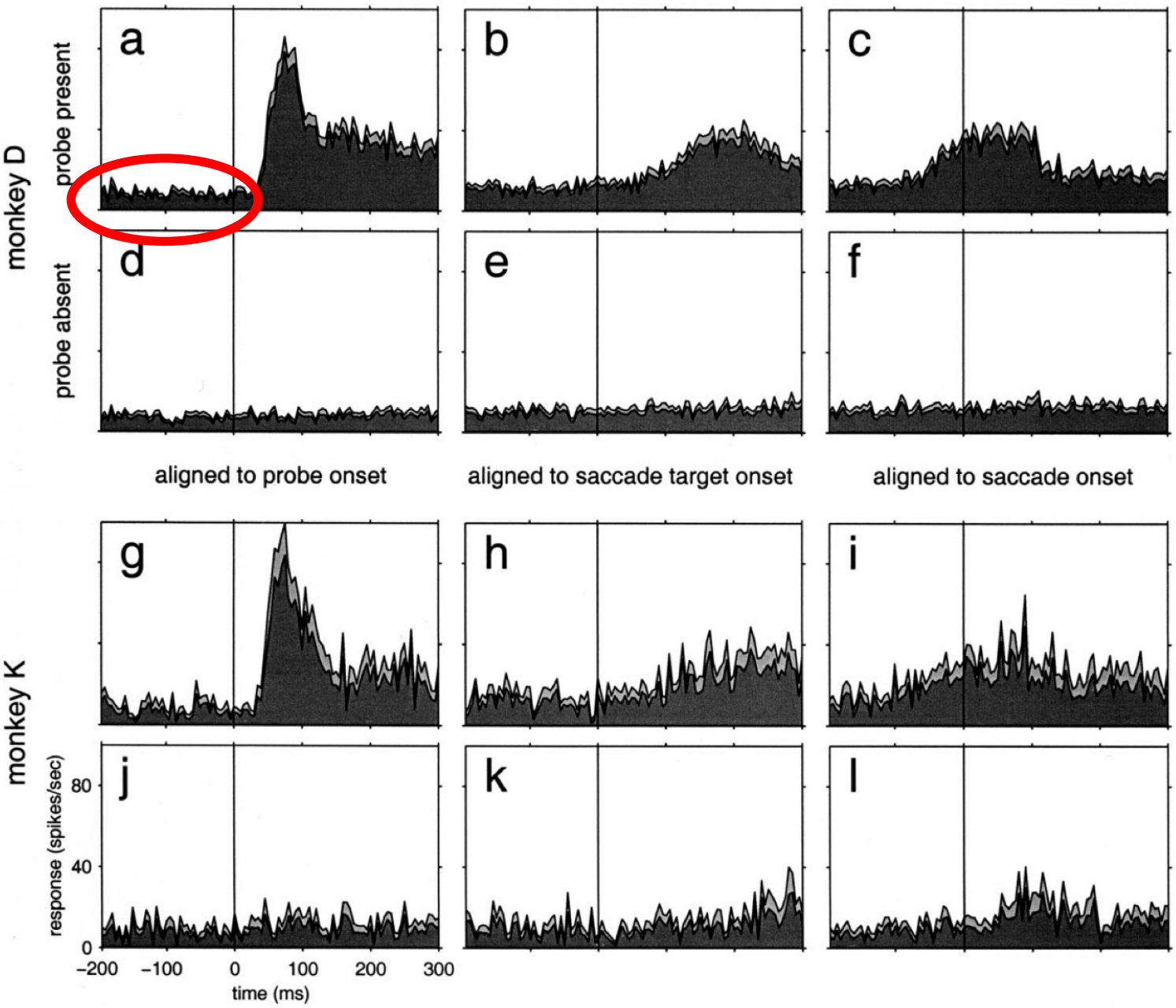
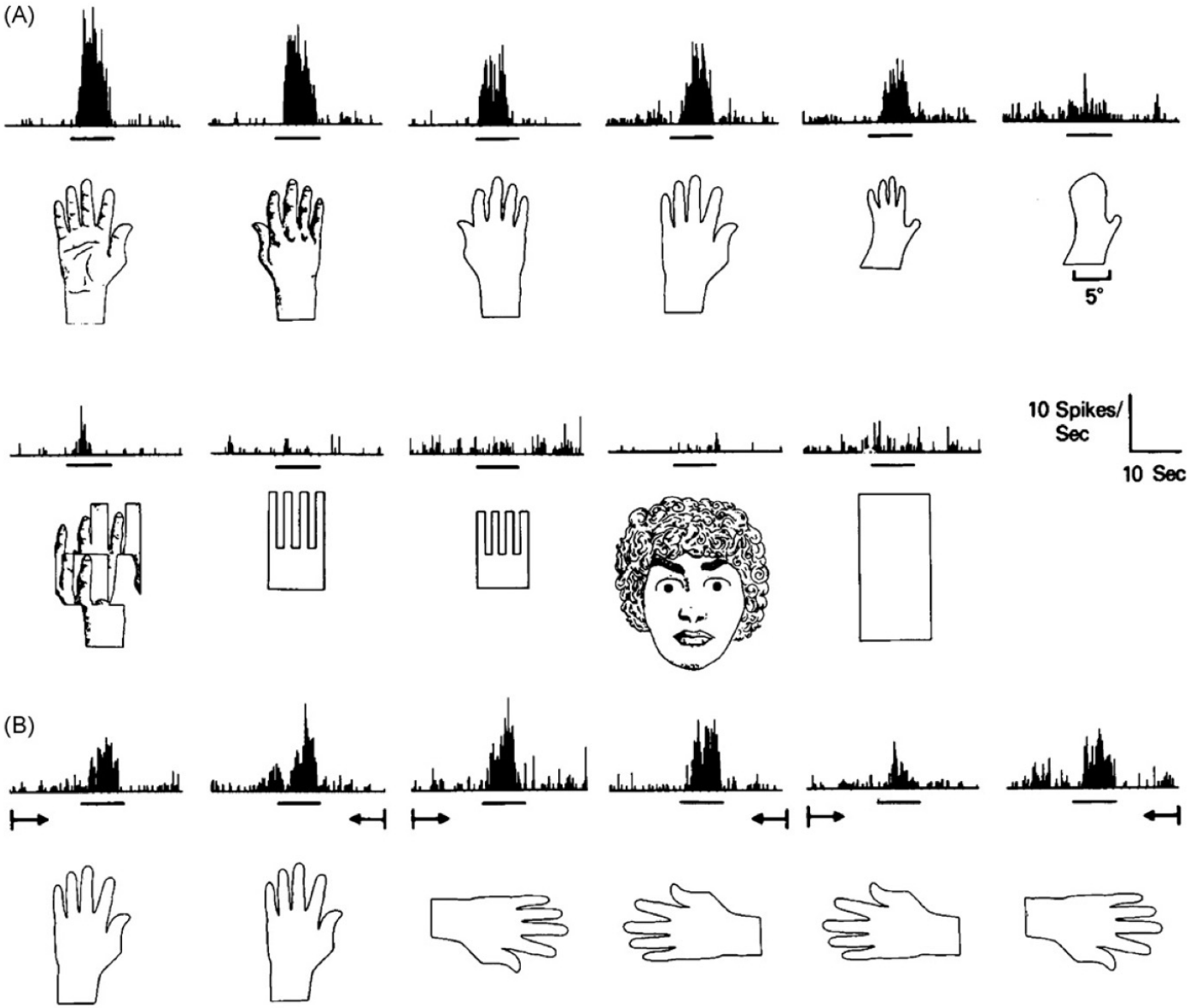


Spike recordings in **Inferior Temporal Neurons**:
(e.g. Desimone et al., 1984, J Neurosci)



Spike recordings in **Lateral Prefrontal Neurons**:
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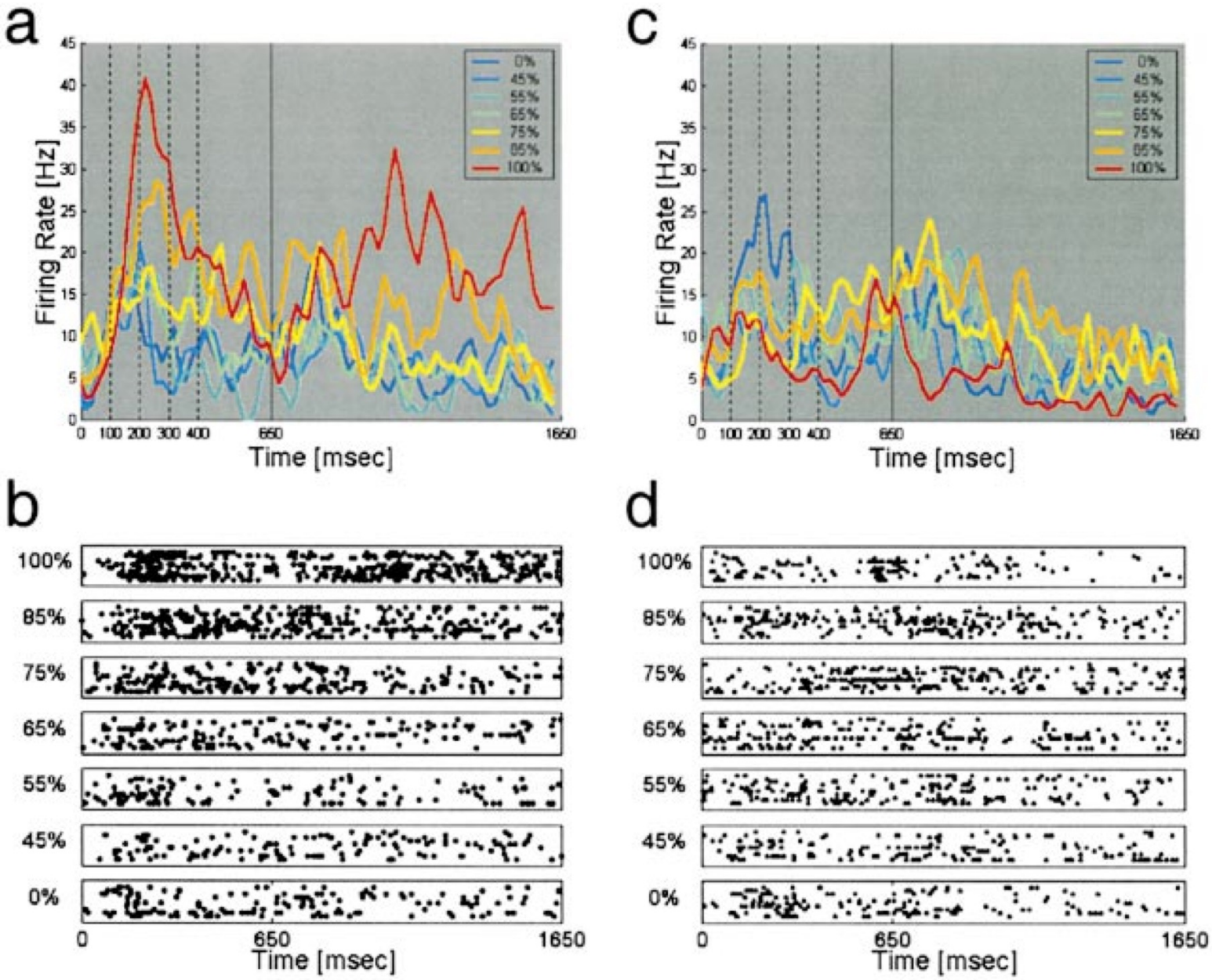

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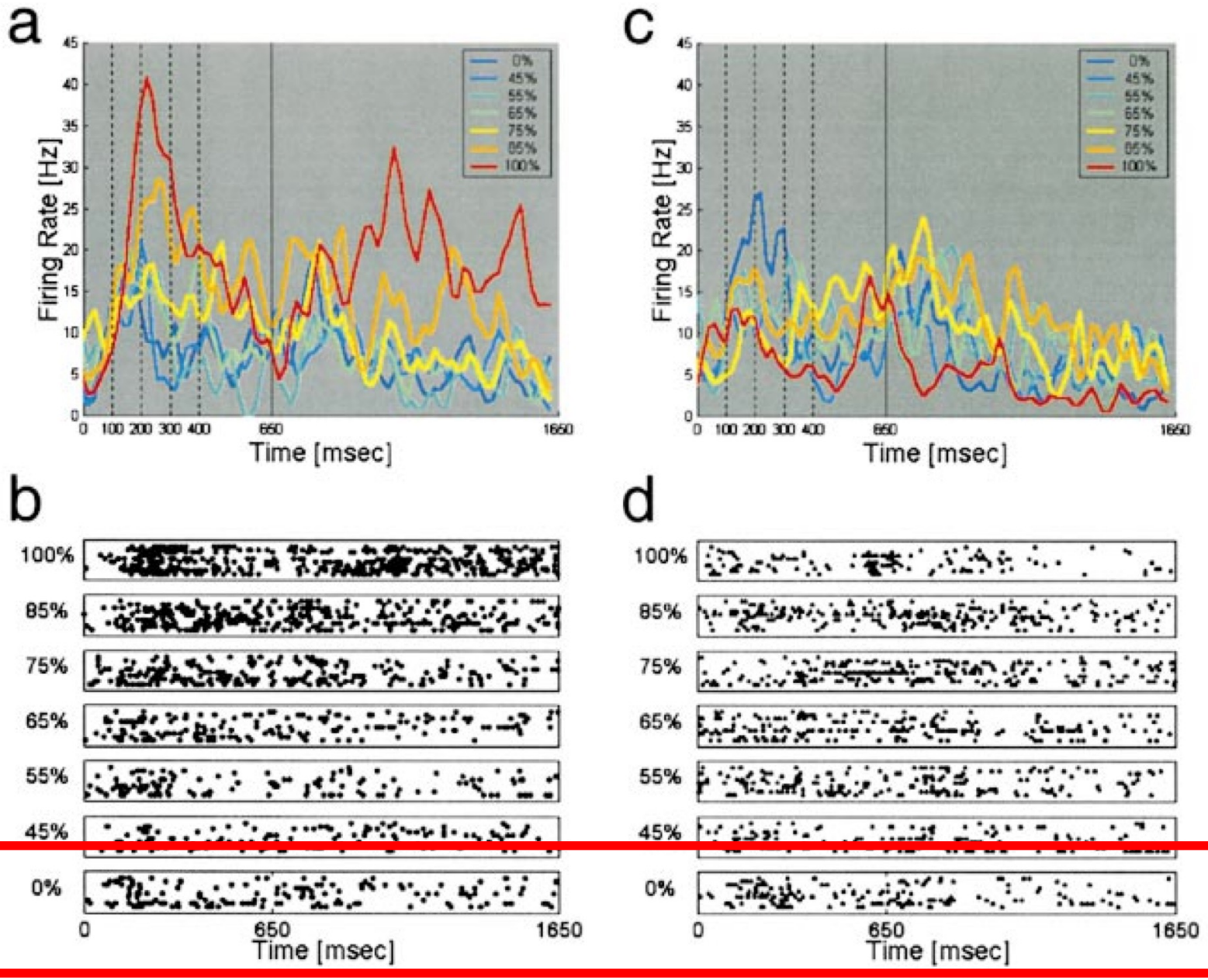

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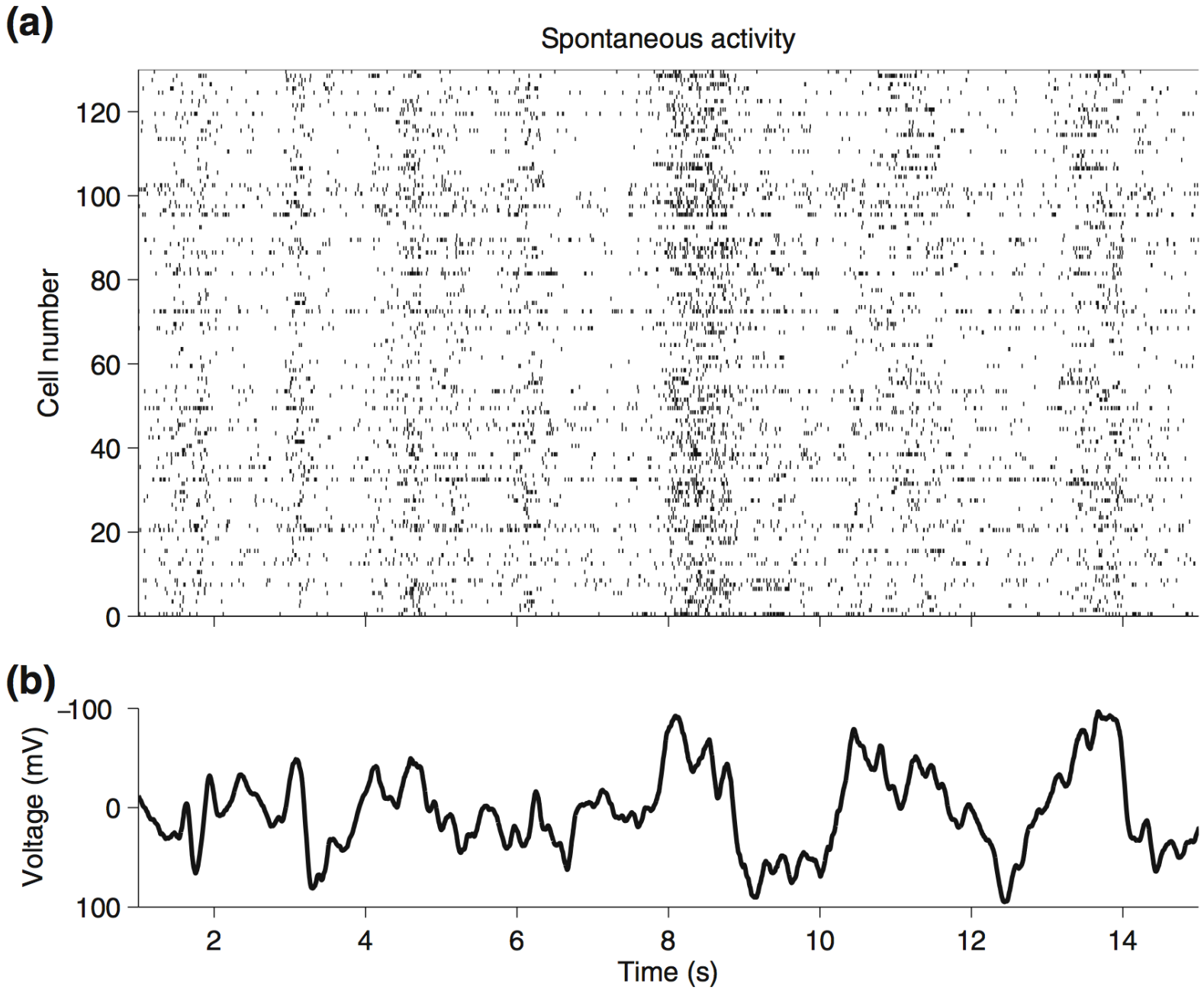
However, with advent of multi-neuron recordings:

Spontaneous spikes are coordinated over large populations of cells

Spike/LFP recordings in **Primary Visual Cortex** using large electrode grid:
(e.g. Kelly et al., 2010, J Comp Neurosci)



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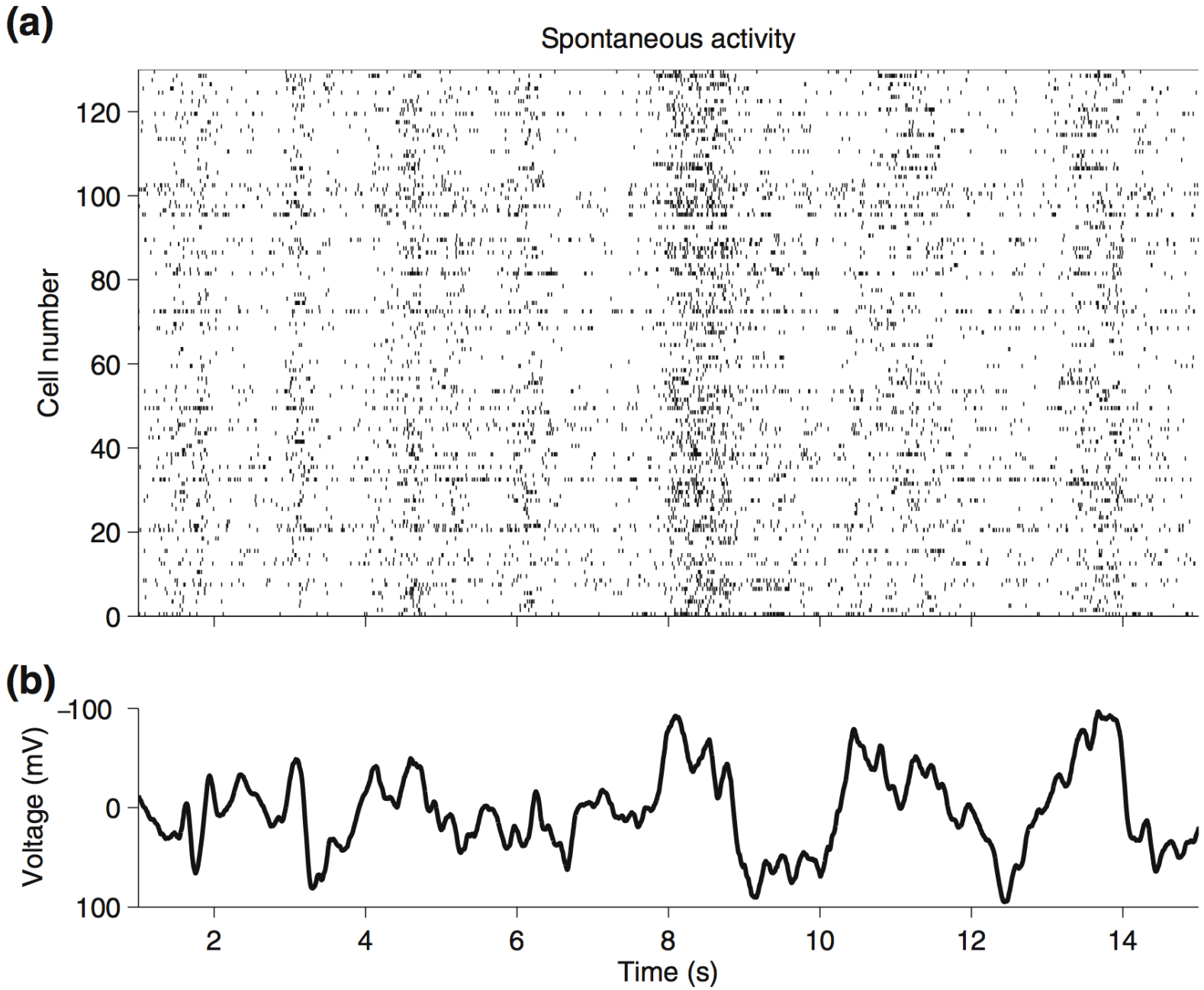
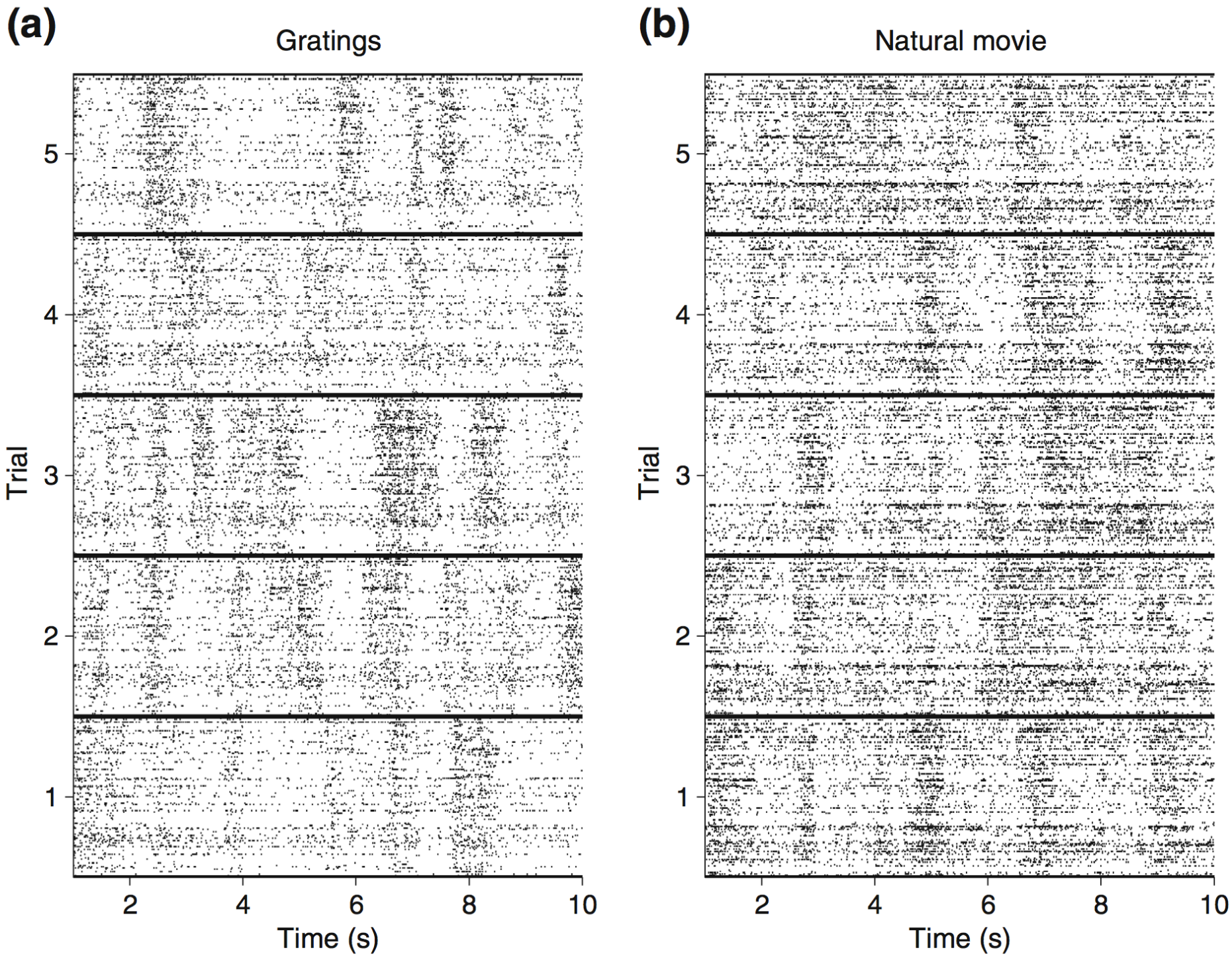
Spikes

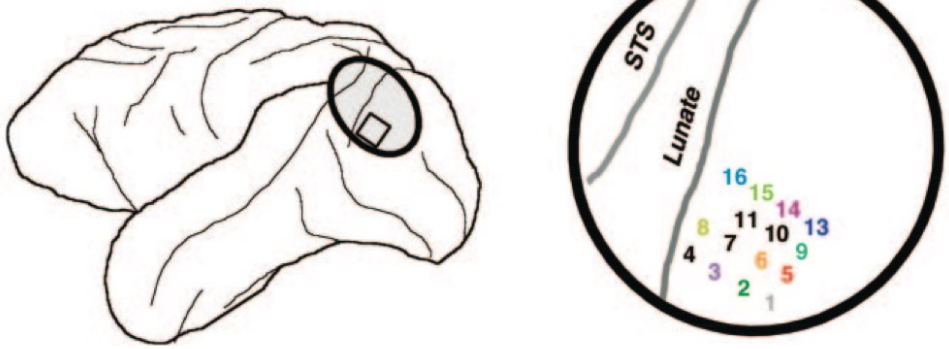
Local Field Potential (LFP)

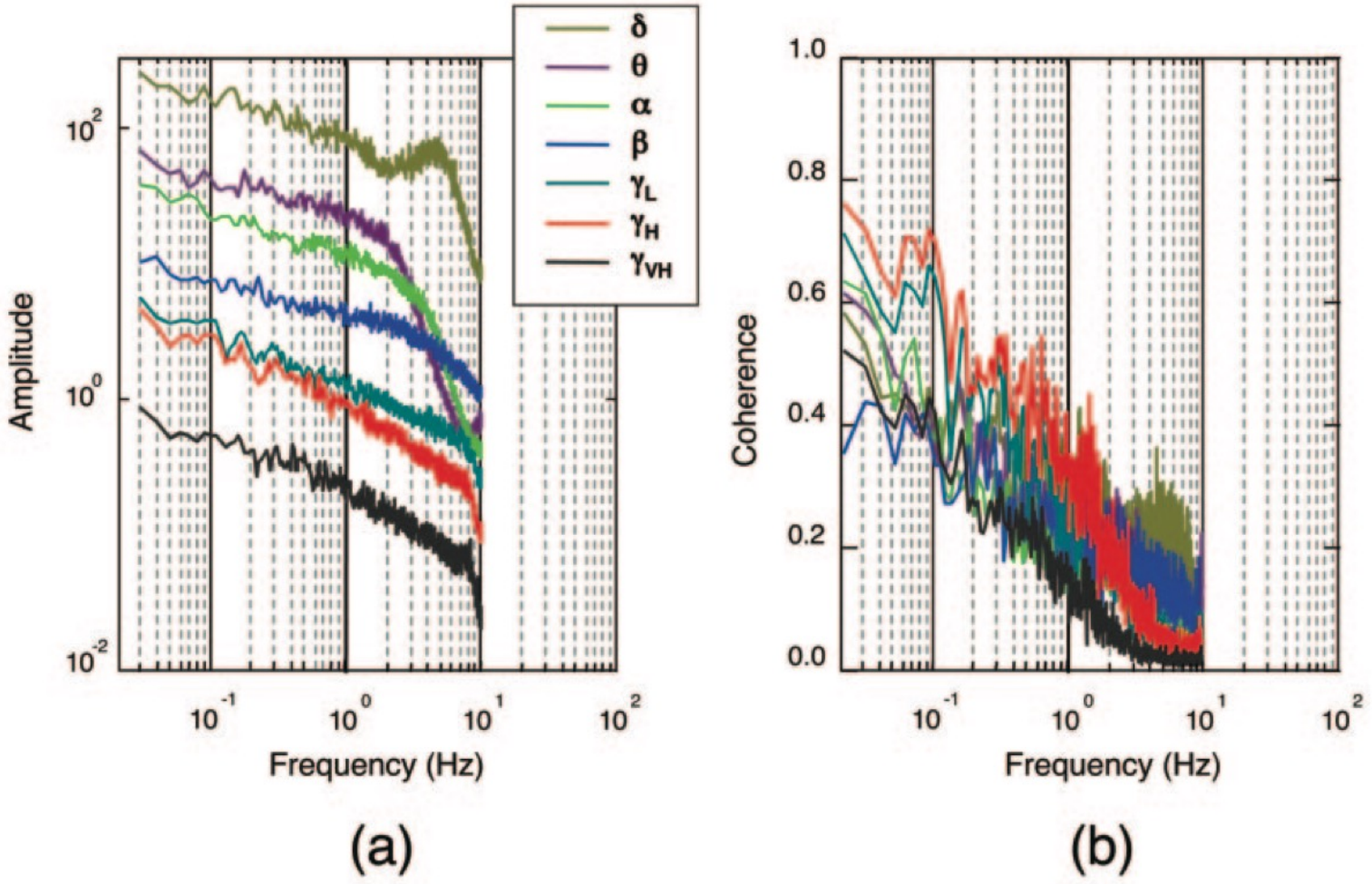



(a)
Gratings
(b)
Natural movie
Trial
1
2
3
4
5
2
4
6
8
10
Time (s)

Leopold et al. (2003). Cereb Cortex

LFPs are Coherent at Slow Frequencies
Over both Short and Long Distances
(e.g. *Schölvinck et al., 2010, PNAS*)





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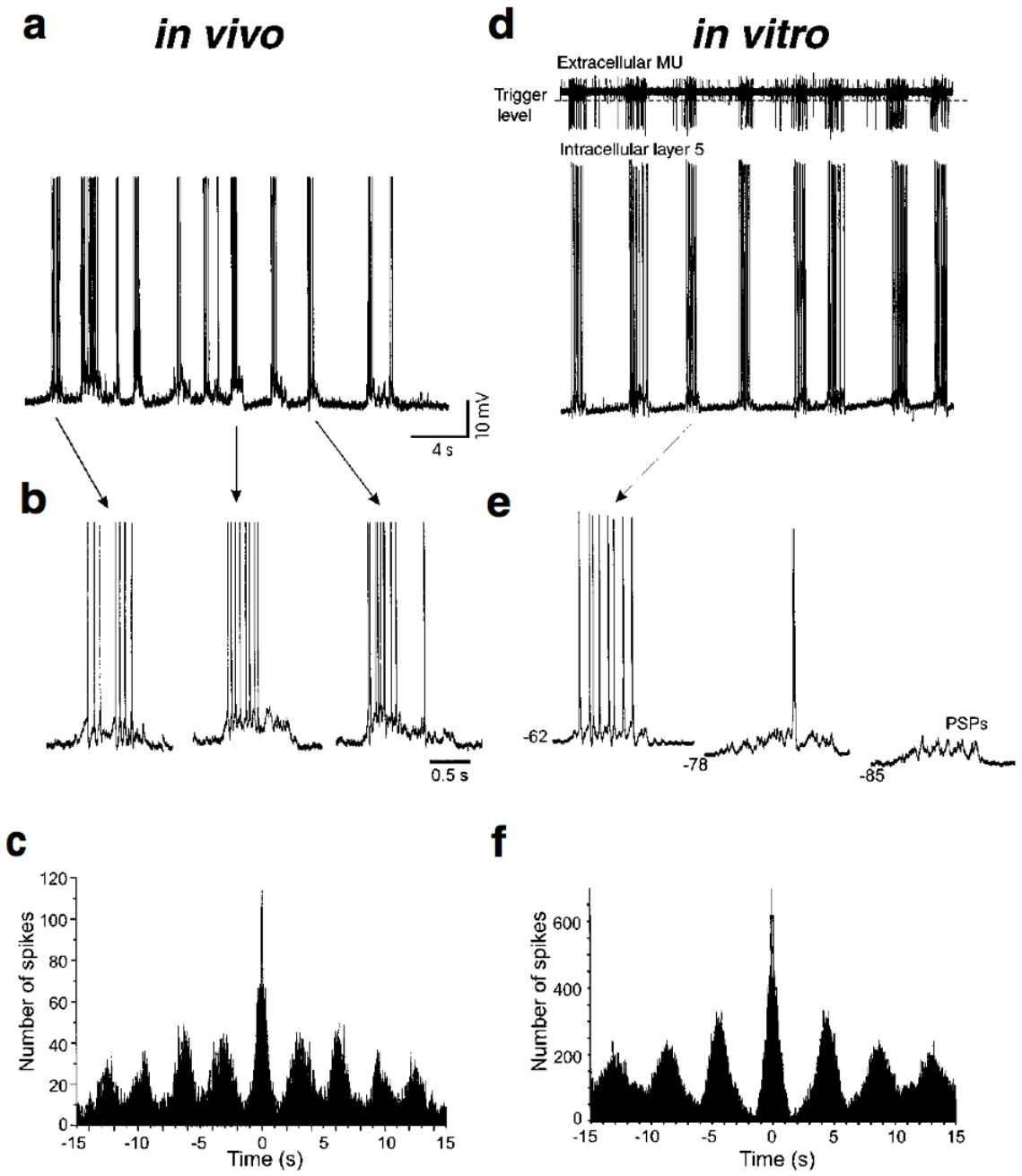
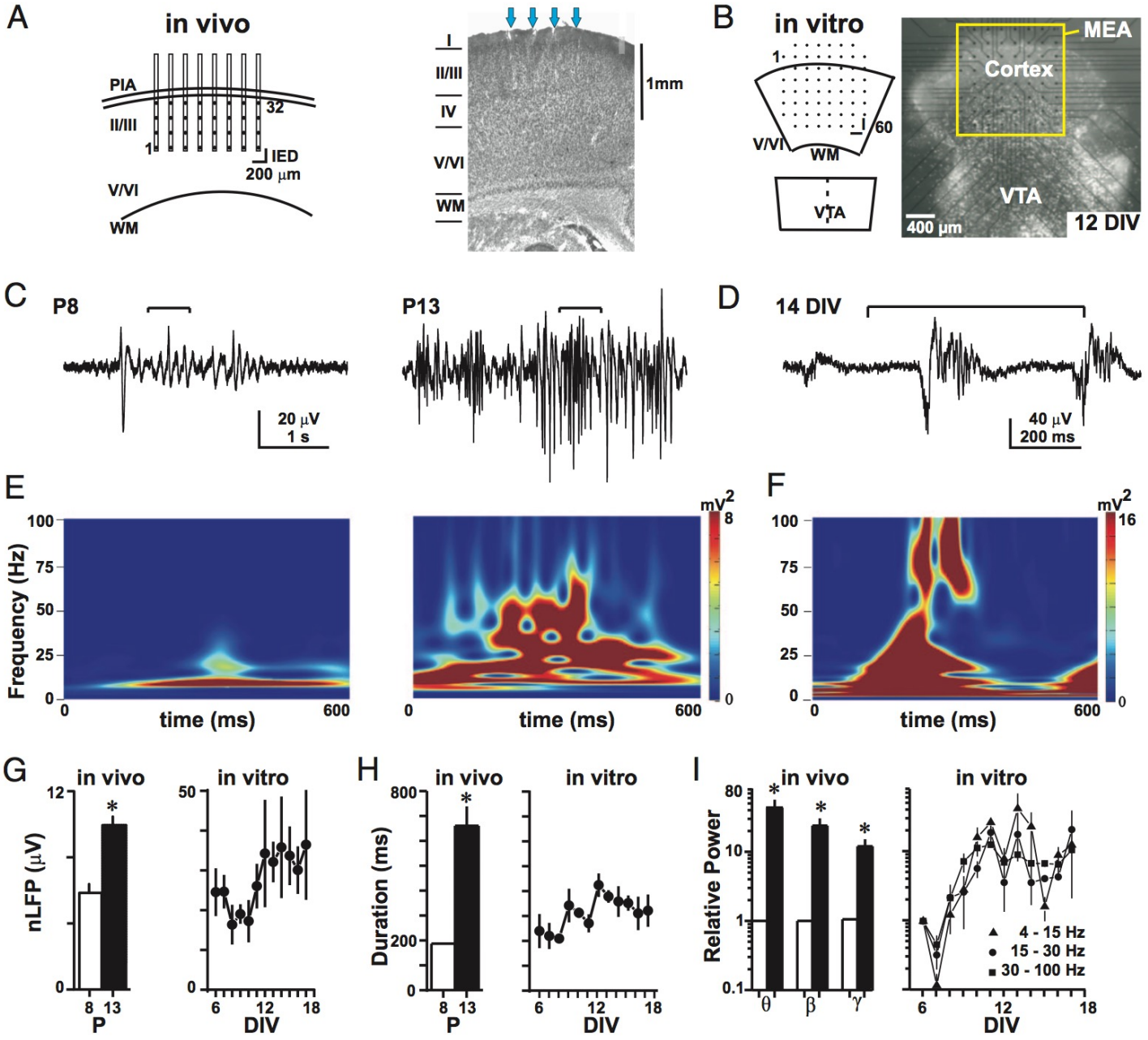
Rest and Task
Under Anesthesia
In cortical slices removed from the brain

Recordings from Primary Visual Cortex, *in vivo* (cat) and slice *in vitro* (ferret): (Sanchez-Vives & McCormick, 2000, Nat Neurosci)



Recordings from Rat Somatosensory cortex, *in vivo* and *in vitro* (slice culture):
(Gireesh & Plenz, 2008, PNAS)



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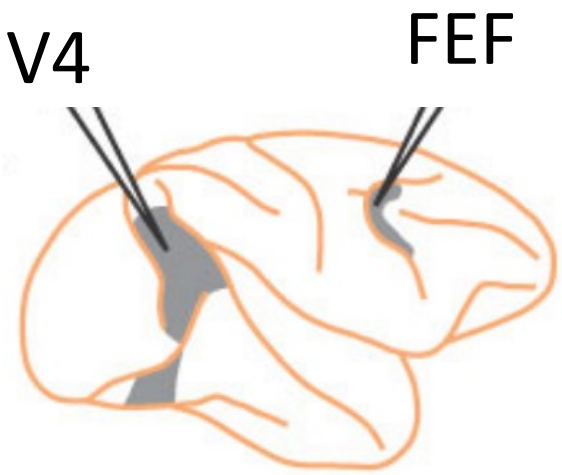
These fluctuations aren't noise, but are generated internally by the brain itself

Example of task-based functional connectivity measured with electrodes

Gregoriou, Gotts, Zhou, & Desimone (2009). Science 324, 1207-10.



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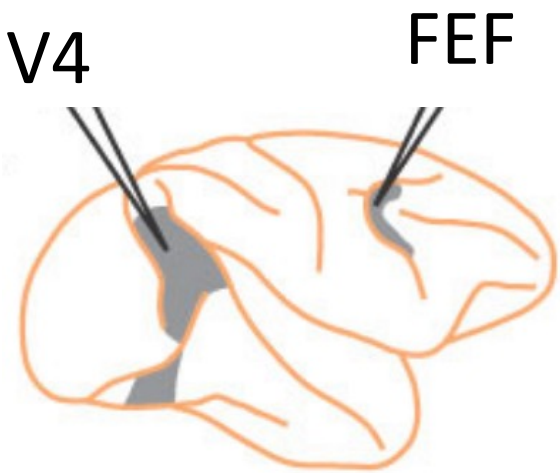

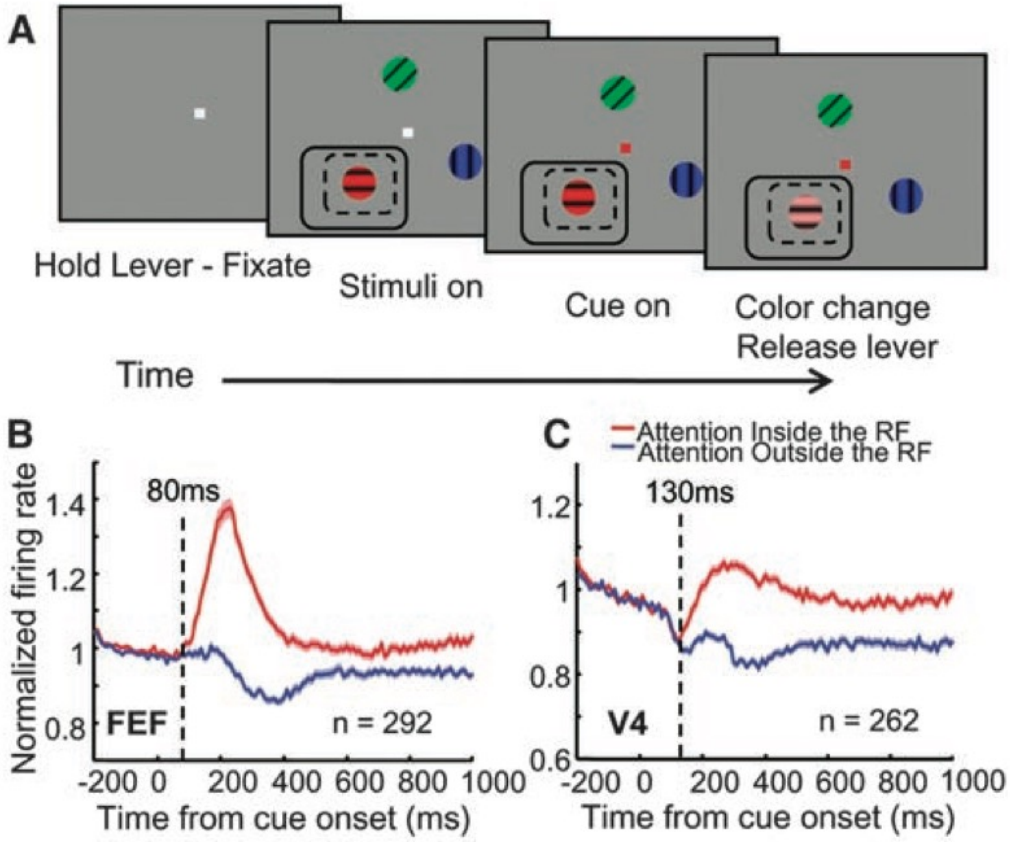

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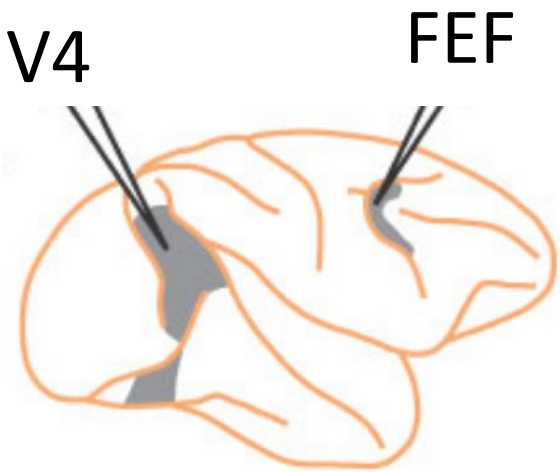

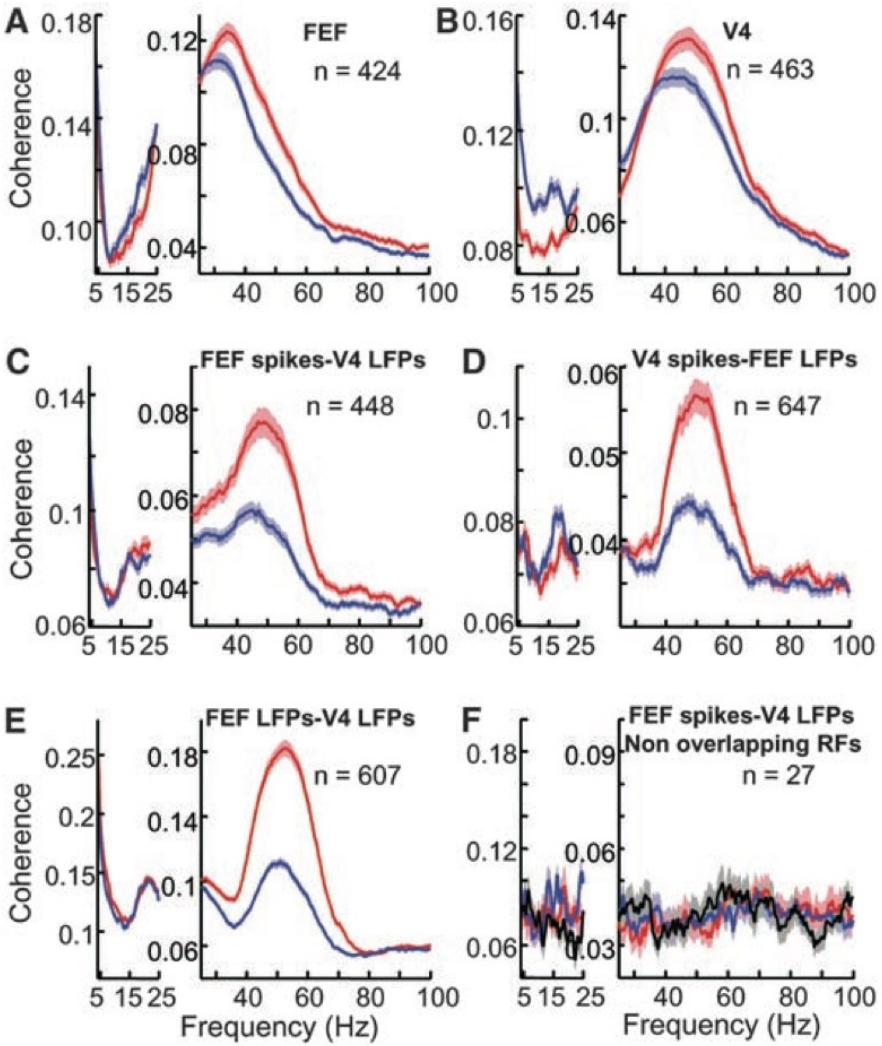

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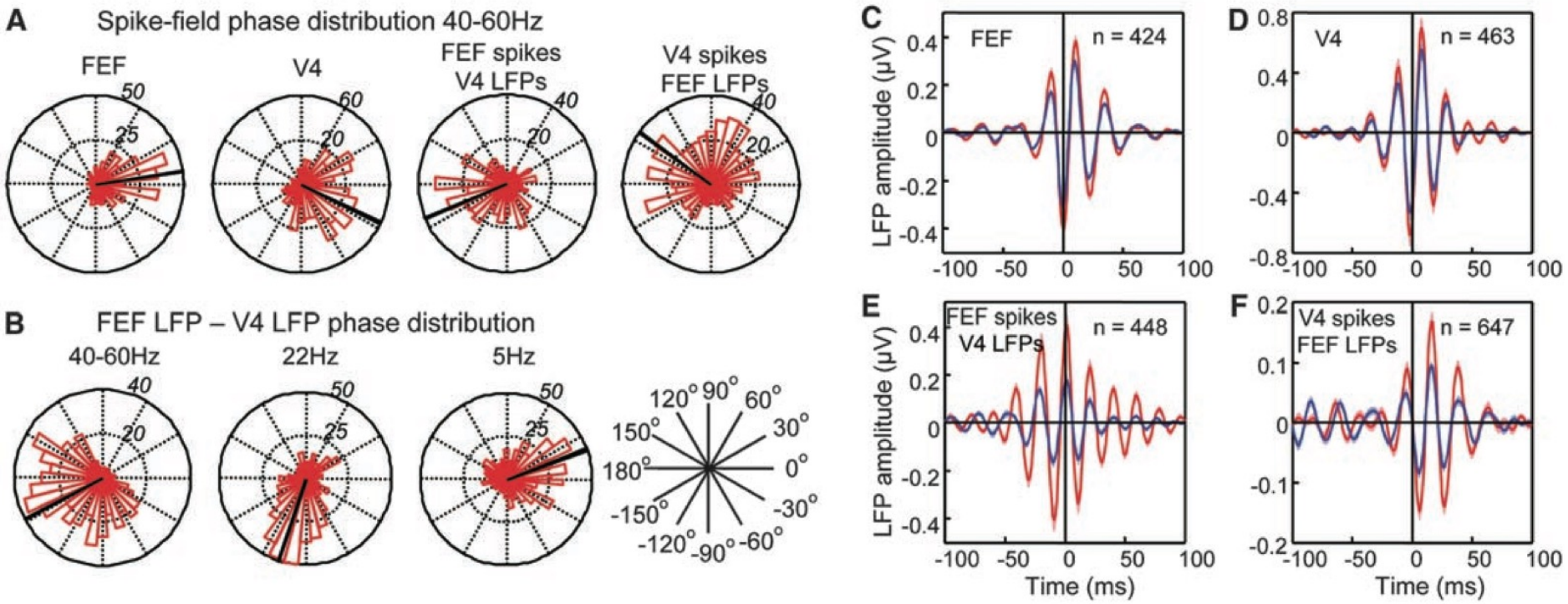

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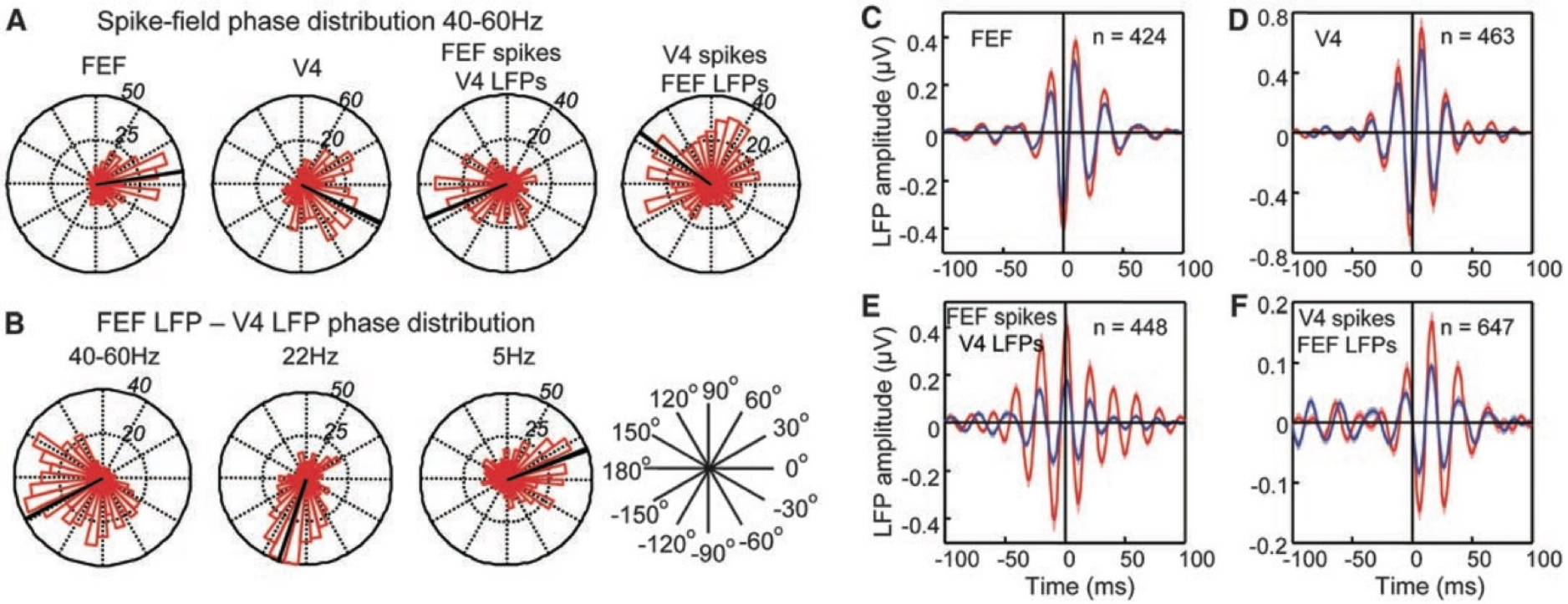
"Functional" Connectivity



"Effective" Connectivity

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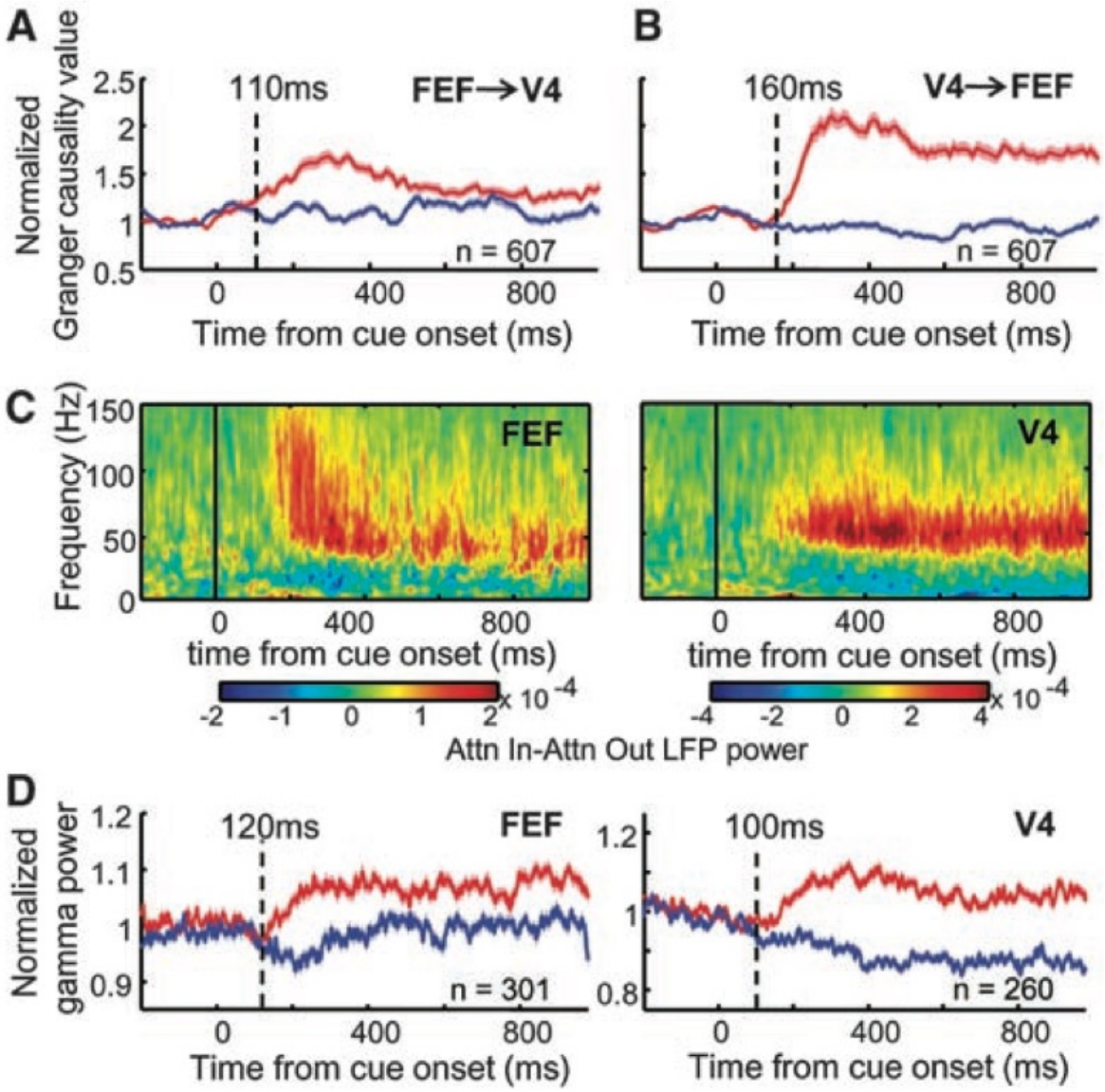

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Can't look at more than a handful of locations at once

Connectivity in fMRI

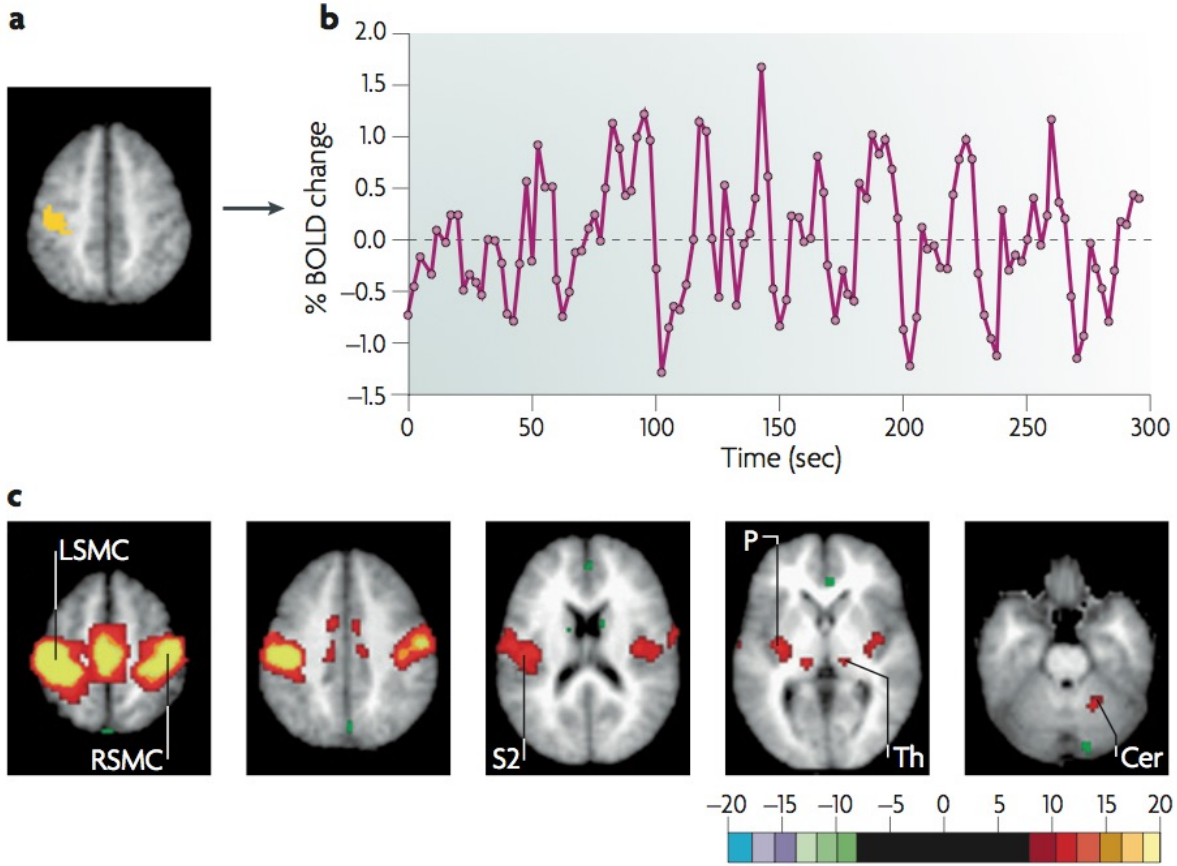
Functional Connectivity of Spontaneous Activity at Rest (i.e. "Resting State")

- very popular (easy and fast to administer)
- subjects passively view a fixation cross
- fluctuations in spontaneous activity (< .1 Hz) are correlated throughout the brain in a spatially restricted manner

For review:

Fox & Raichle (2007).
Nat Rev Neurosci

Fox & Greicius (2010).
Front Syst Neurosci



Connectivity in fMRI

Connectivity in fMRI

Functional Connectivity fMRI in Basic Research

- Cognitive, Systems, and Developmental Neuroscience

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Functional Connectivity fMRI in Clinical Science

- Studying psychiatric disorders such as Autism and Schizophrenia, and Mood/Affective Disorders
- Neurodegenerative Disorders (PLS), Stroke, Neurosurgery

Connectivity in fMRI

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- Cognitive, Systems, and Developmental Neuroscience

Functional Connectivity fMRI in Clinical Science

- Studying psychiatric disorders such as Autism and Schizophrenia, and Mood/Affective Disorders
- Neurodegenerative Disorders (PLS), Stroke, Neurosurgery

In all cases, we'd like to separate neurogenic and artifactual sources of variation (but no perfect way of doing it)

Connectivity in fMRI

Functional Connectivity fMRI in Basic Research

- Cognitive, Systems, and Developmental Neuroscience

Functional Connectivity fMRI in Clinical Science

- Studying psychiatric disorders such as Autism and Schizophrenia, and Mood/Affective Disorders
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In all cases, we'd like to separate neurogenic and artifactual sources of variation (but no perfect way of doing it)

Agreement of connectivity, task effects, and behavior is our best approach currently

fMRI Connectivity in Basic Research

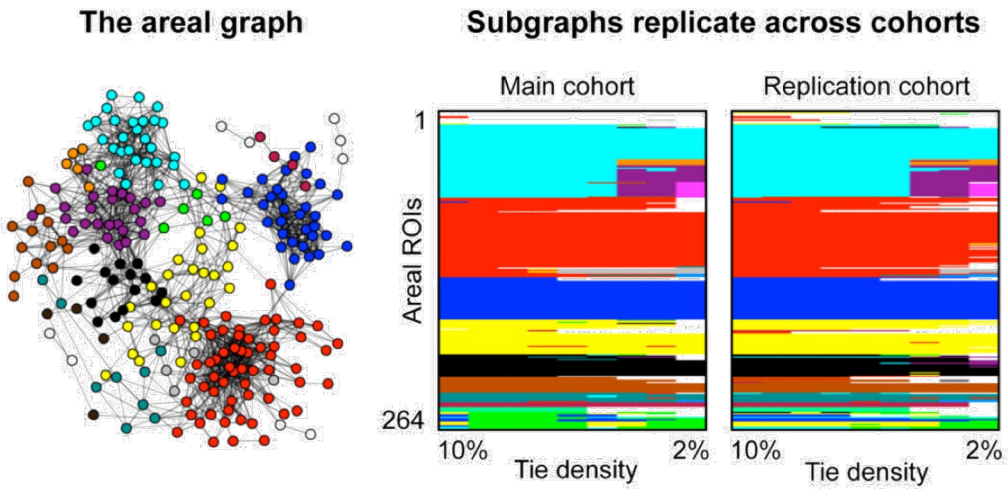
Examples:

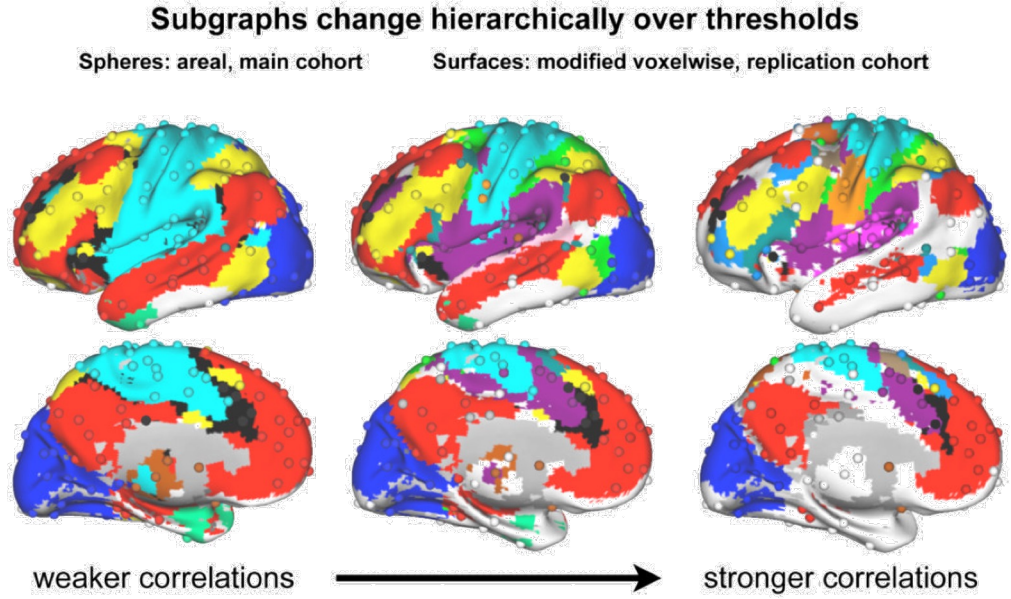
Parcellating the systems/circuit-level structure of functional interactions (e.g. Buckner and Petersen/Schlaggar labs)

Studying development (e.g. Fair)

Evaluating trait-like variation in behavioral abilities across subjects (Face Processing, Functional Lateralization)

Power et al. (2011). Neuron

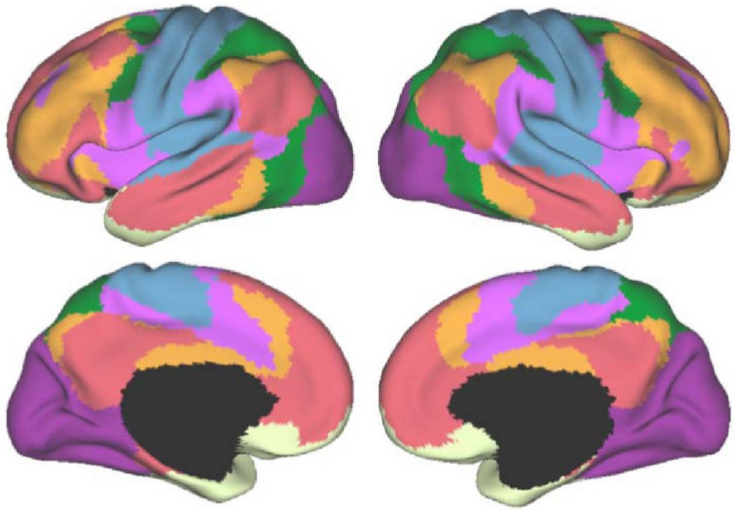




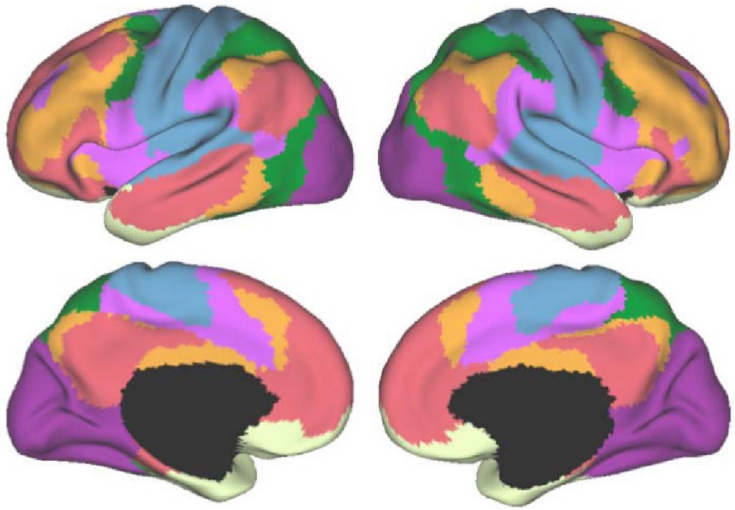
Yeo et al. (2011). J Neurophysiol

7 Network Cluster Solution

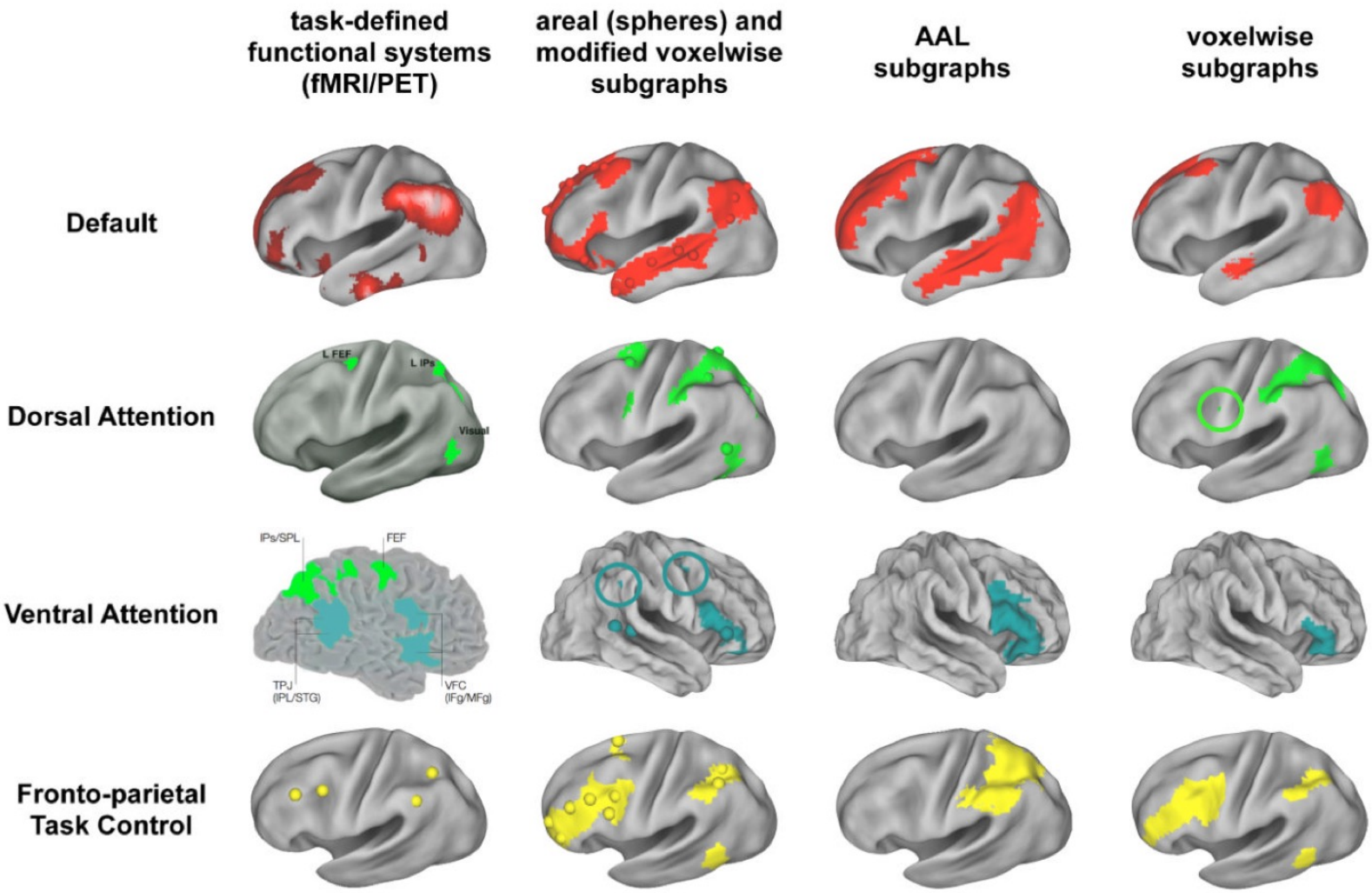
Discovery Sample (n = 500)



Replication Sample (n = 500)

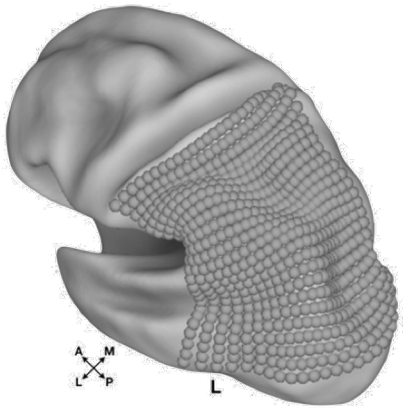


Power et al. (2011). Neuron

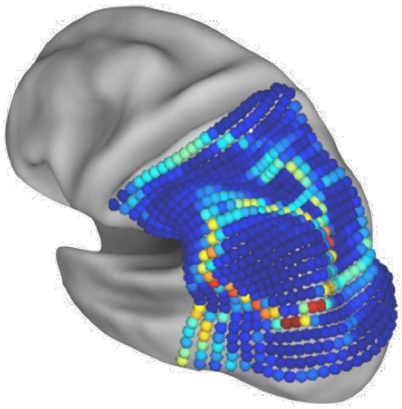


Alternative Parcellation Approach: Using Local Changes in Seed-based Correlation Maps

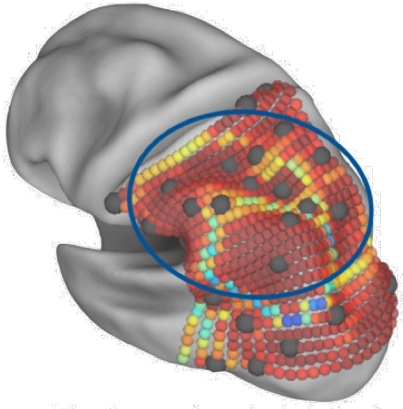
Nelson et al. (2010). Neuron



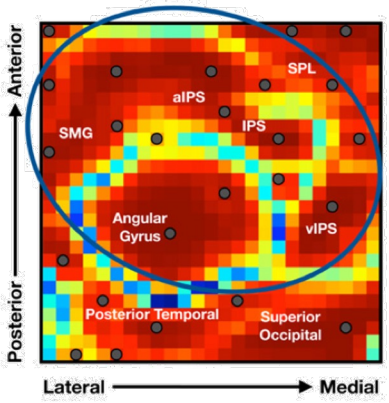
Square patch of 729 foci (27x27 grid) placed over LLPC

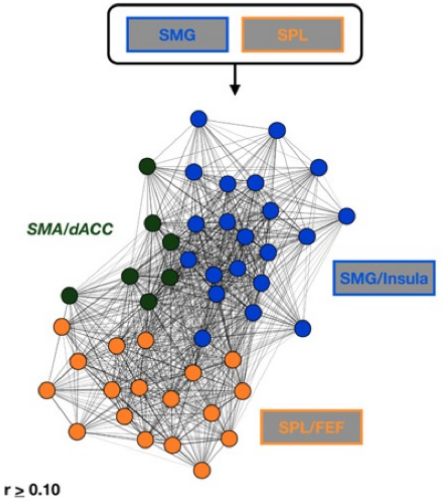


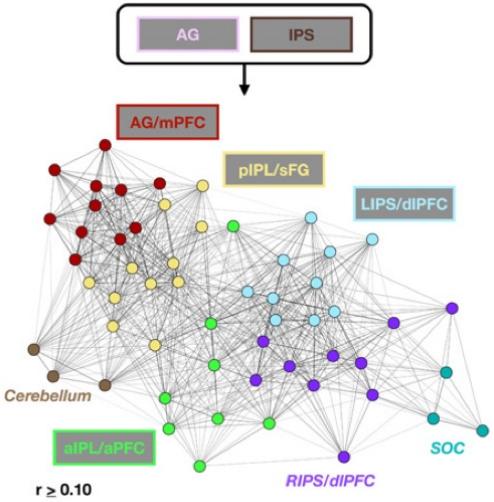
Boundaries generated using Canny method

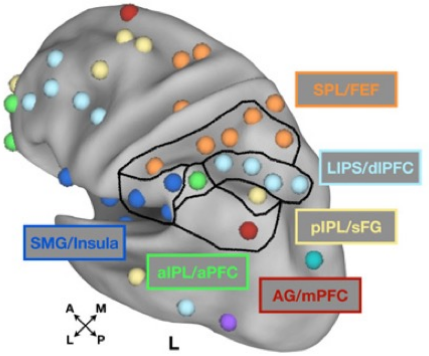


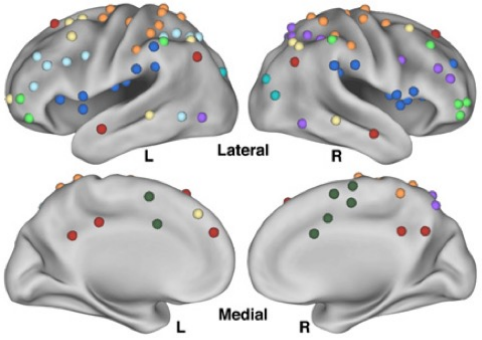
Boundary map inversion to find peaks











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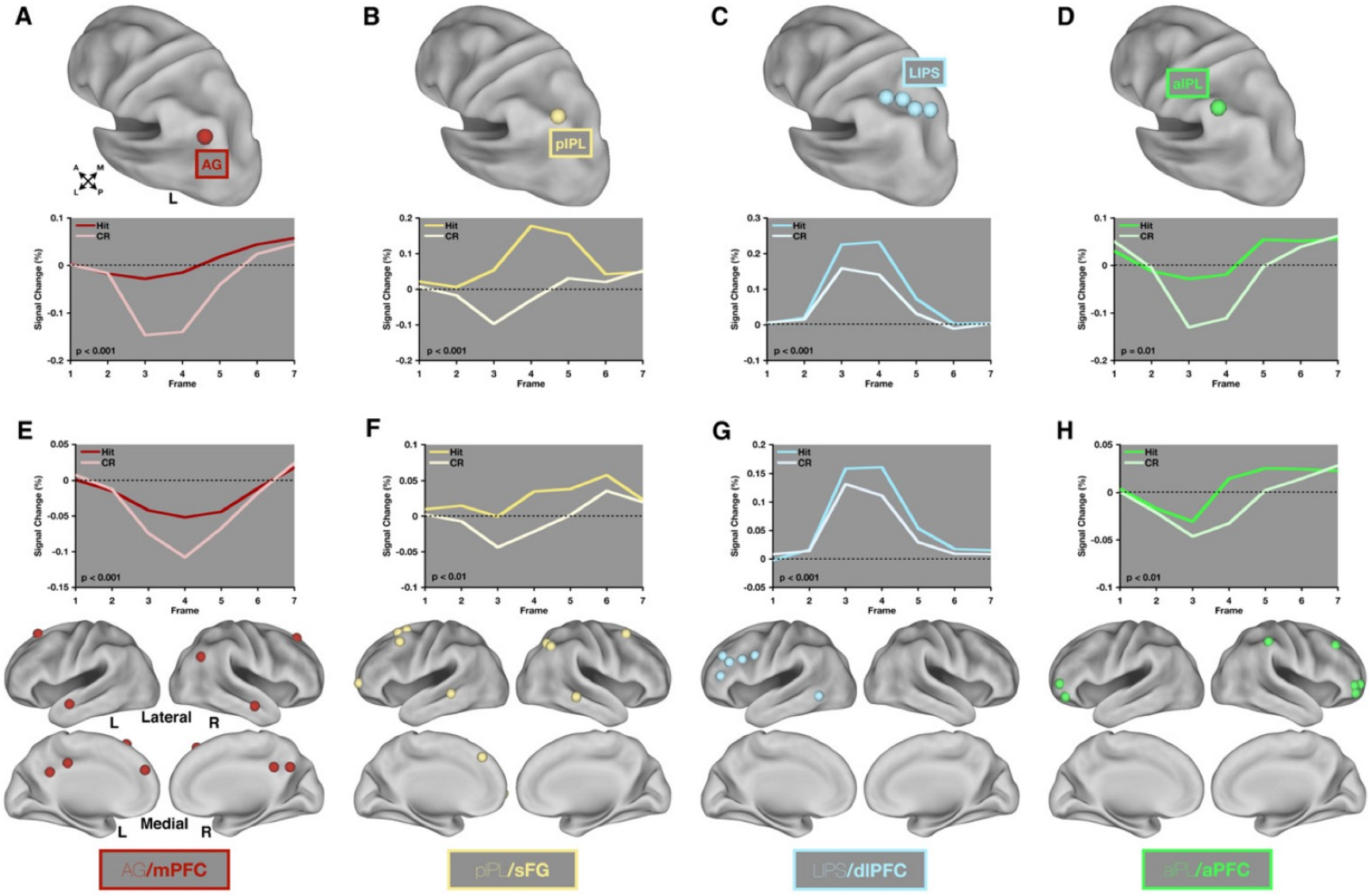
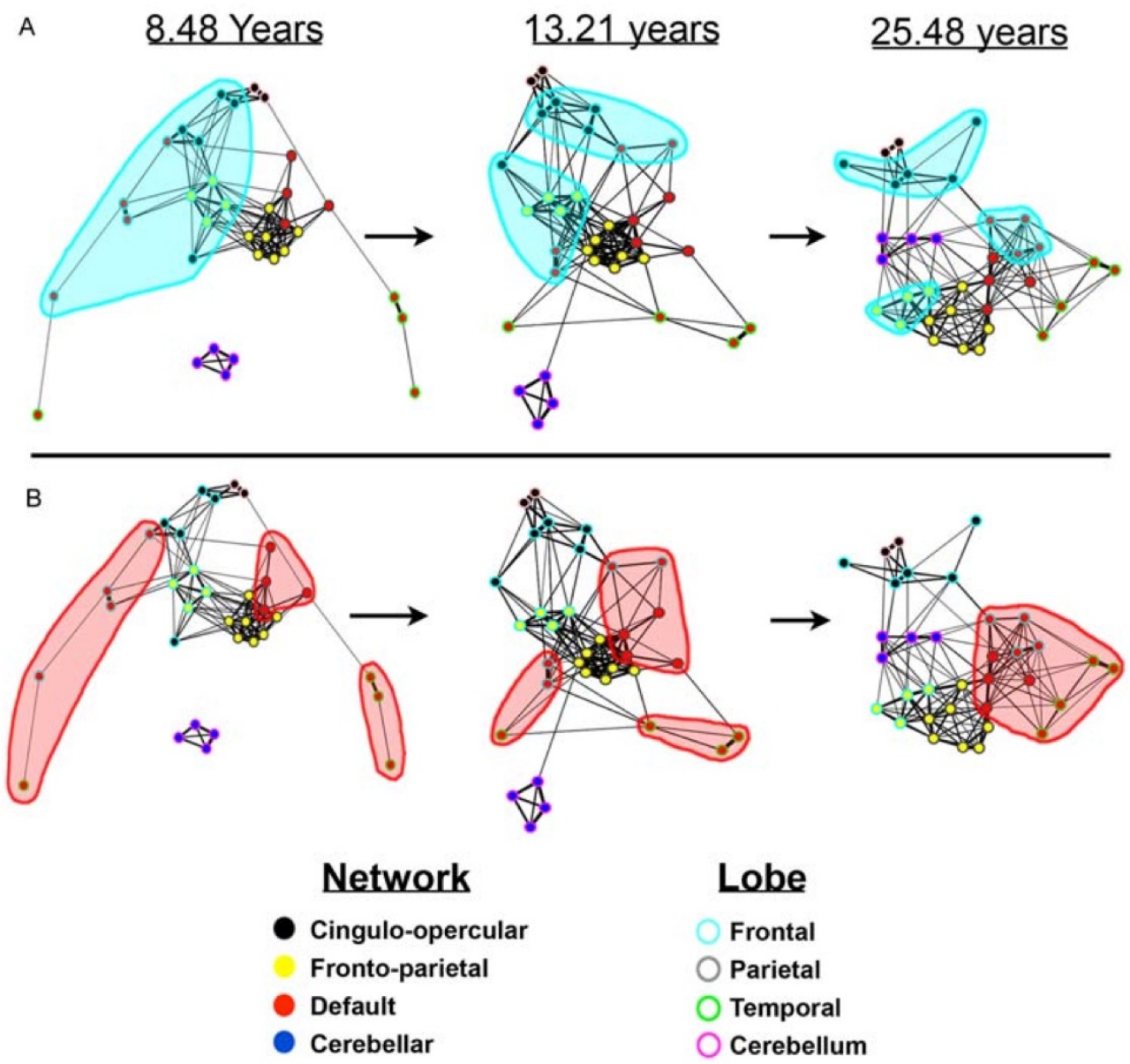


Development of Functional Brain Networks

Fair et al. (2009). PLoS Comp Biol



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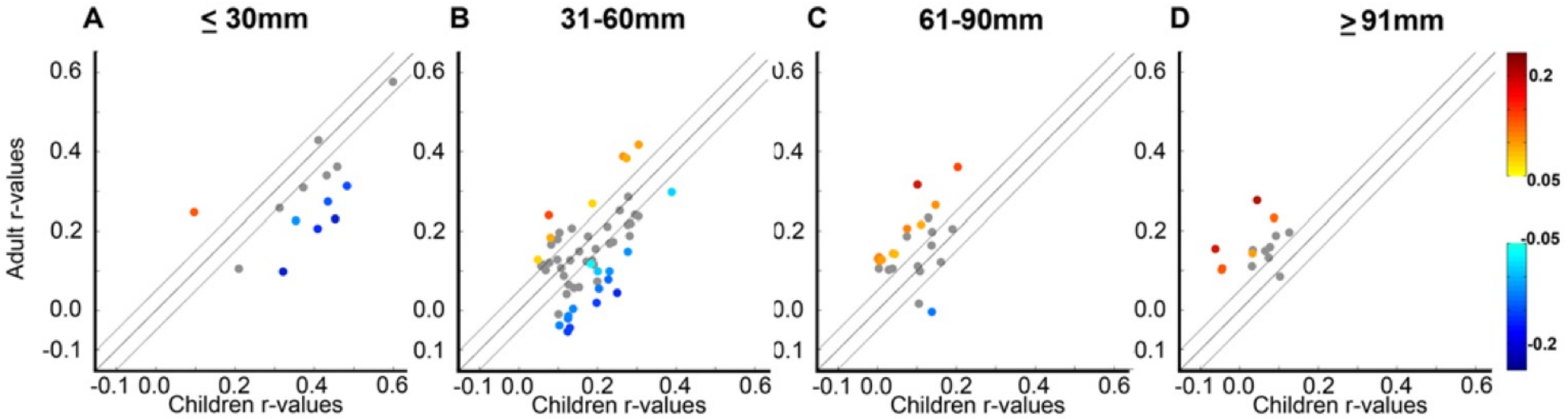

Resting-state Correlations Among Face-Selective Regions Predict Face Processing Ability Behaviorally

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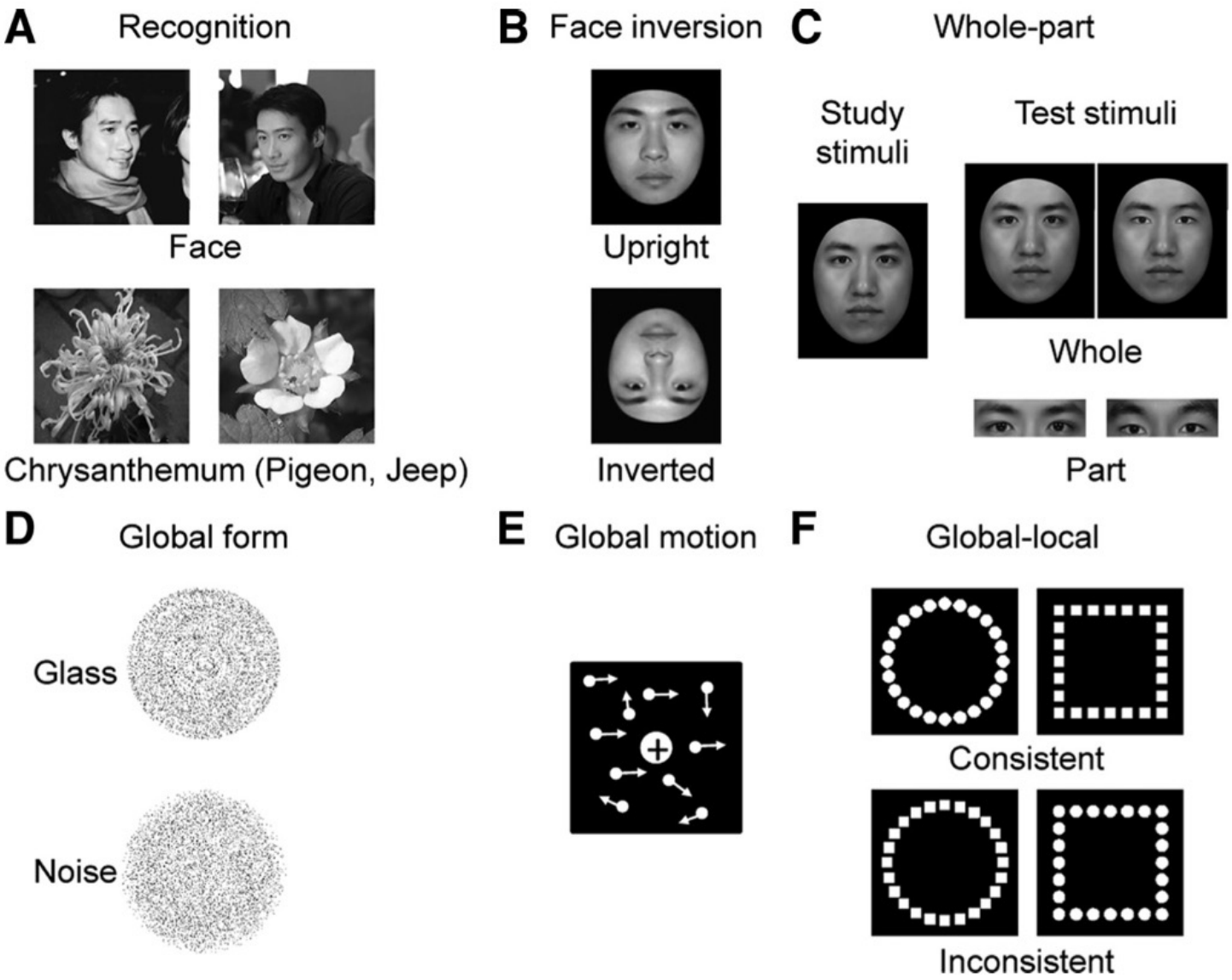
Zhu et al. (2011). J Neurosci



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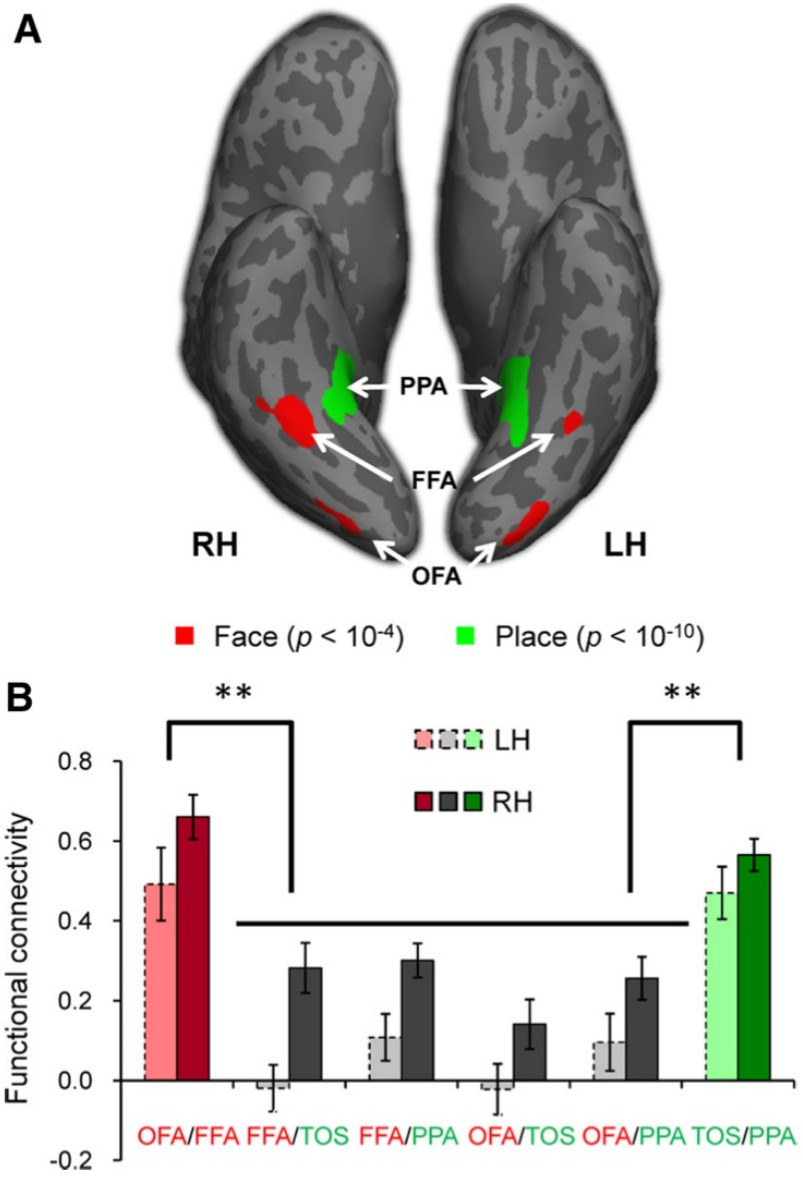

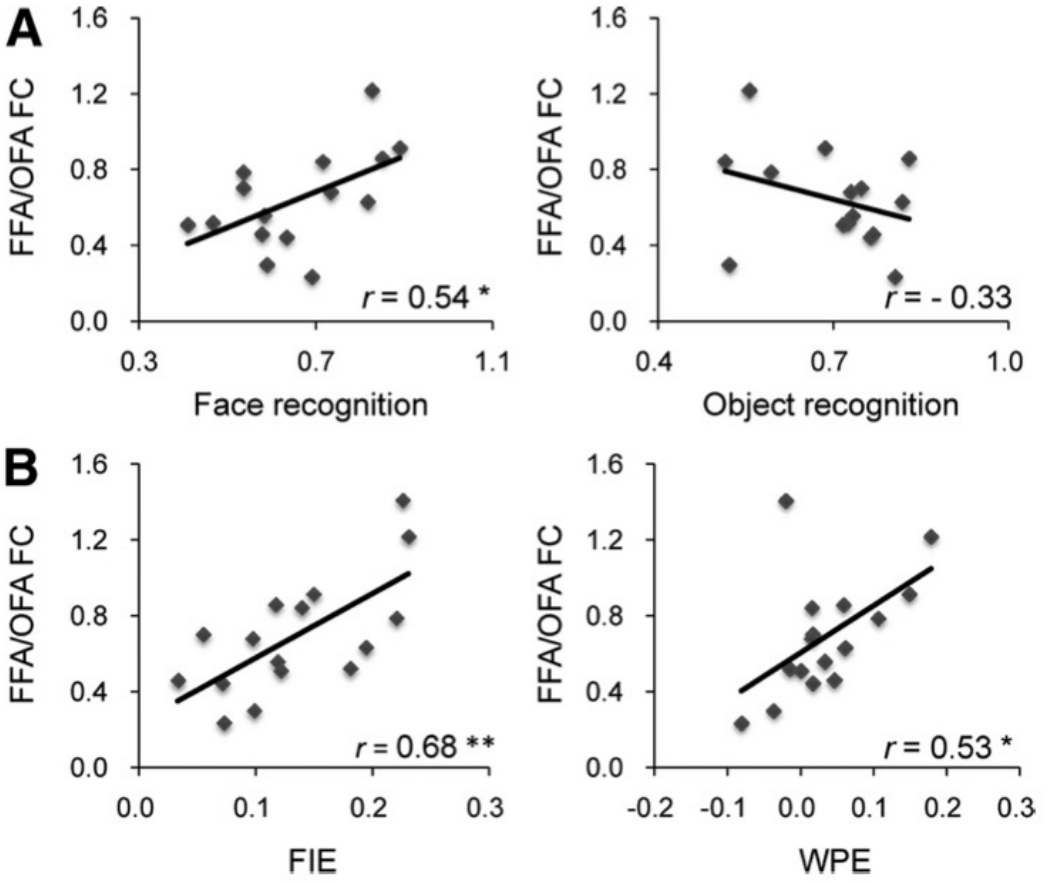

Inversion Effect

Whole-part Effect

Example from Our Lab: Functional Lateralization of Verbal, Visuospatial, and Motor Abilities

Example from Our Lab: Functional Lateralization of Verbal, Visuospatial, and Motor Abilities

PNAS PLUS

Two distinct forms of functional lateralization in the human brain

Stephen J. Gotts[a,1], Hang Joon Jo[b,1,2], Gregory L. Wallace[a], Ziad S. Saad[b], Robert W. Cox[b], and Alex Martin[a]

[a]Section on Cognitive Neuropsychology, Laboratory of Brain and Cognition, and [b]Scientific and Statistical Computing Core, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892

Edited by Geoffrey K. Aguirre, University of Pennsylvania, Philadelphia, PA, and accepted by the Editorial Board July 25, 2013 (received for review February 8, 2013)

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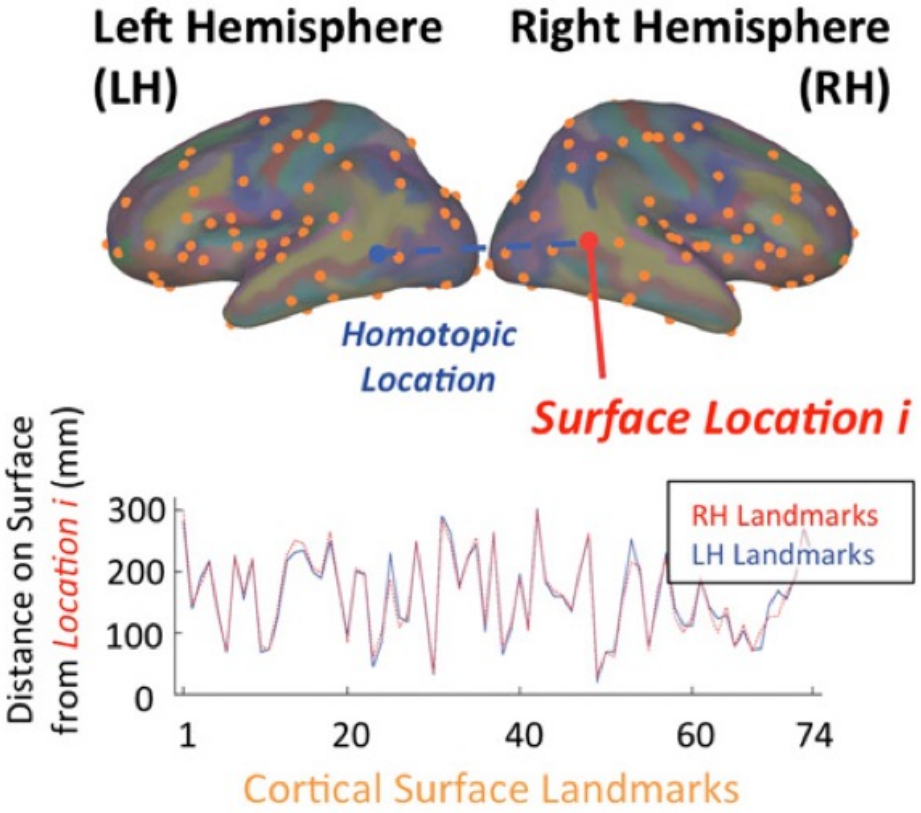
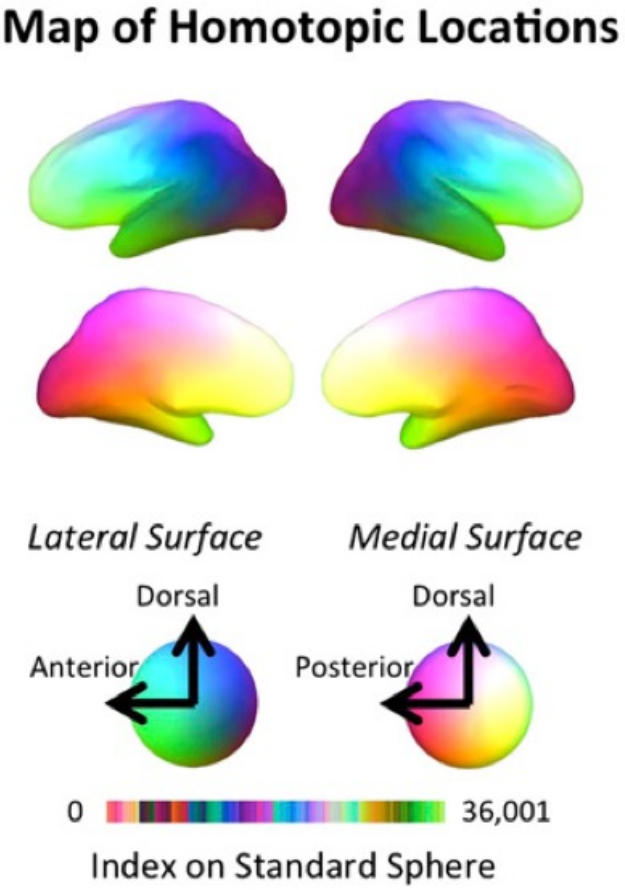
Do the hemispheres differ in their within- vs between-hemisphere interactions ?

Does lateralization magnitude predict goodness of function?

Finding corresponding points in the two hemispheres:





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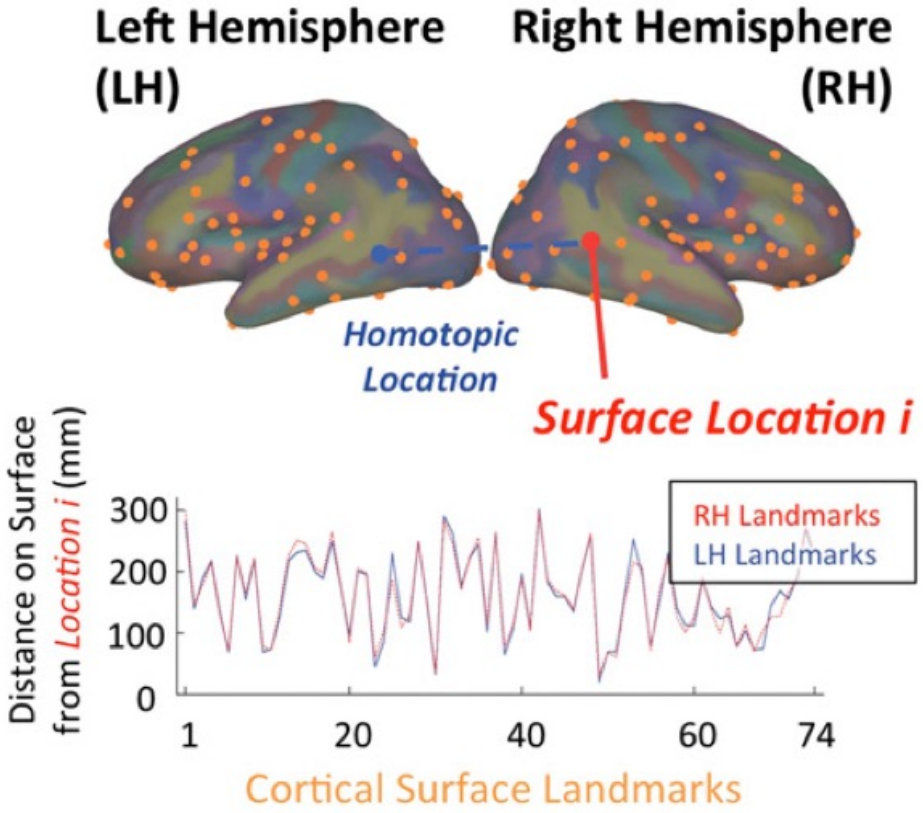
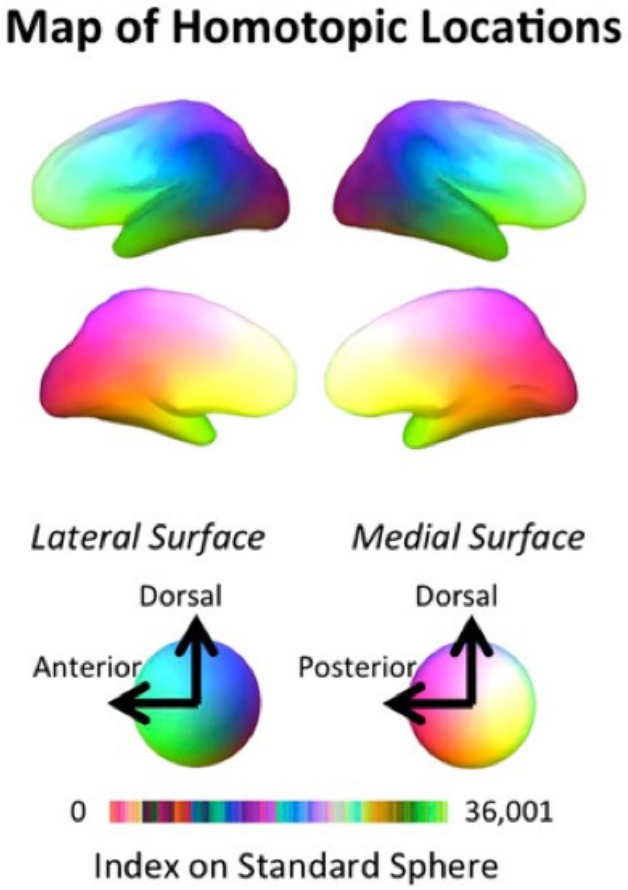
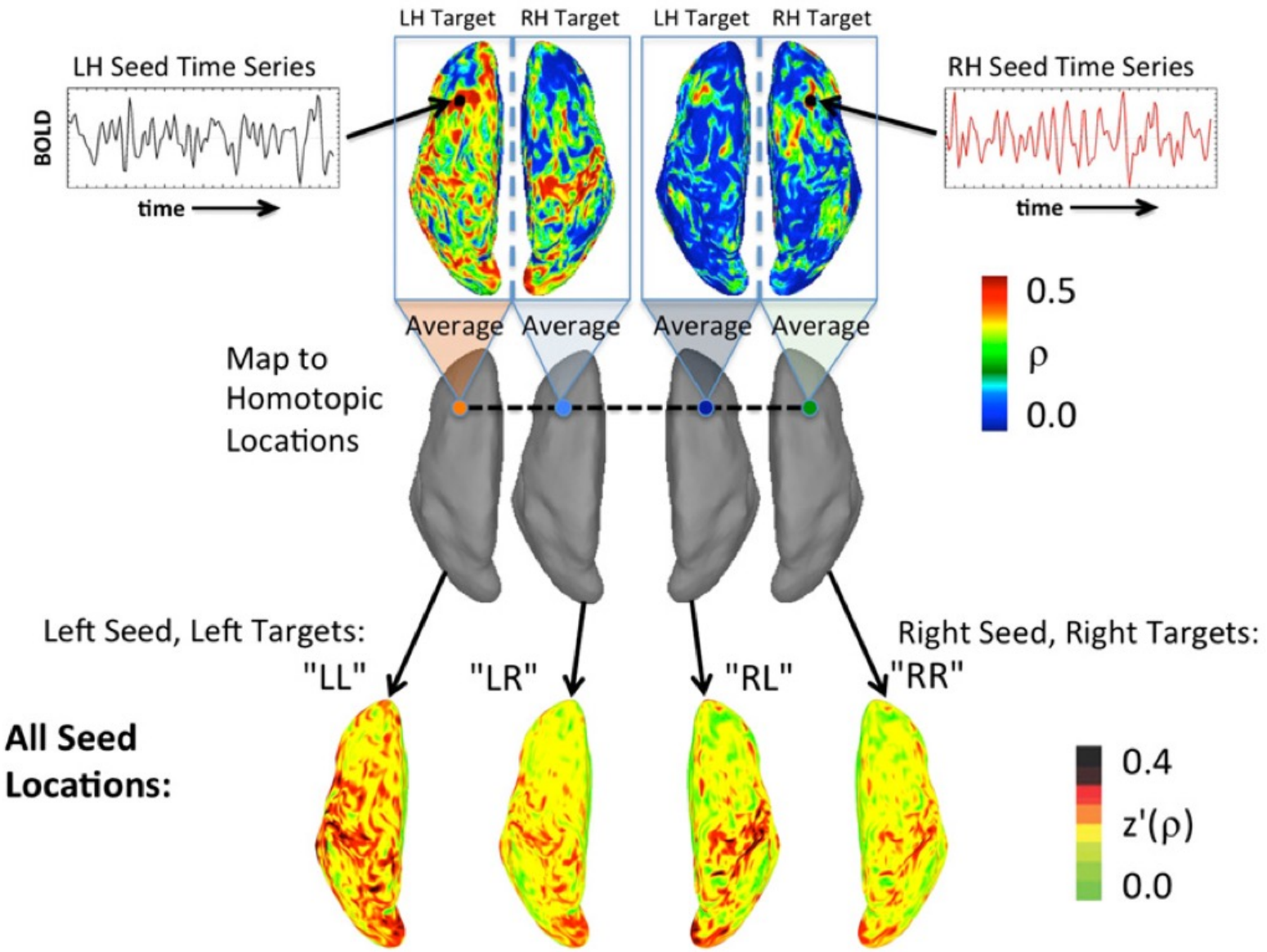




See also Jo et al. (2012). PLoS ONE

Comparing within- vs. between-hemisphere correlation at corresponding points:



Qualitatively Different Forms of Lateralization on Left vs Right

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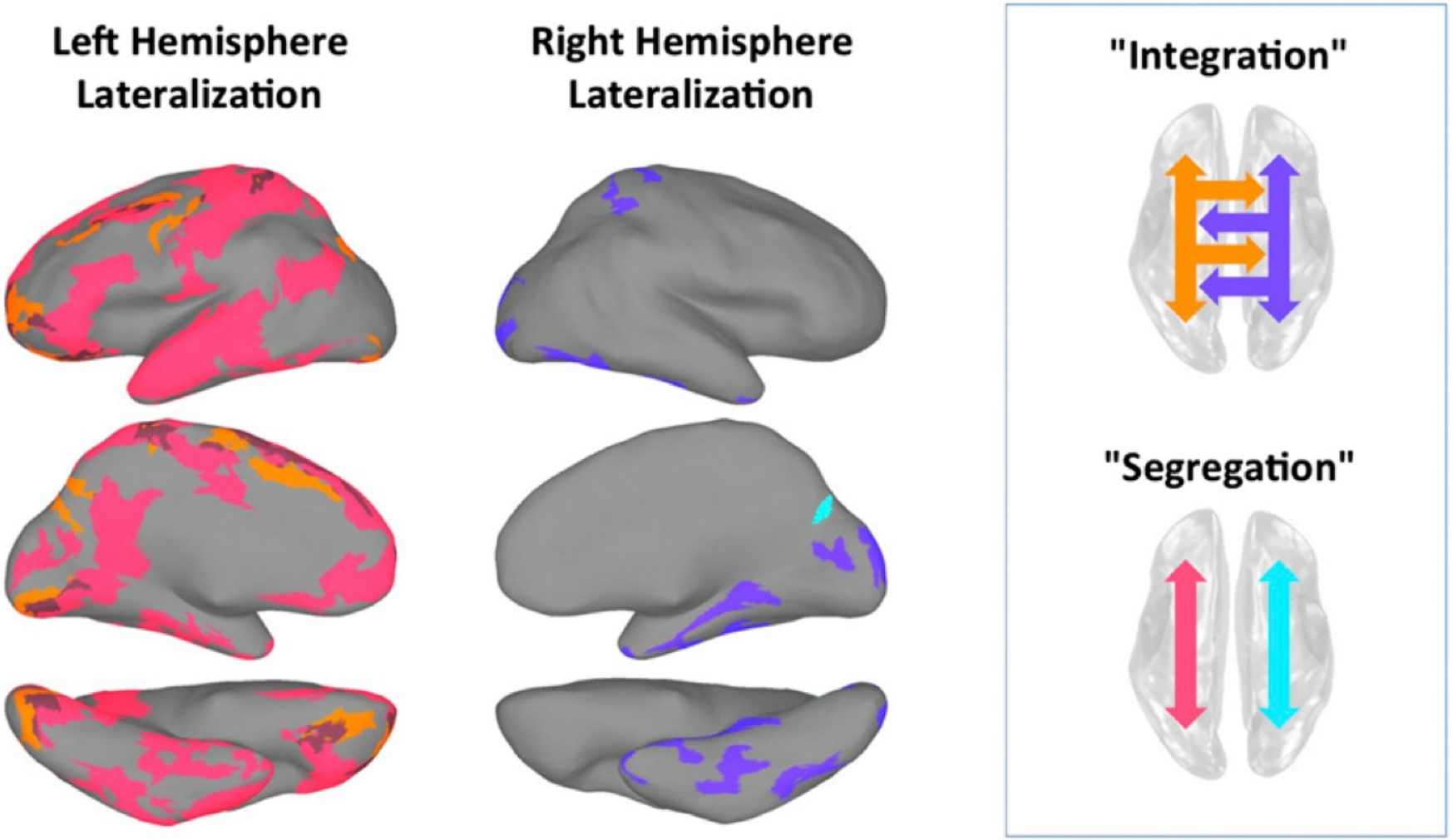

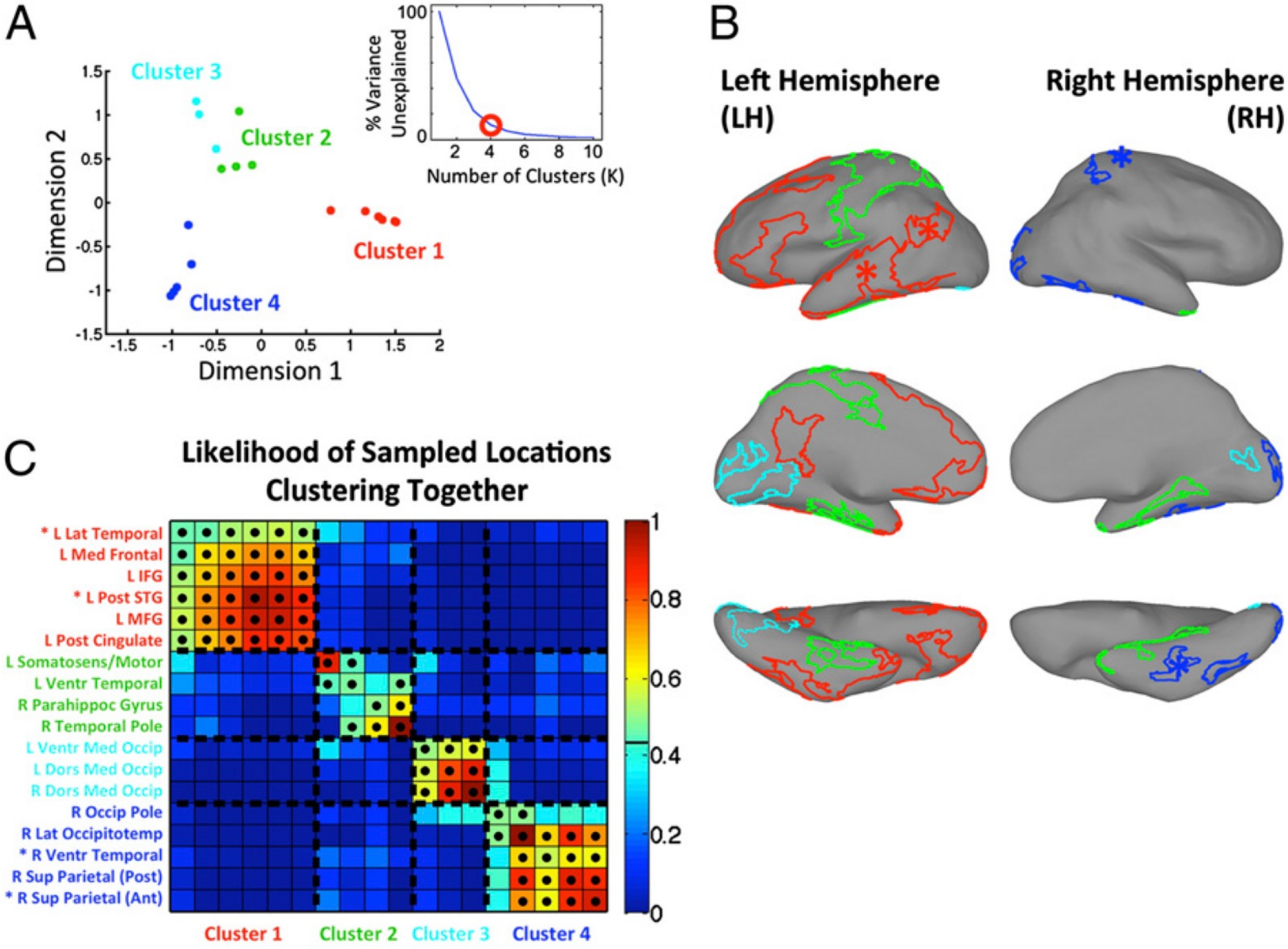
A
Cluster 3
Cluster 2
Cluster 1
Cluster 4
Dimension 2
Dimension 1
% Variance Unexplained
Number of Clusters (K)
B
Left Hemisphere (LH)
Right Hemisphere (RH)
C
Likelihood of Sampled Locations Clustering Together
* L Lat Temporal
L Med Frontal
L IFG
* L Post STG
L MFG
L Post Cingulate
L Somatosens/Motor
L Ventr Temporal
R Parahippoc Gyrus
R Temporal Pole
L Ventr Med Occip
L Dors Med Occip
R Dors Med Occip
R Occip Pole
R Lat Occipitotemp
* R Ventr Temporal
R Sup Parietal (Post)
* R Sup Parietal (Ant)
Cluster 1
Cluster 2
Cluster 3
Cluster 4

Lateralization Magnitude Predicts Cognitive Ability

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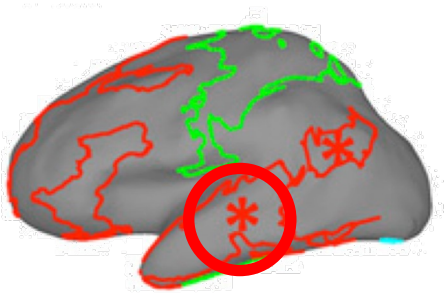

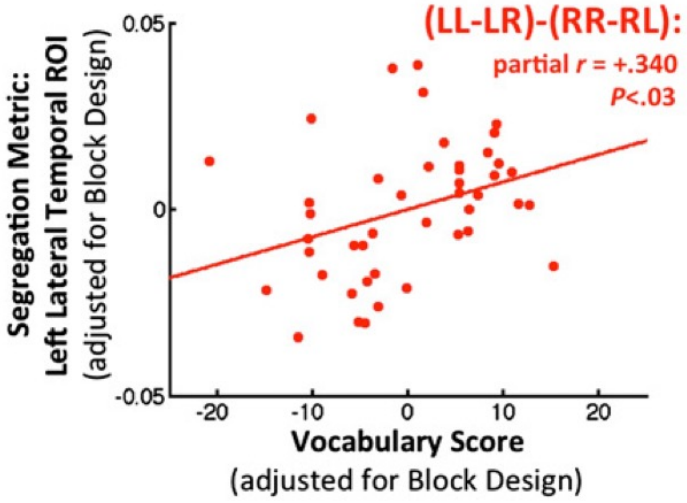

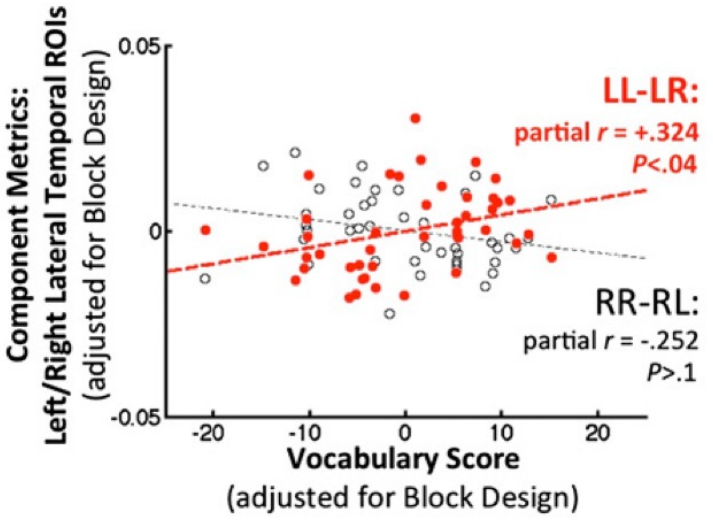

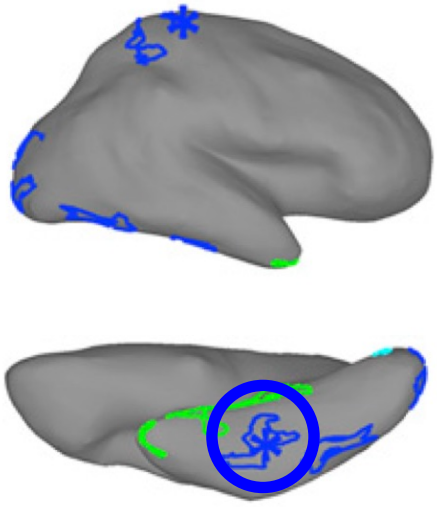

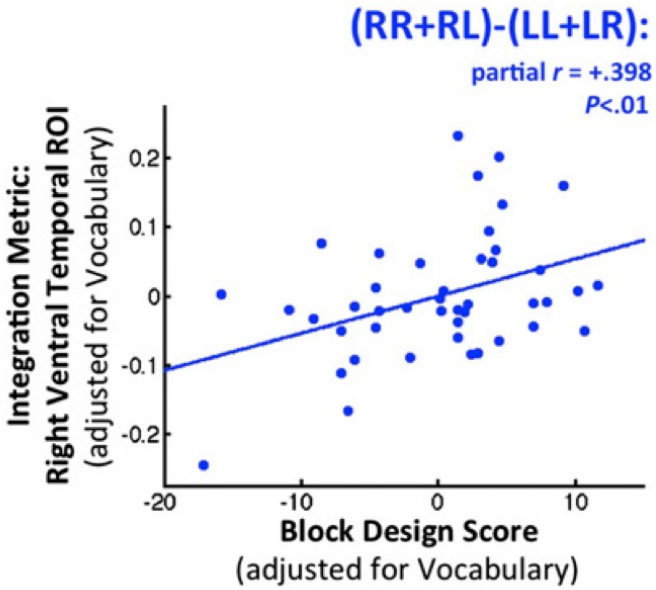

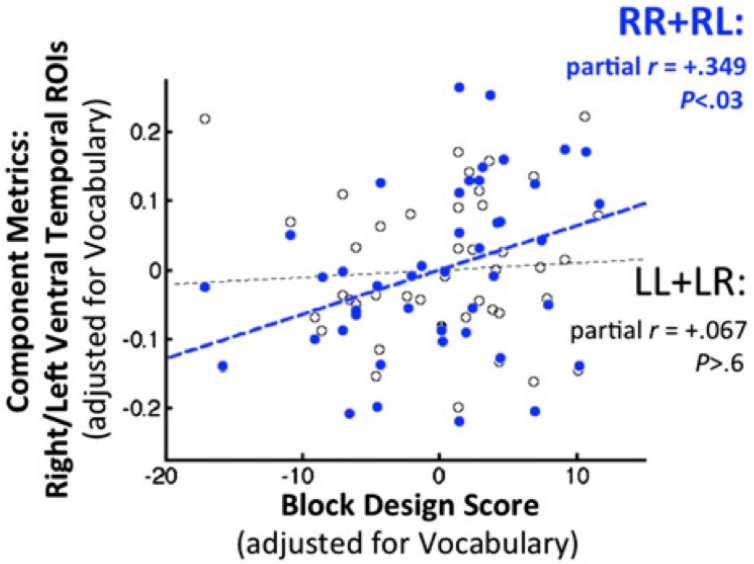

fMRI Connectivity in Clinical Research

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Examples:

fMRI Connectivity in Clinical Research

Examples:

Psychiatric Disorders:

Autism, Schizophrenia, Bipolar Disorder

fMRI Connectivity in Clinical Research

Examples:

Psychiatric Disorders:

Autism, Schizophrenia, Bipolar Disorder

Neurological Disorders:

Primary Lateral Sclerosis (PLS), Stroke

Autism (ASD) vs. Typically Developing (TD)

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doi:10.1093/brain/aws160 Brain 2012: 135; 2711–2725 | 2711

BRAIN
A JOURNAL OF NEUROLOGY

Fractionation of social brain circuits in autism spectrum disorders

Stephen J. Gotts,[1] W. Kyle Simmons,[2] Lydia A. Milbury,[1] Gregory L. Wallace,[1] Robert W. Cox[3] and Alex Martin[1]

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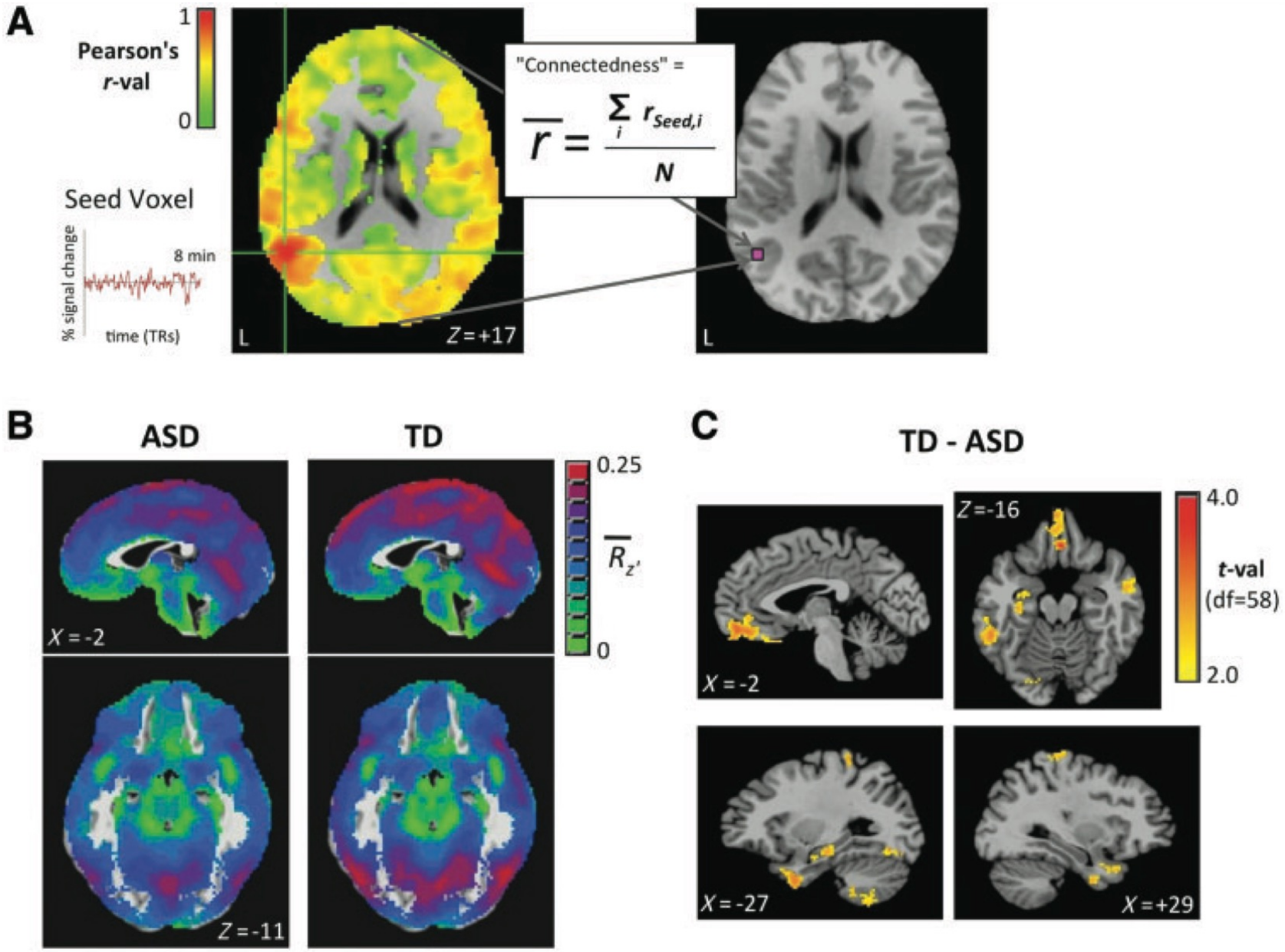
Are the largest differences in functional connectivity concentrated among regions of the "social brain" ?

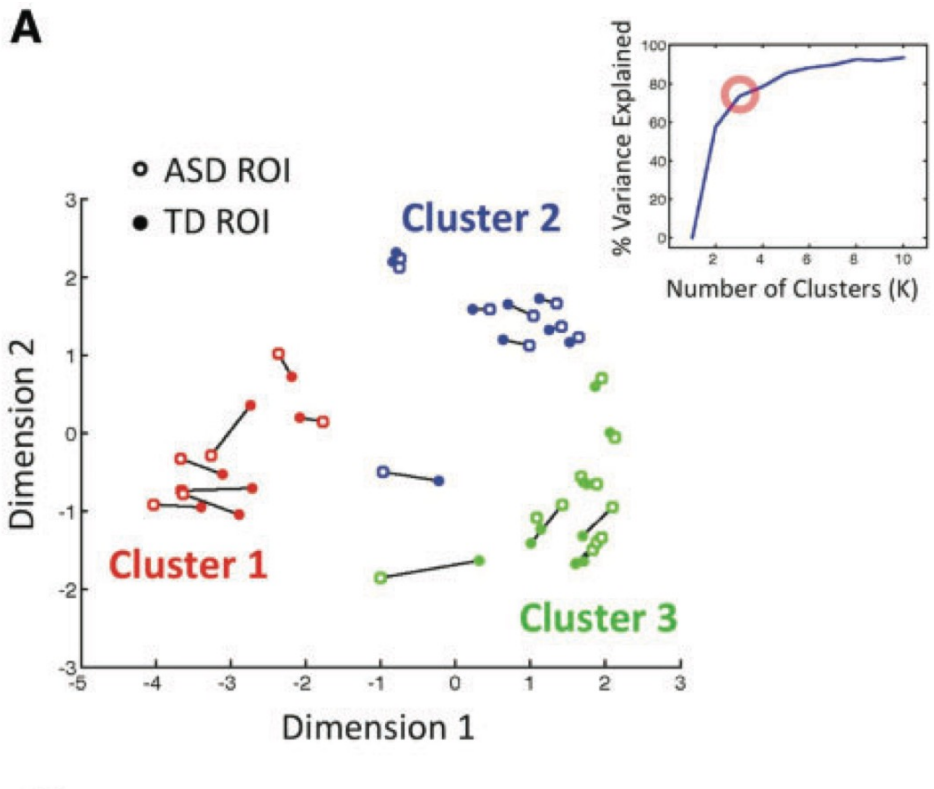
The "Social Brain"

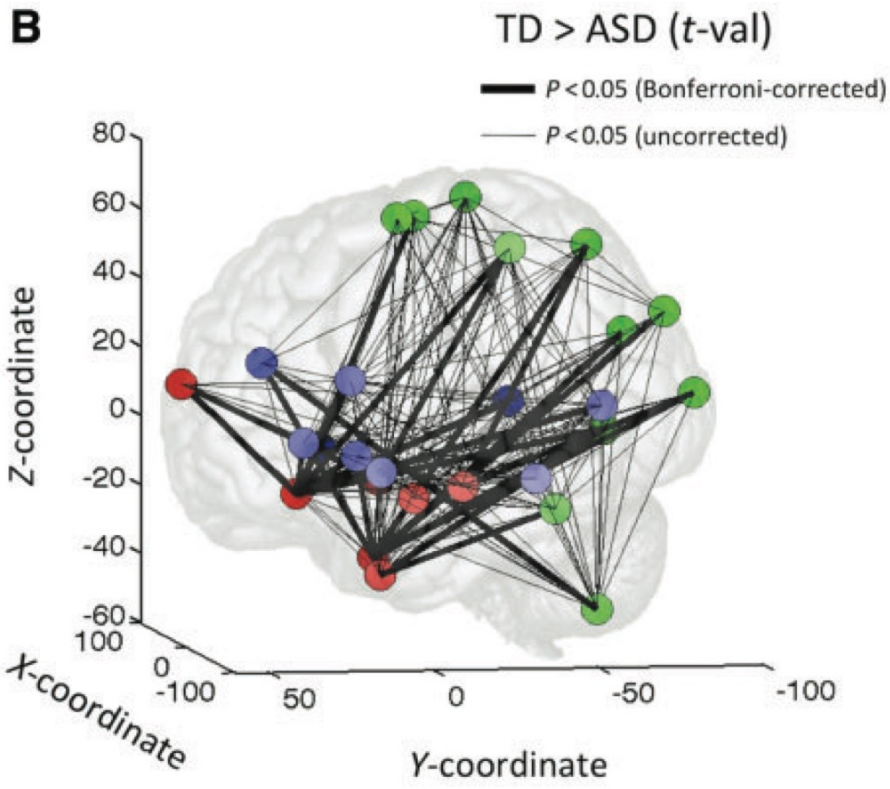
(a la Brothers, 1990; Frith & Frith, 2007; Adolphs, 2009)

Empirical Determination of "Seeds":



Whole-brain Differences in Functional Connectivity: TD > ASD





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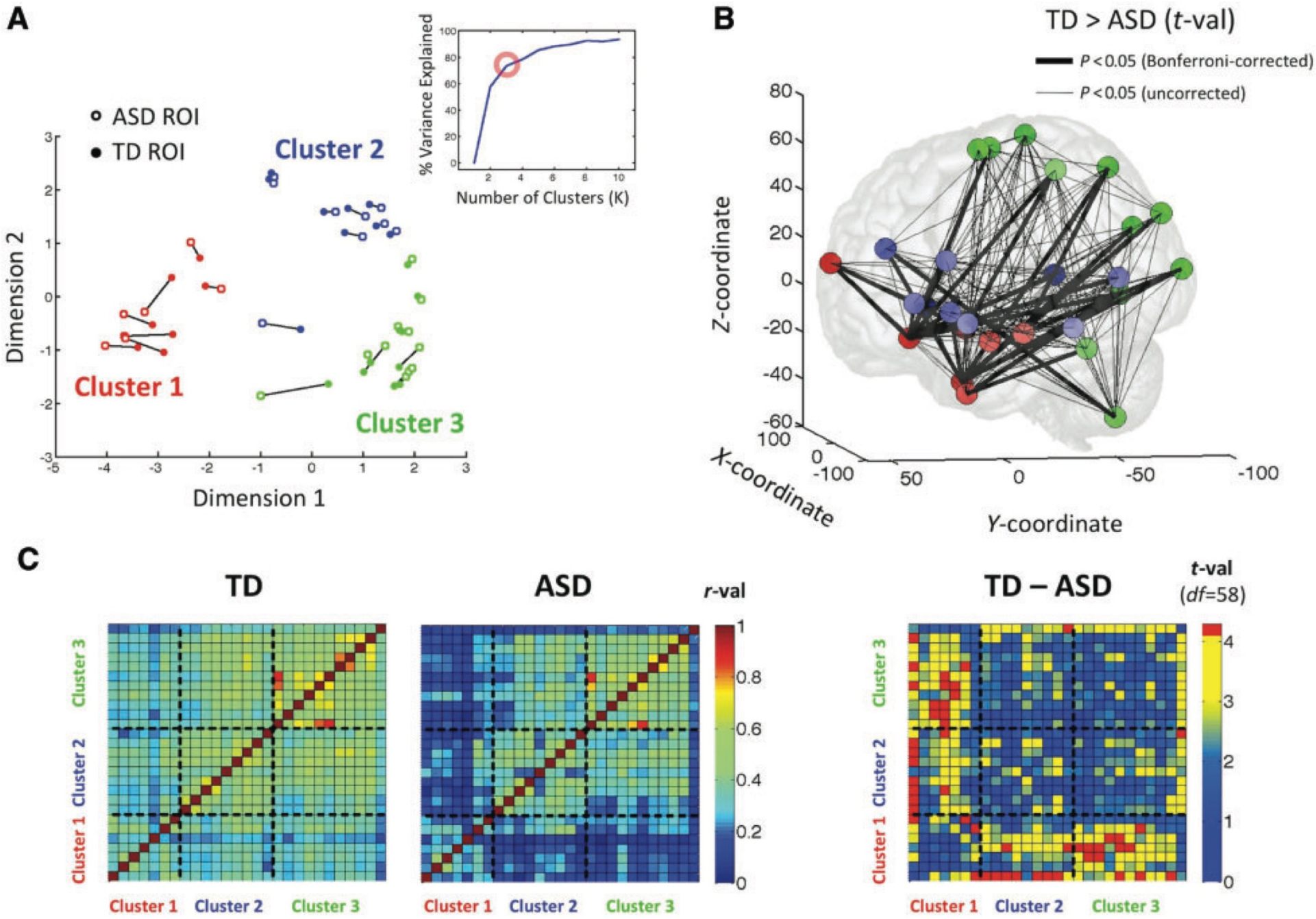
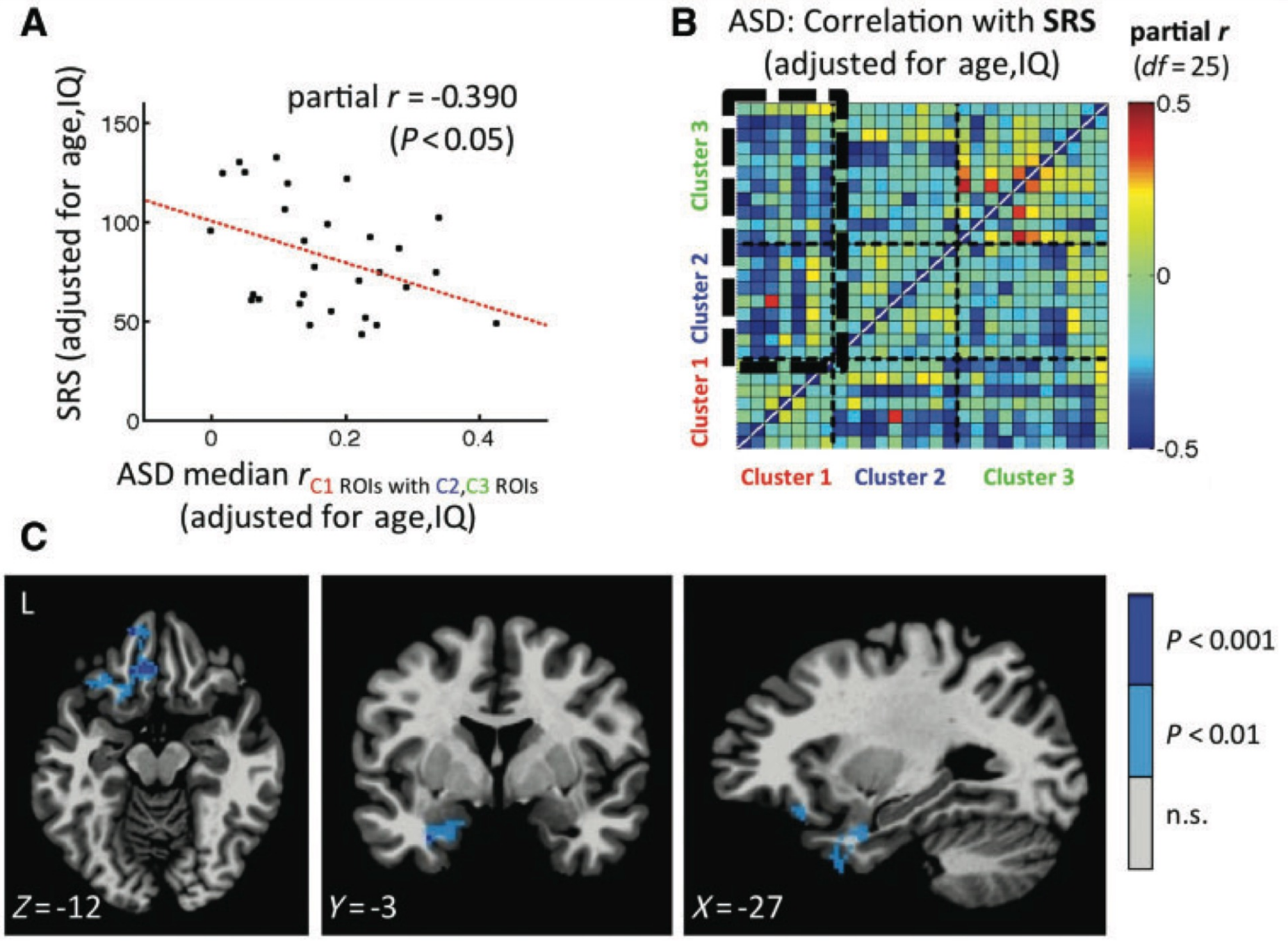


Agreement with Social Symptom Correlations (ASD only)



Applying the same method to Childhood Onset Schizophrenia (vs. Typ. Developing)

Collaboration (SG, AM) with:

Becky Berman

Harrison McAdams

Nitin Gogtay

Judy Rapoport

Berman et al. (2016). Brain 139, 276-91

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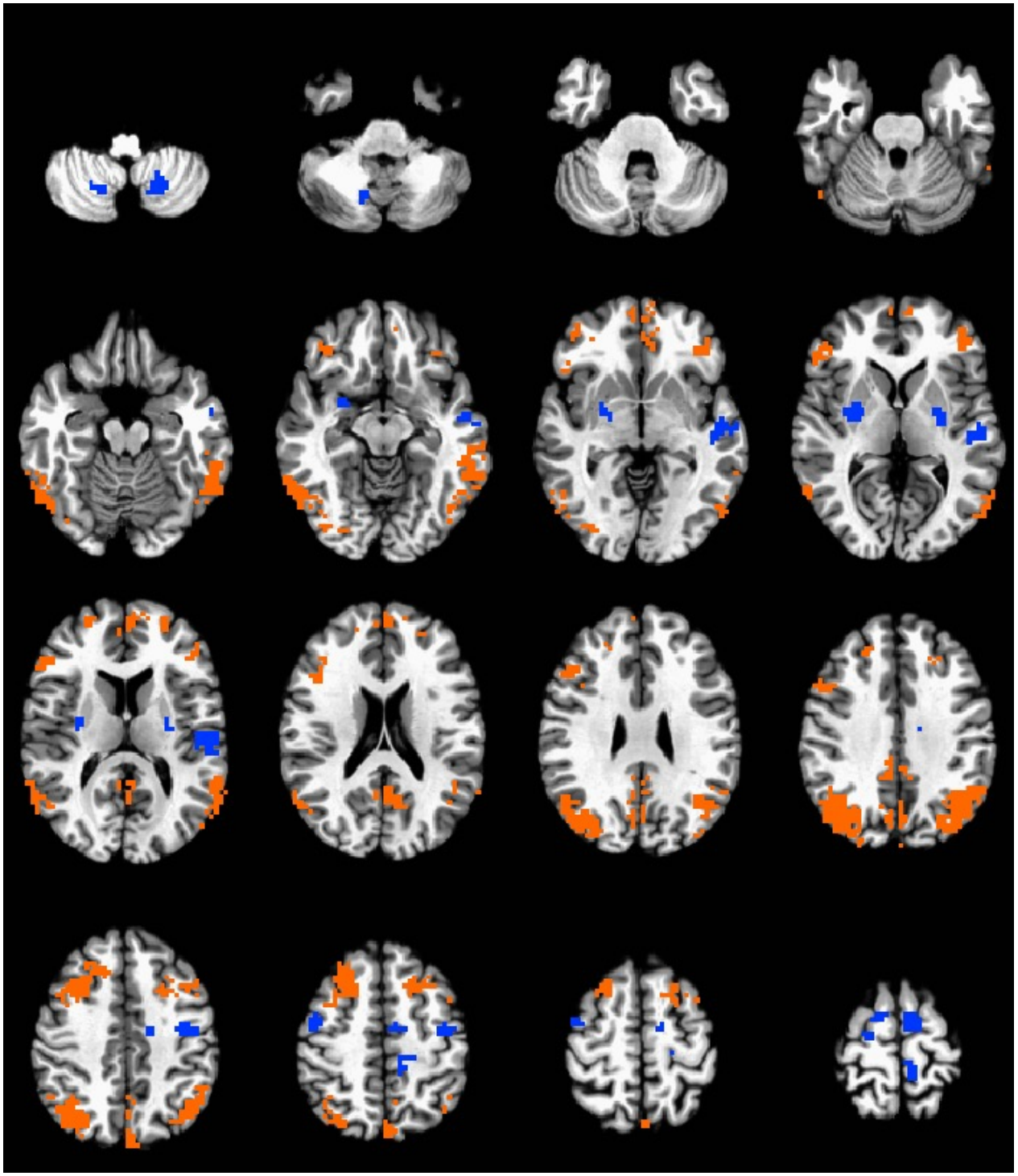

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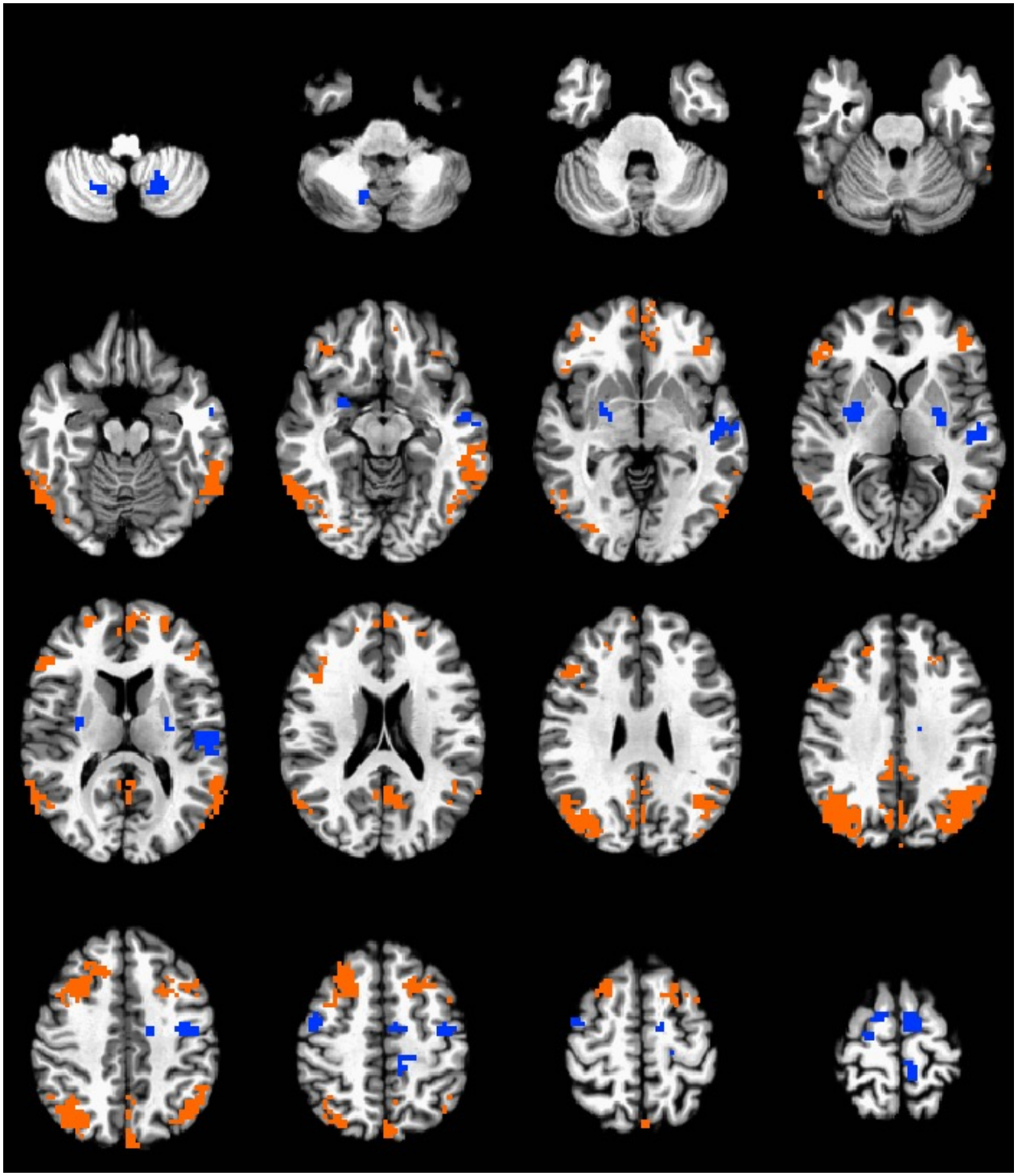
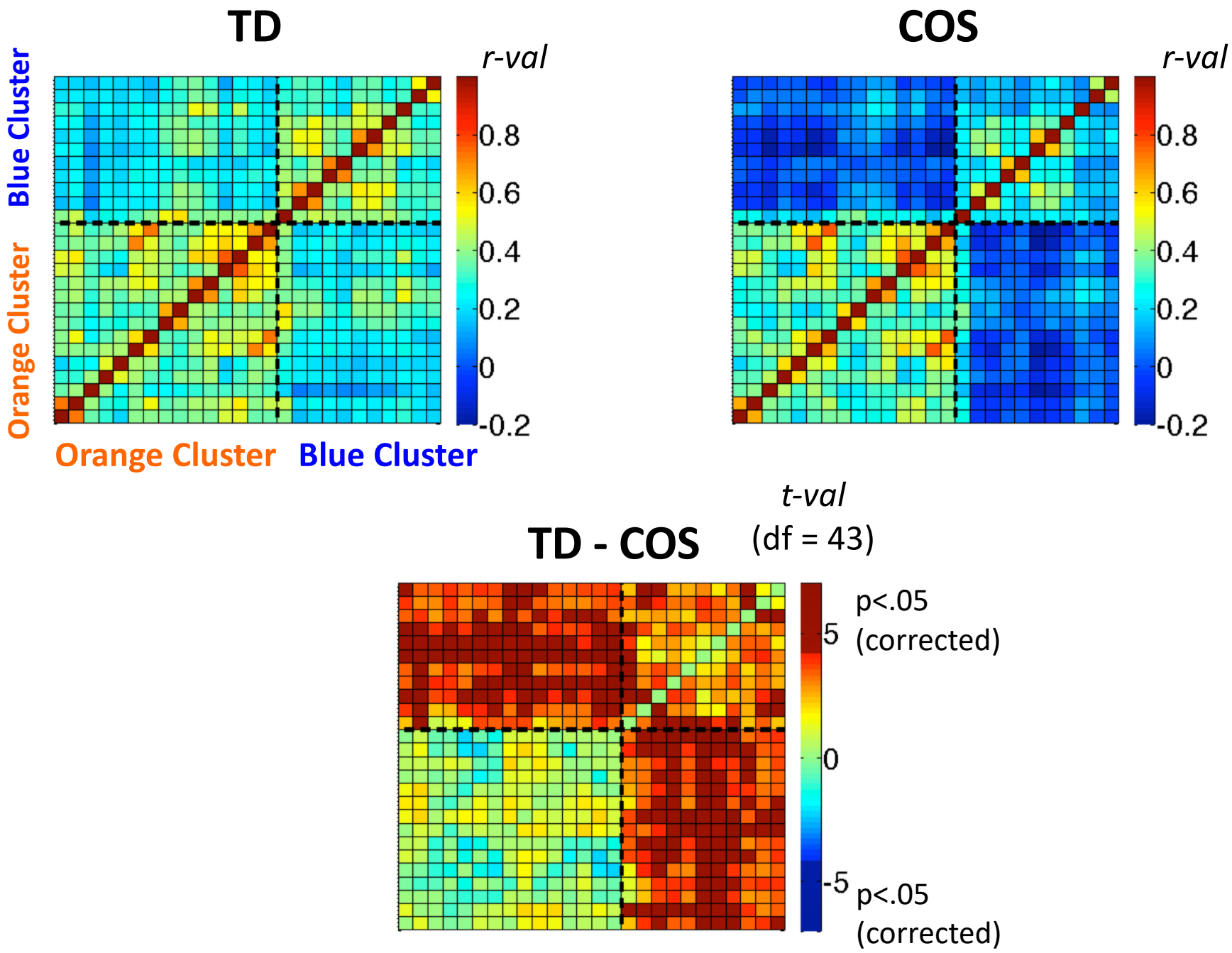
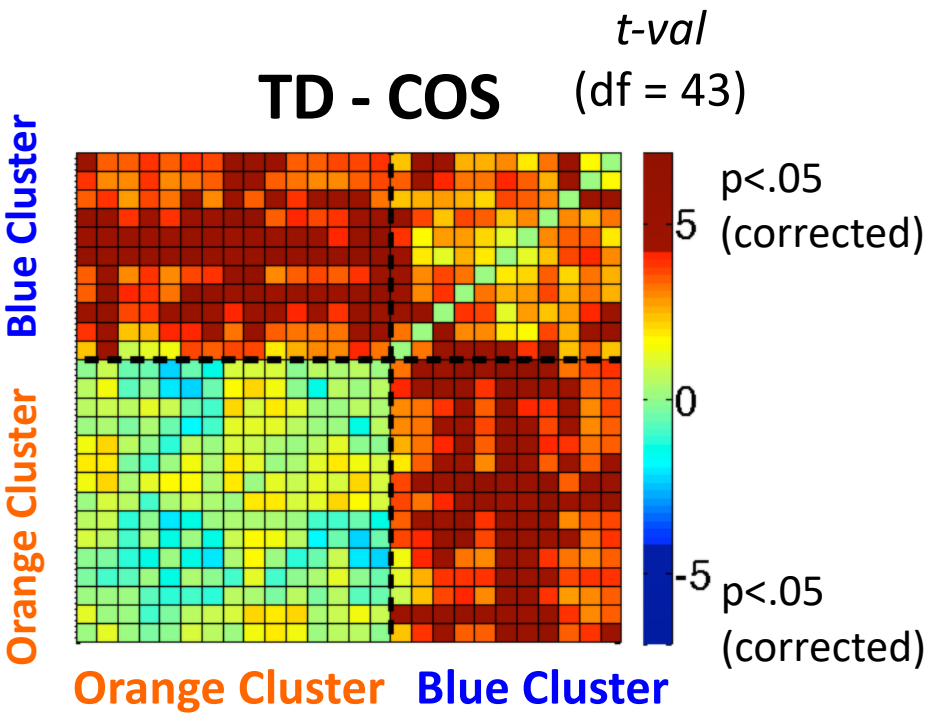
2 Clusters of Regions with reduced correlation in COS relative to TD:

Social/Cognitive vs. Somatosensory/Motor

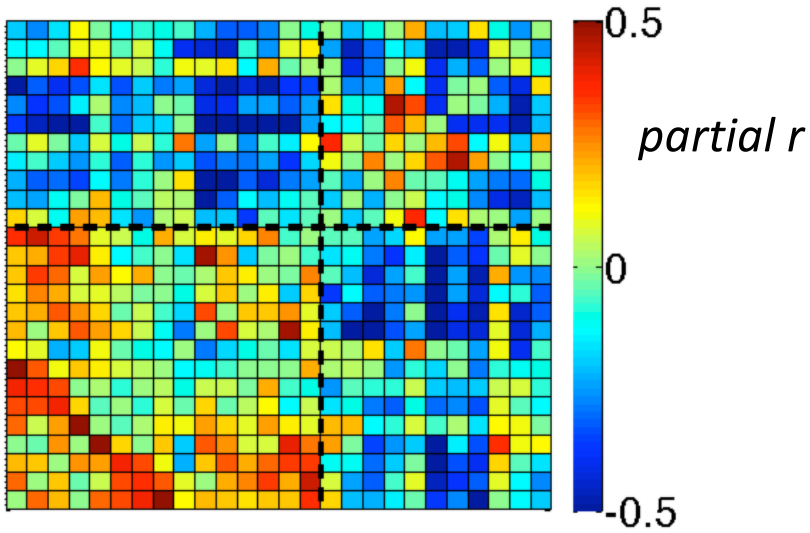



TD
r-val
0.8
0.6
0.4
0.2
0
-0.2
Blue Cluster
Orange Cluster
Orange Cluster
Blue Cluster
COS
r-val
0.8
0.6
0.4
0.2
0
-0.2
TD - COS
t-val
(df = 43)
5
0
-5
p<.05
(corrected)
p<.05
(corrected)

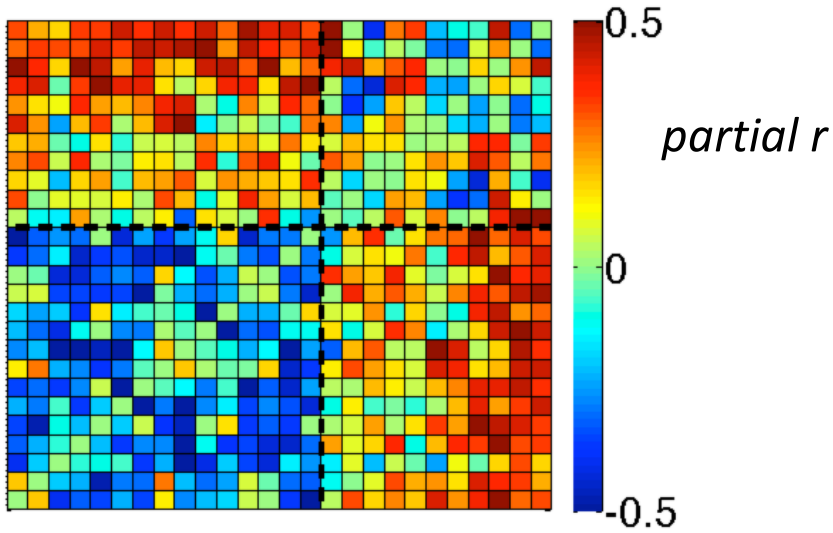
Group Differences Are Associated with Positive/Negative Symptoms in COS



Correlation with Positive Symptoms (SAPS)
(covarying Age, Motion)



Correlation with Negative Symptoms (SANS)
(covarying Age, Motion)



Increased Resting Correlations in Primary Lateral Sclerosis (PLS)

Collaboration with Mary Kay Floeter (NINDS) and Avner Meoded (Johns Hopkins):

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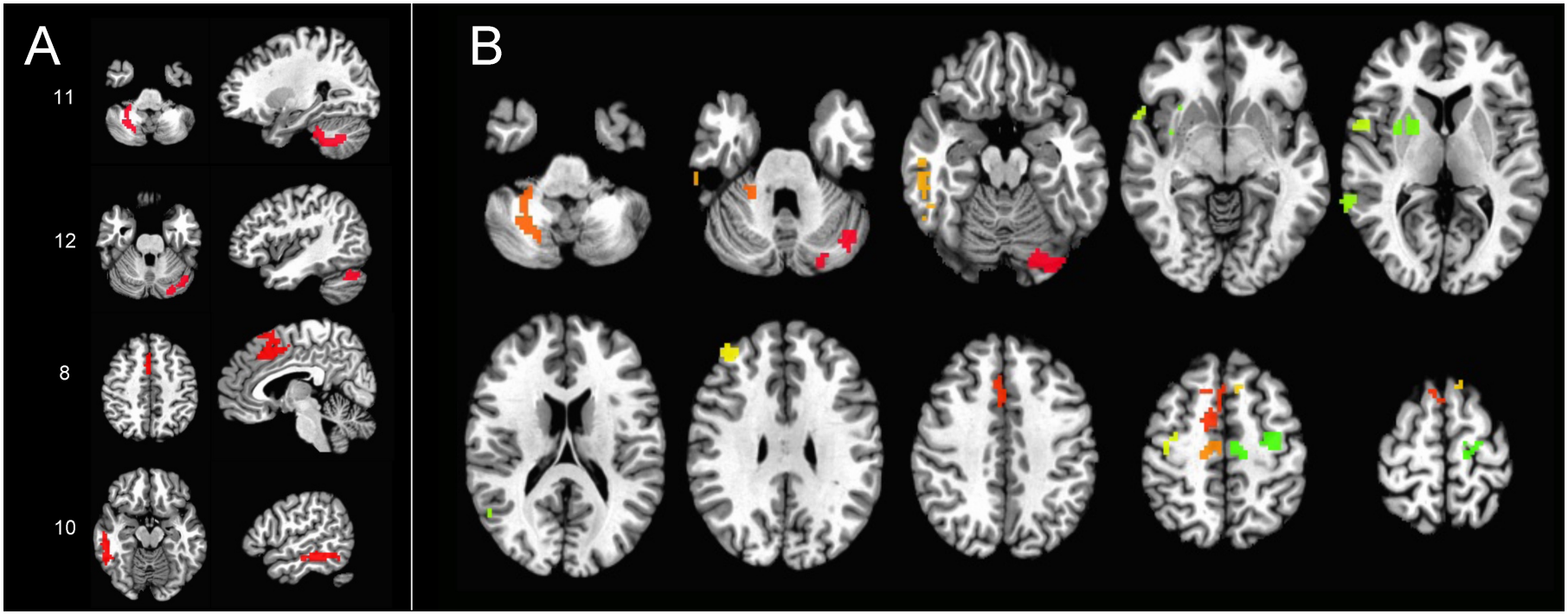

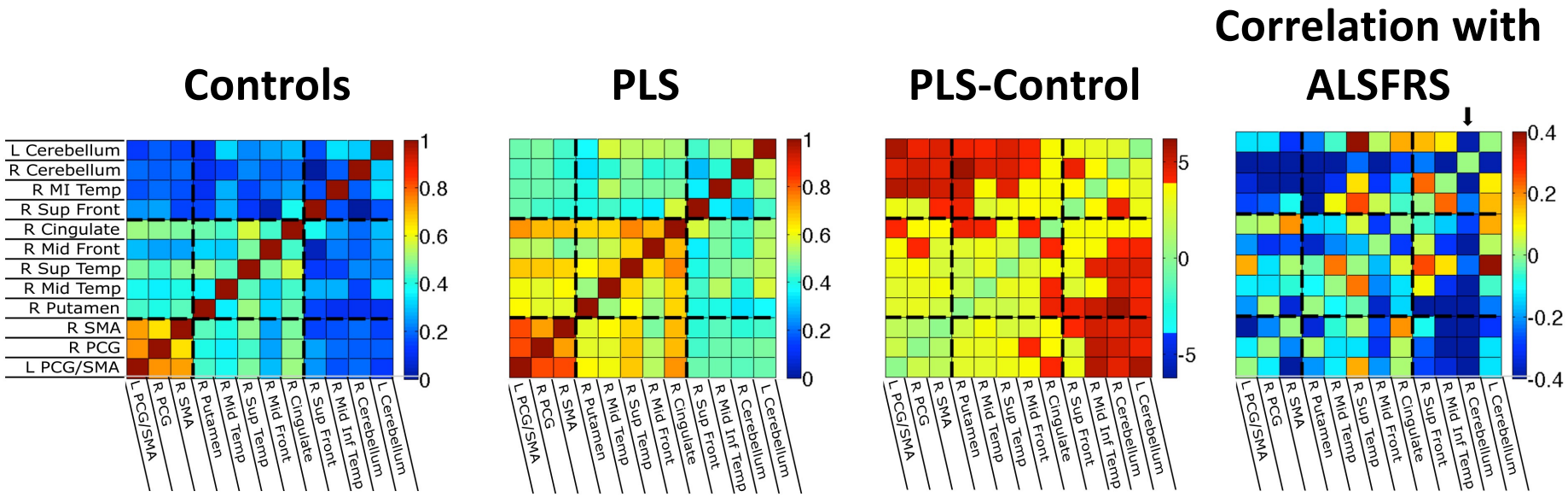

5 Patients with Left Hemisphere Lesions due to left CVA

Collaboration with Laurel Buxbaum and Christine Watson (Moss Rehab Research Institute):

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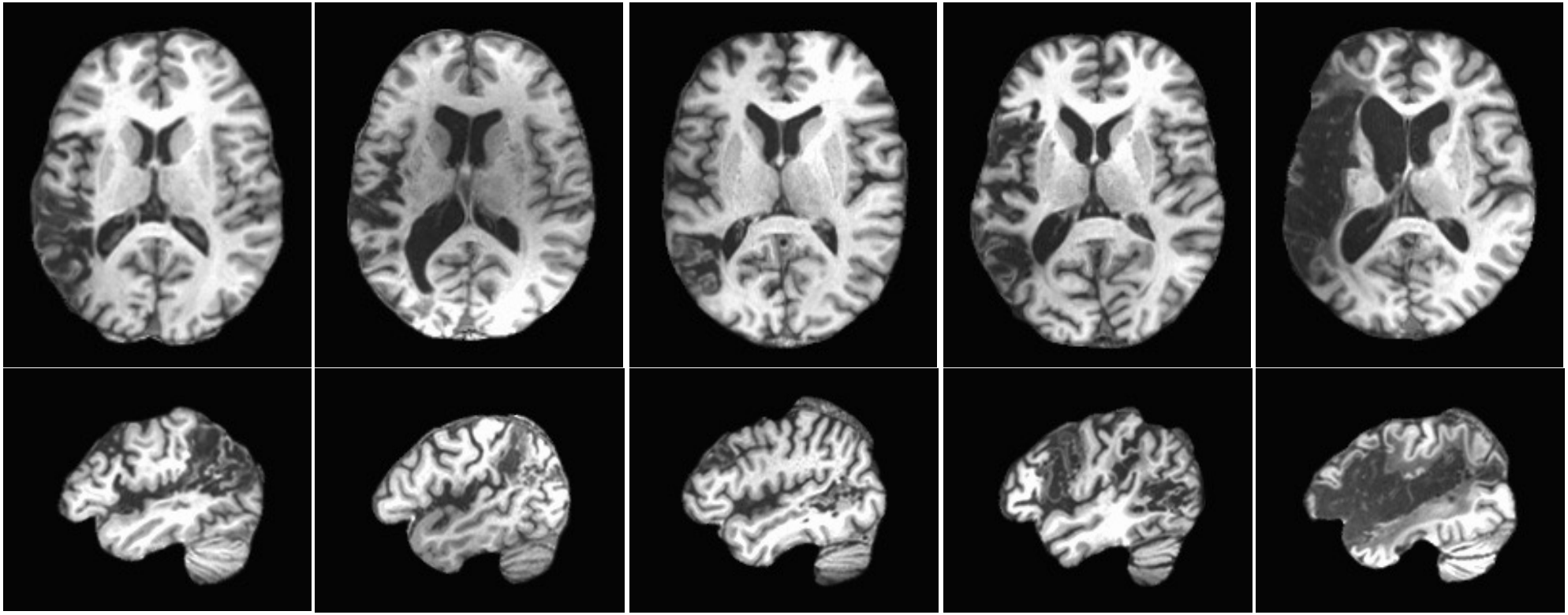
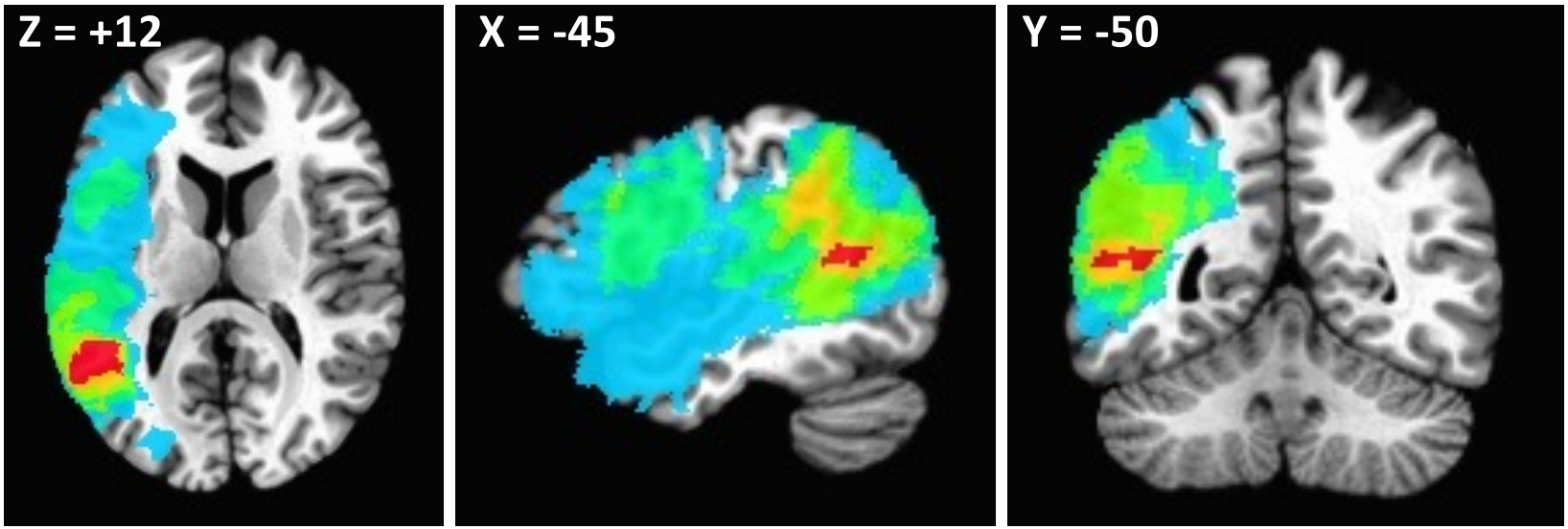
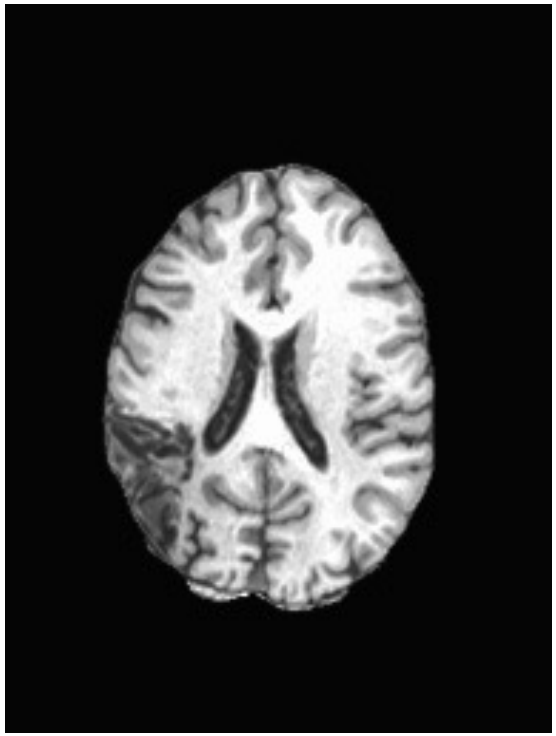
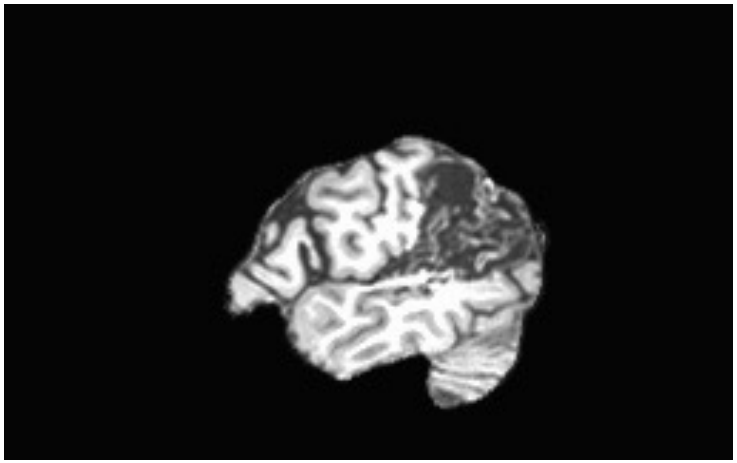




Example Patient

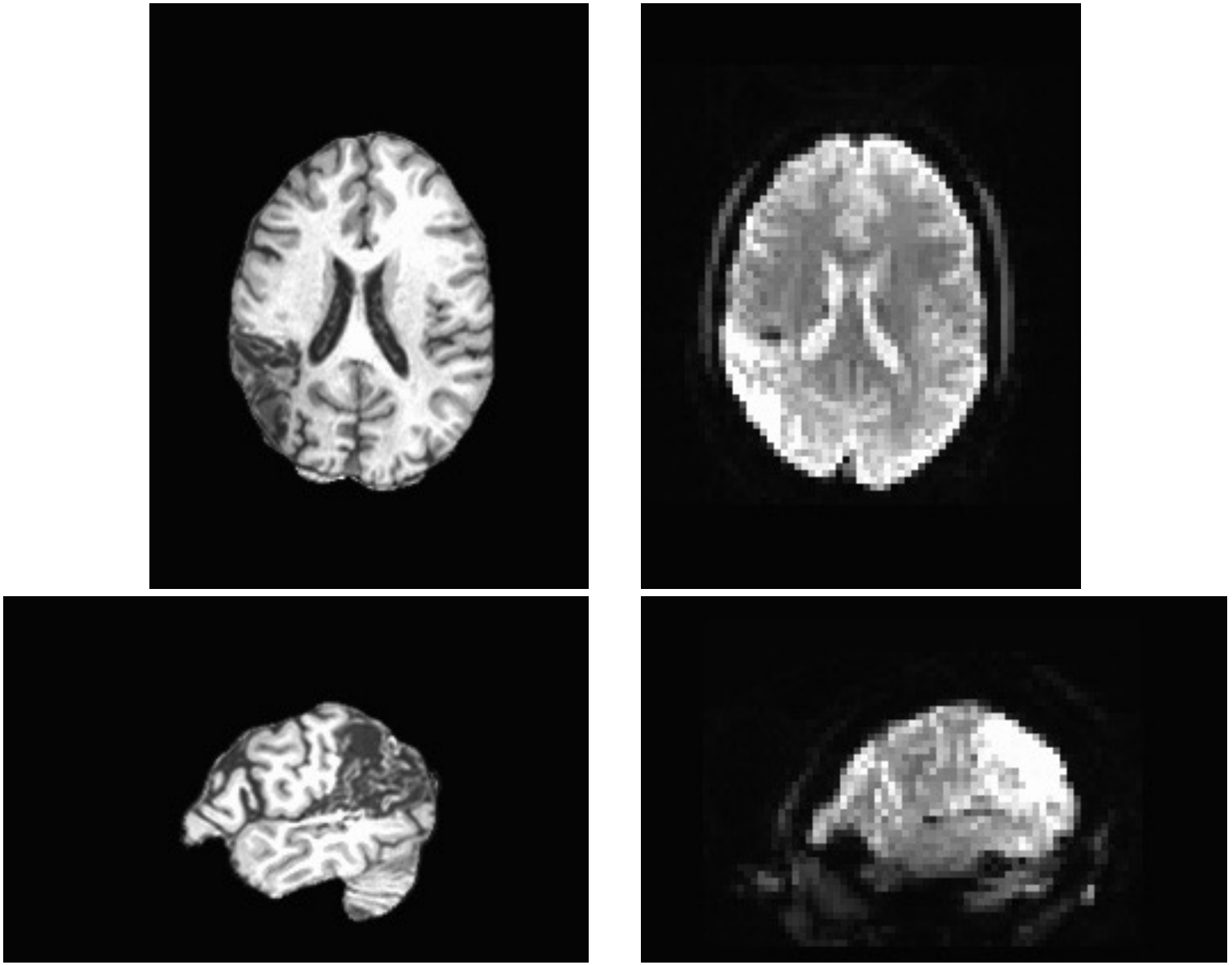
MPRAGE





Example Patient

MPRAGE **EPI**

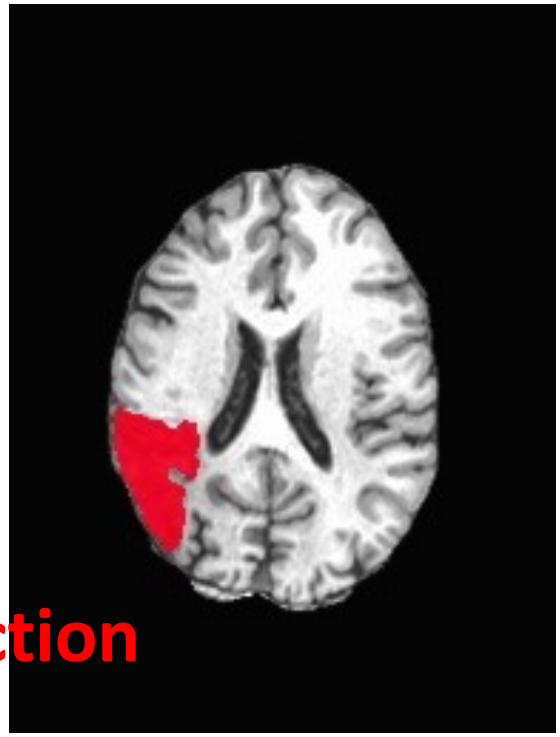


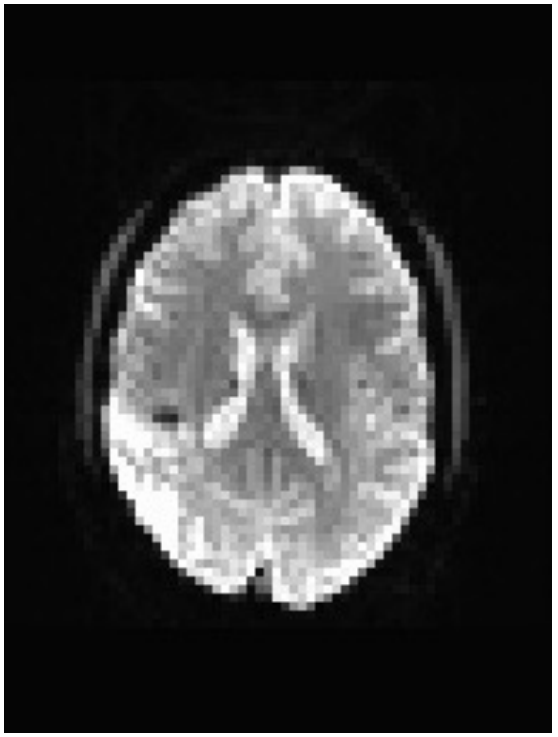
Example Patient

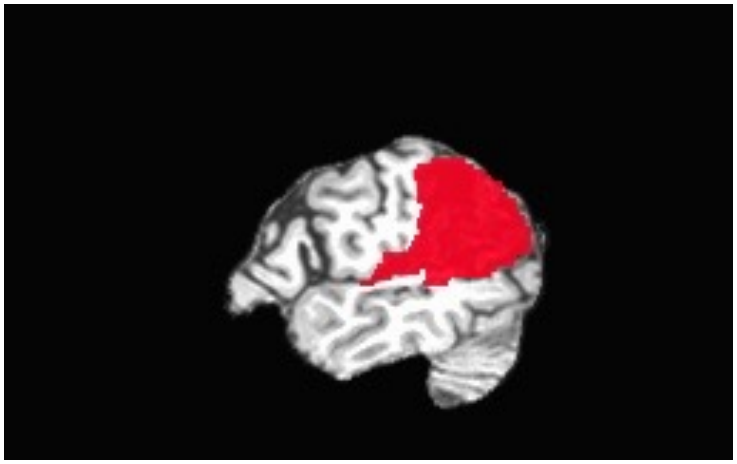
MPRAGE

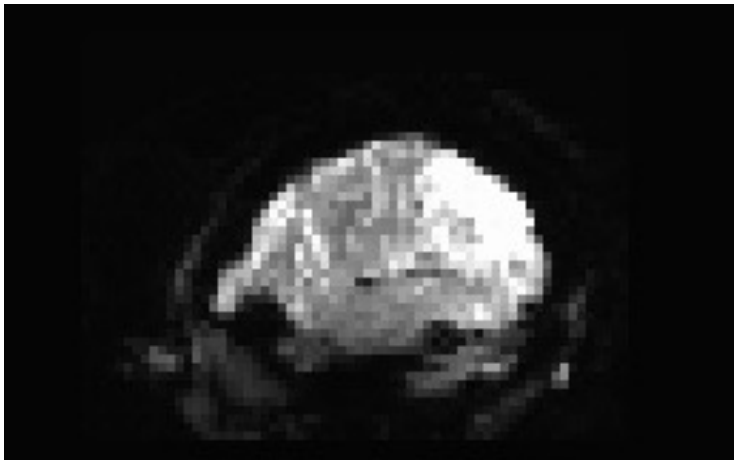
EPI

Lesion Reconstruction







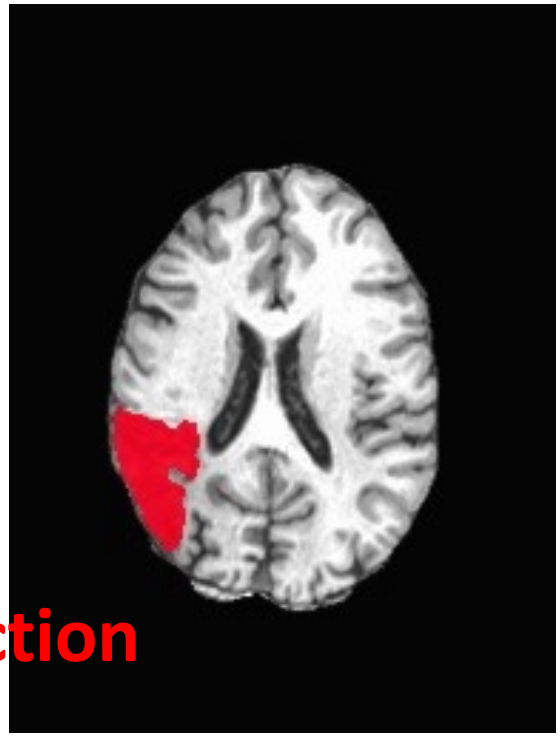


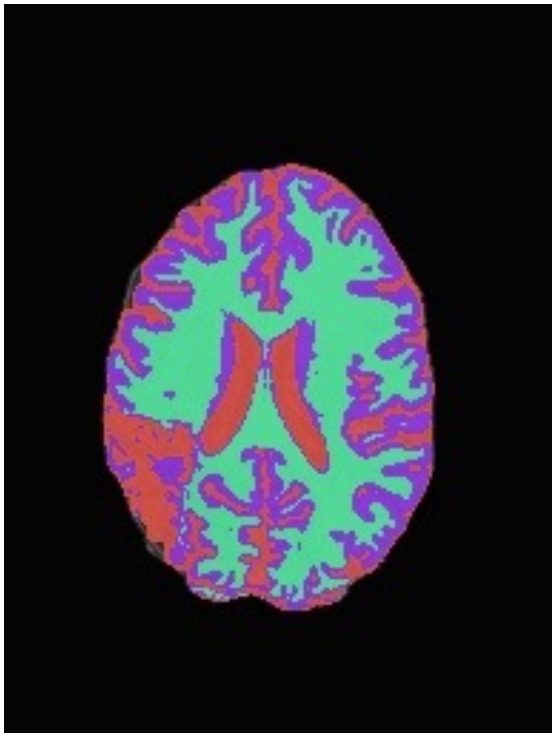
Example Patient

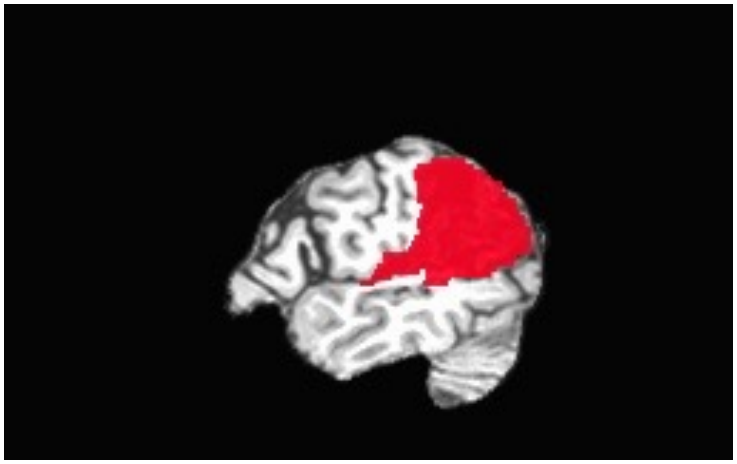
MPRAGE

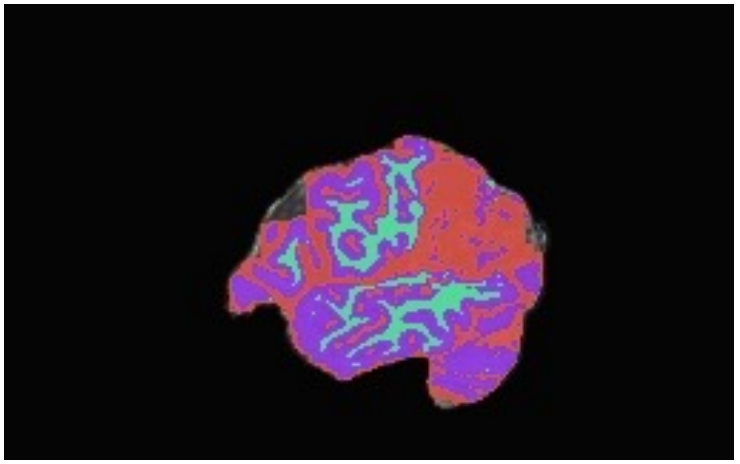
Tissue Masks

Lesion Reconstruction





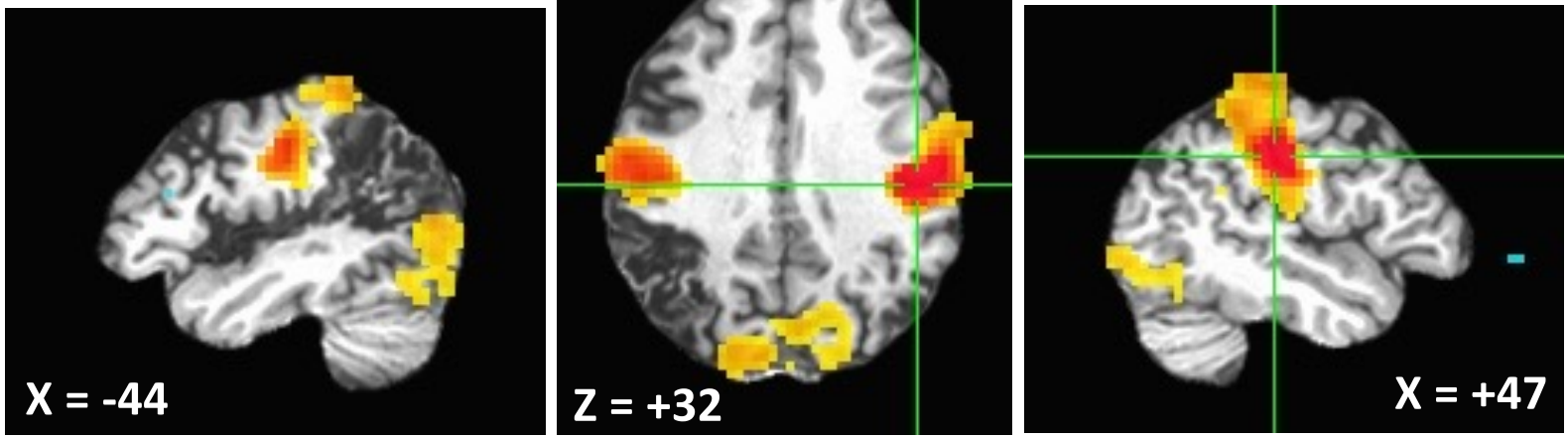




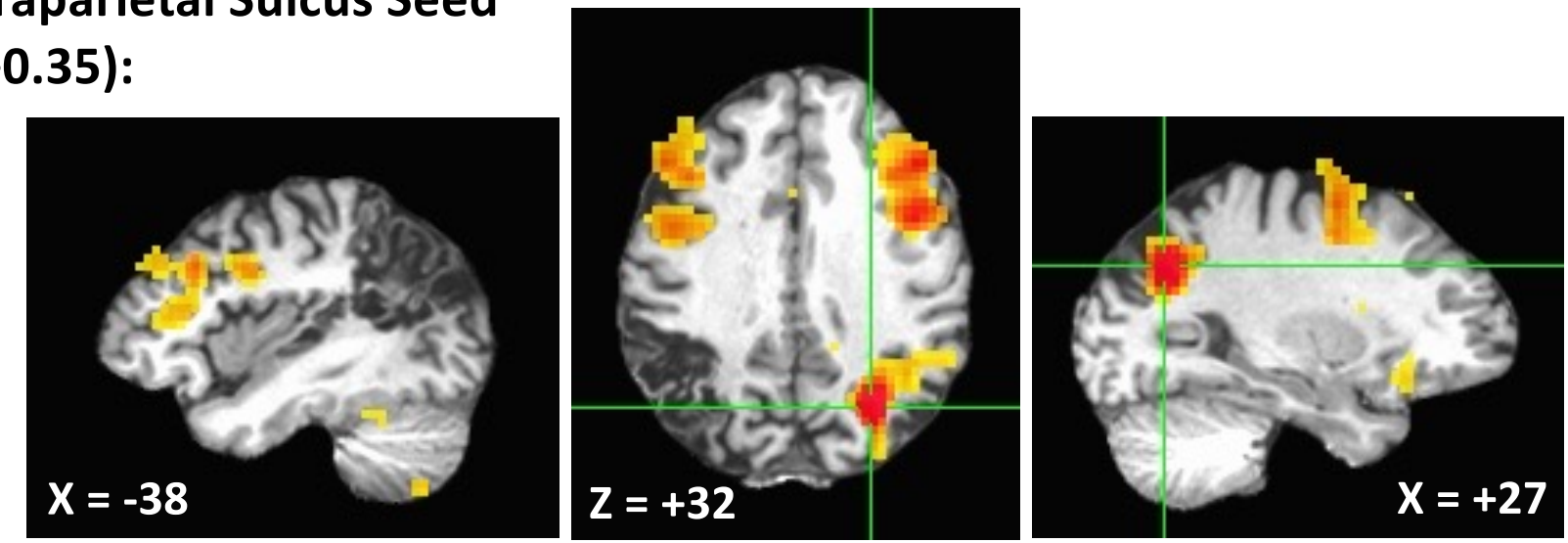
Example Patient (After Data Cleaning)

R Postcentral Gyrus Seed (r > +0.35):

6mm-Radius Sphere

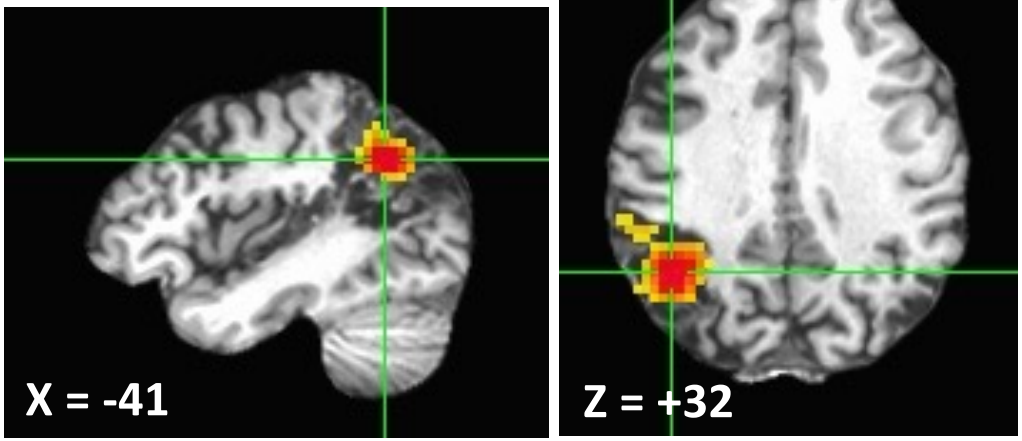


R Intraparietal Sulcus Seed (r > +0.35):



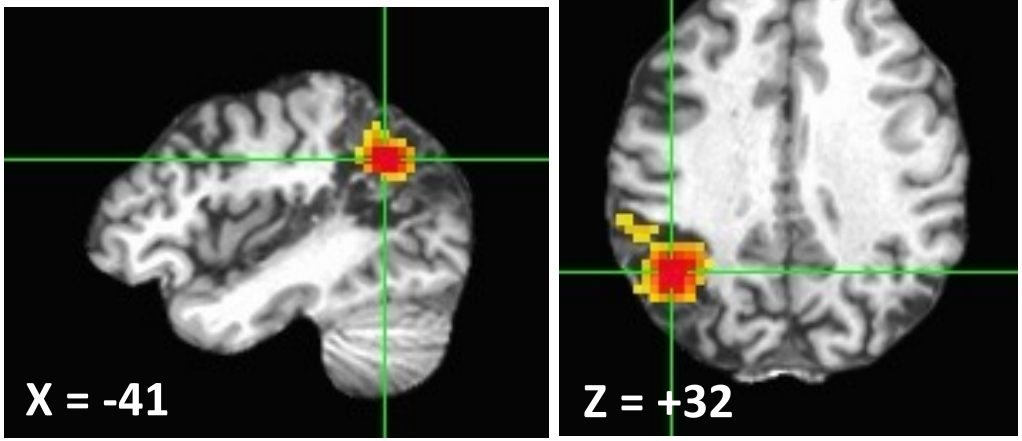
Example Patient (After Data Cleaning)

Seed in Lesion
(r > +0.35):



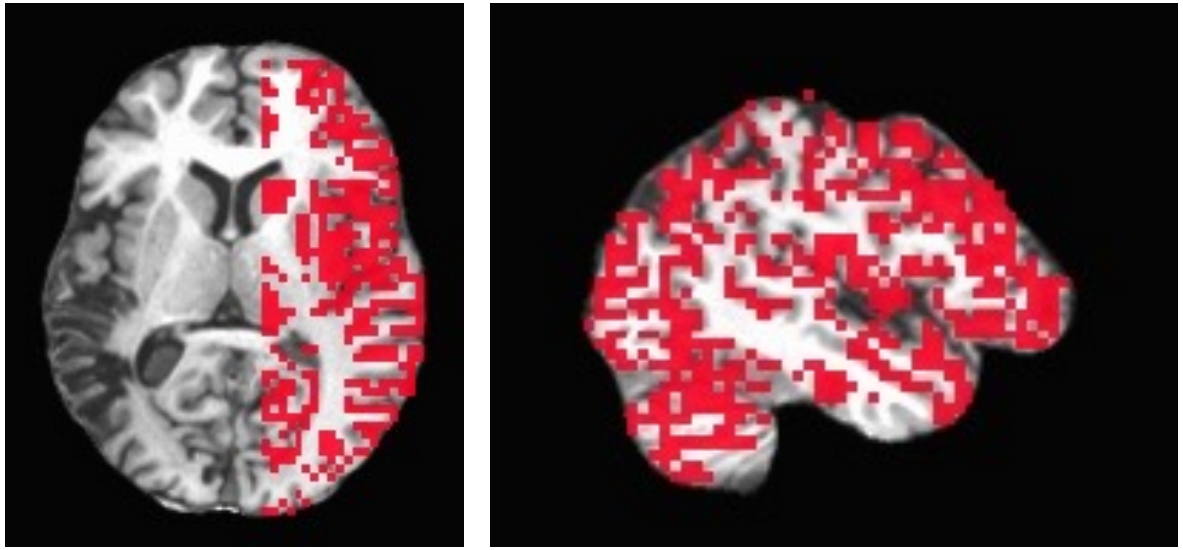
Example Patient (After Data Cleaning)

Seed in Lesion
(r > +0.35):



How do we find unusual correlation levels over the entire brain? (more systematically)

Mask of Right Hemisphere Gray Matter Voxels (X>+10mm)



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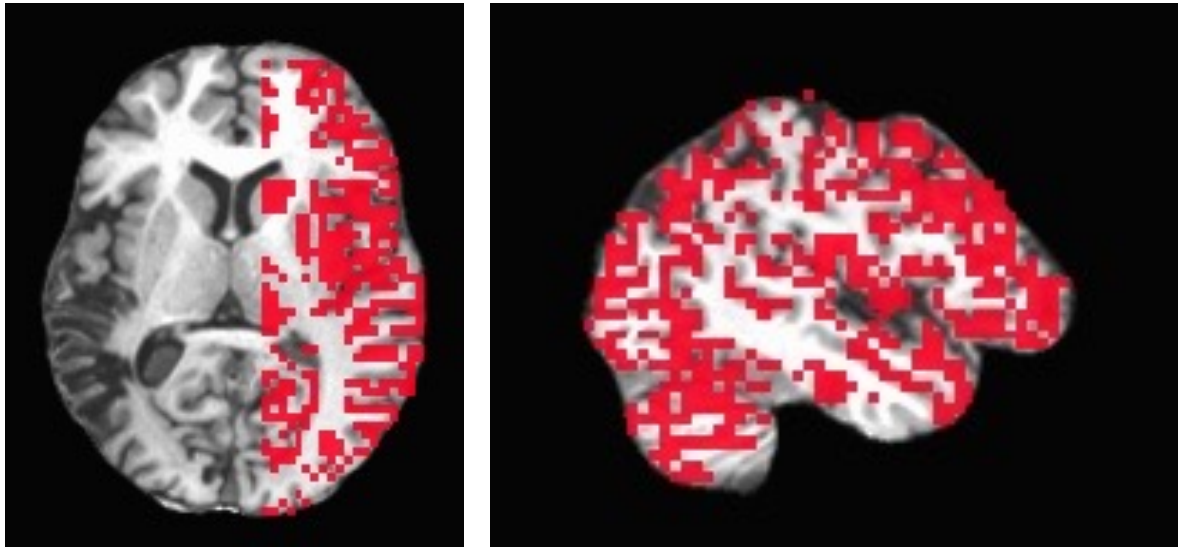

1) Find the correlation of every voxel with the RH voxels

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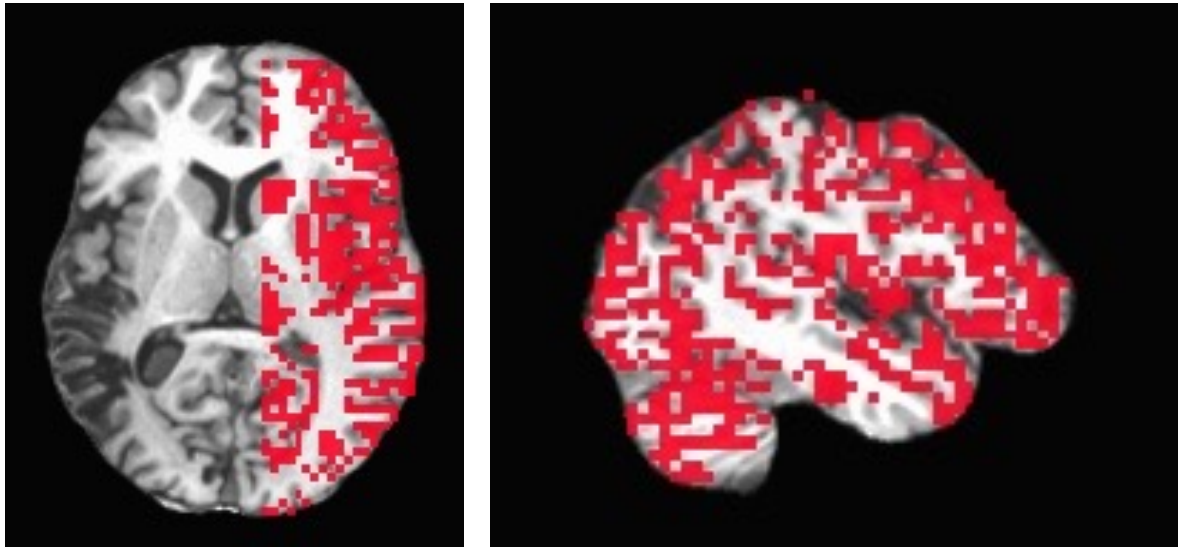
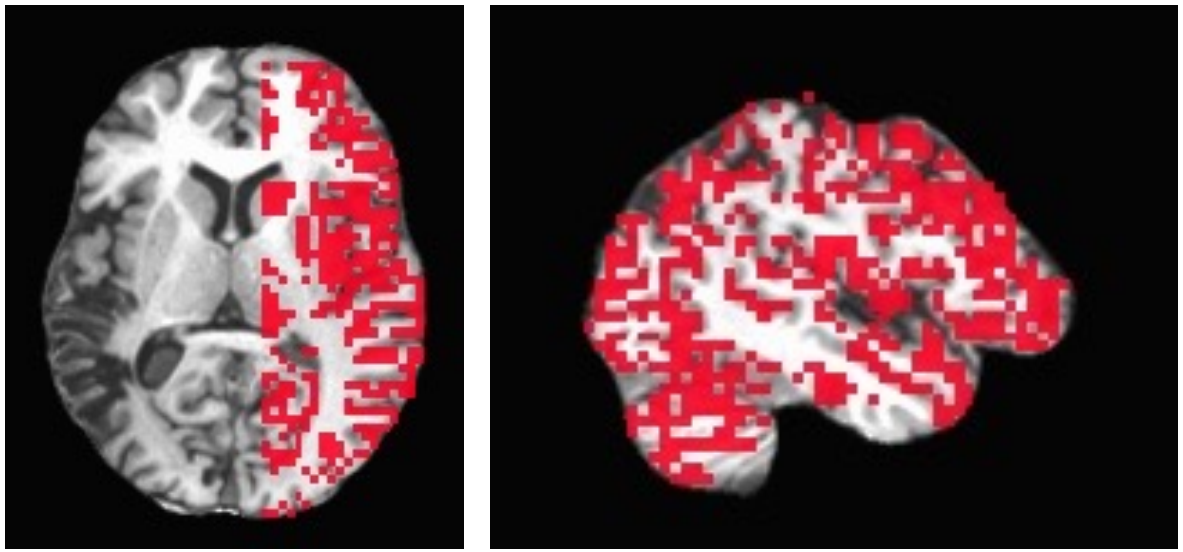


1) Find the correlation of every voxel with the RH voxels

2) then average OR threshold above a certain value
(e.g. > 0.2 or 0.3; as in Buckner et al., 2009, J Neurosci),

Mask of Right Hemisphere Gray Matter Voxels (X>+10mm)

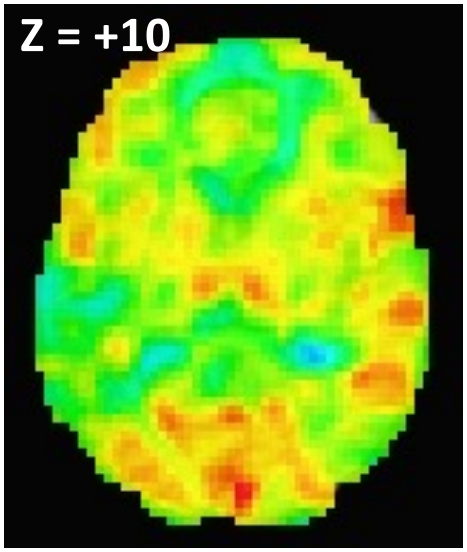


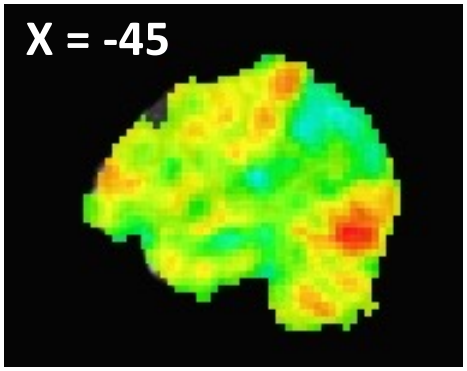
1) Find the correlation of every voxel with the RH voxels

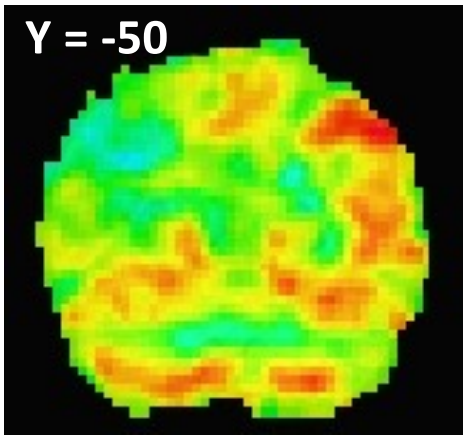
2) then average OR threshold above a certain value
(e.g. > 0.2 or 0.3; as in Buckner et al., 2009, J Neurosci),

3) store the average OR voxel counts (> thresh) back in each voxel

Average r-value
(-.15 < r < .15)



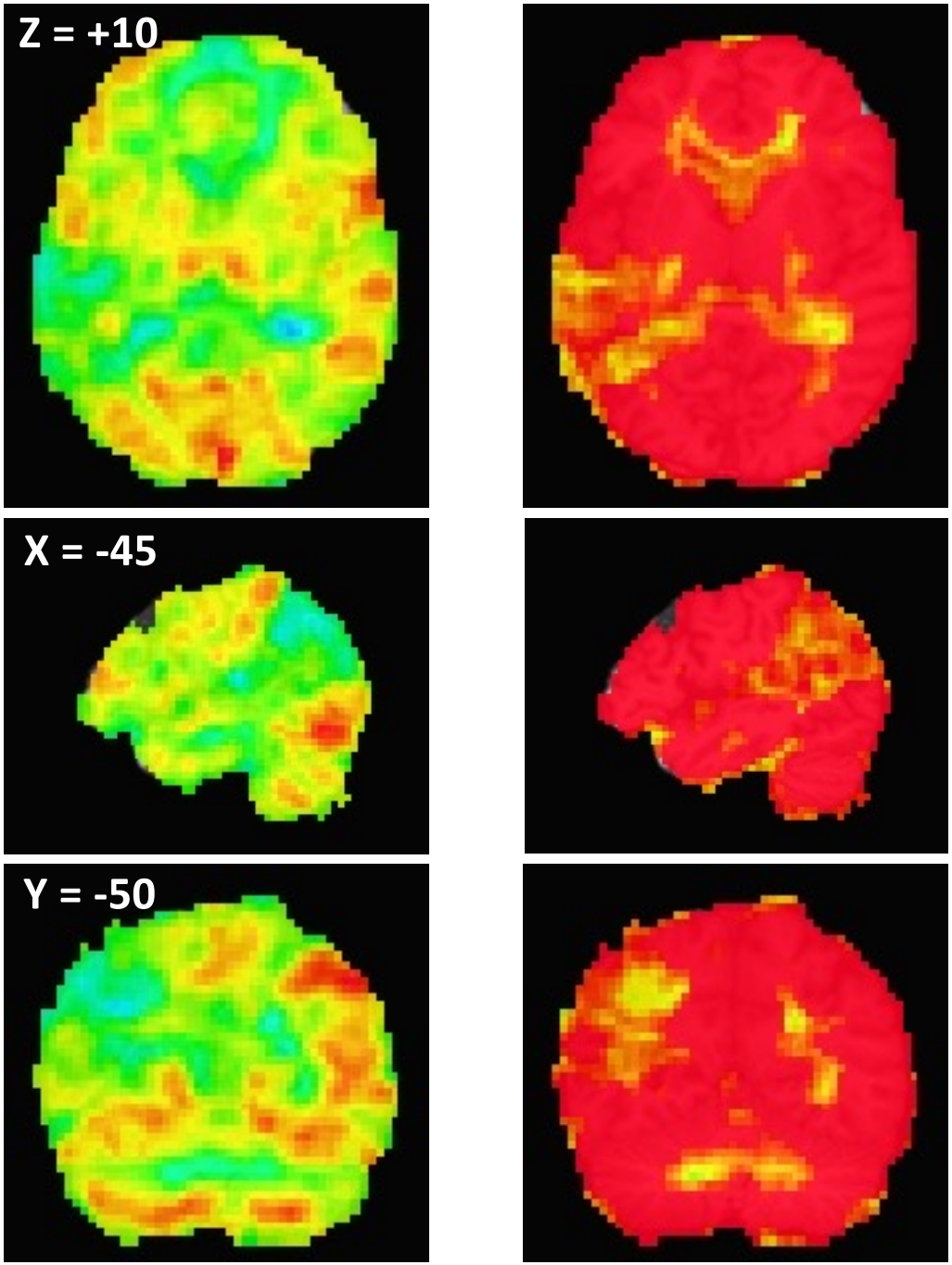


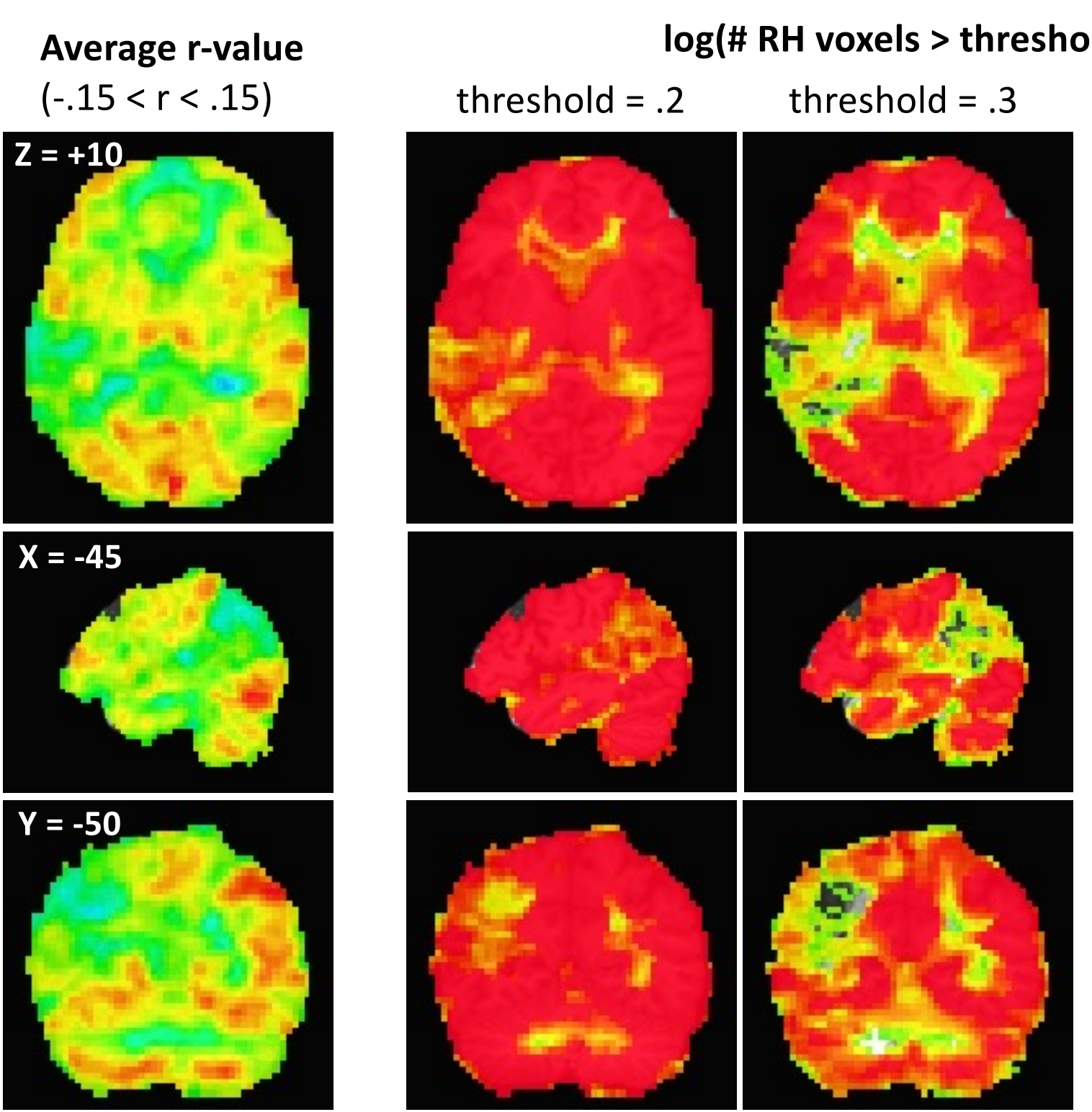


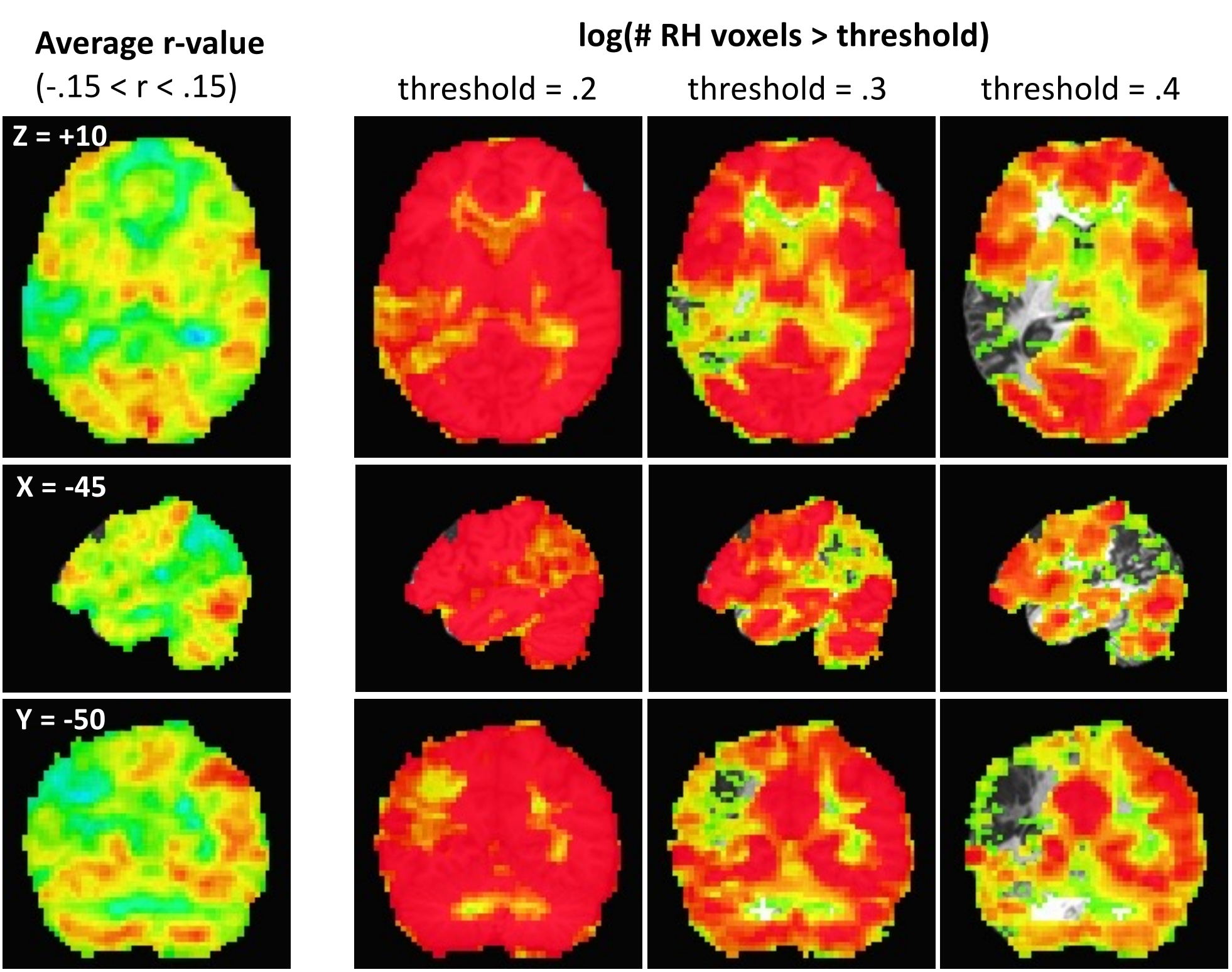
log(# RH voxels > threshold)

Average r-value
(-.15 < r < .15)

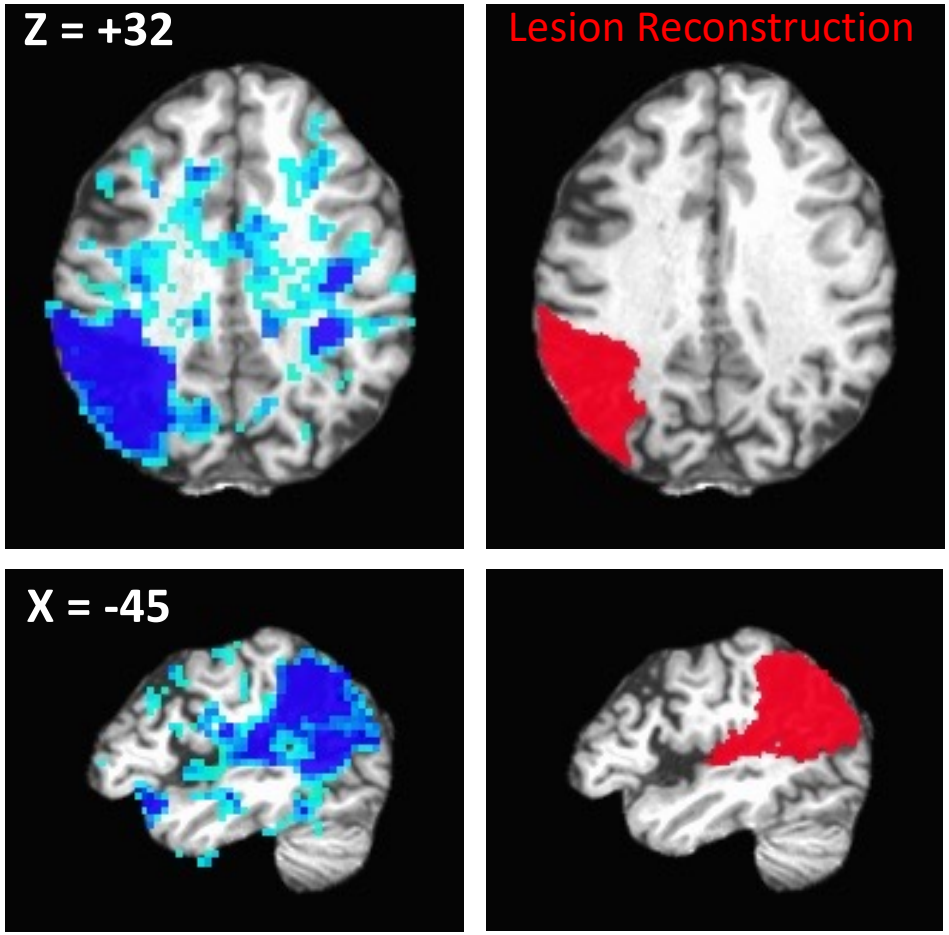
log(# RH voxels > threshold)
threshold = .2

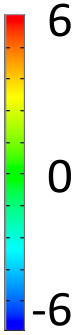



Average r-value
(-.15 < r < .15)
log(# RH voxels > threshold)
threshold = .2
threshold = .3
Z = +10
X = -45
Y = -50


Average r-value
(-.15 < r < .15)
log(# RH voxels > threshold)
threshold = .2
threshold = .3
threshold = .4
Z = +10
X = -45
Y = -50

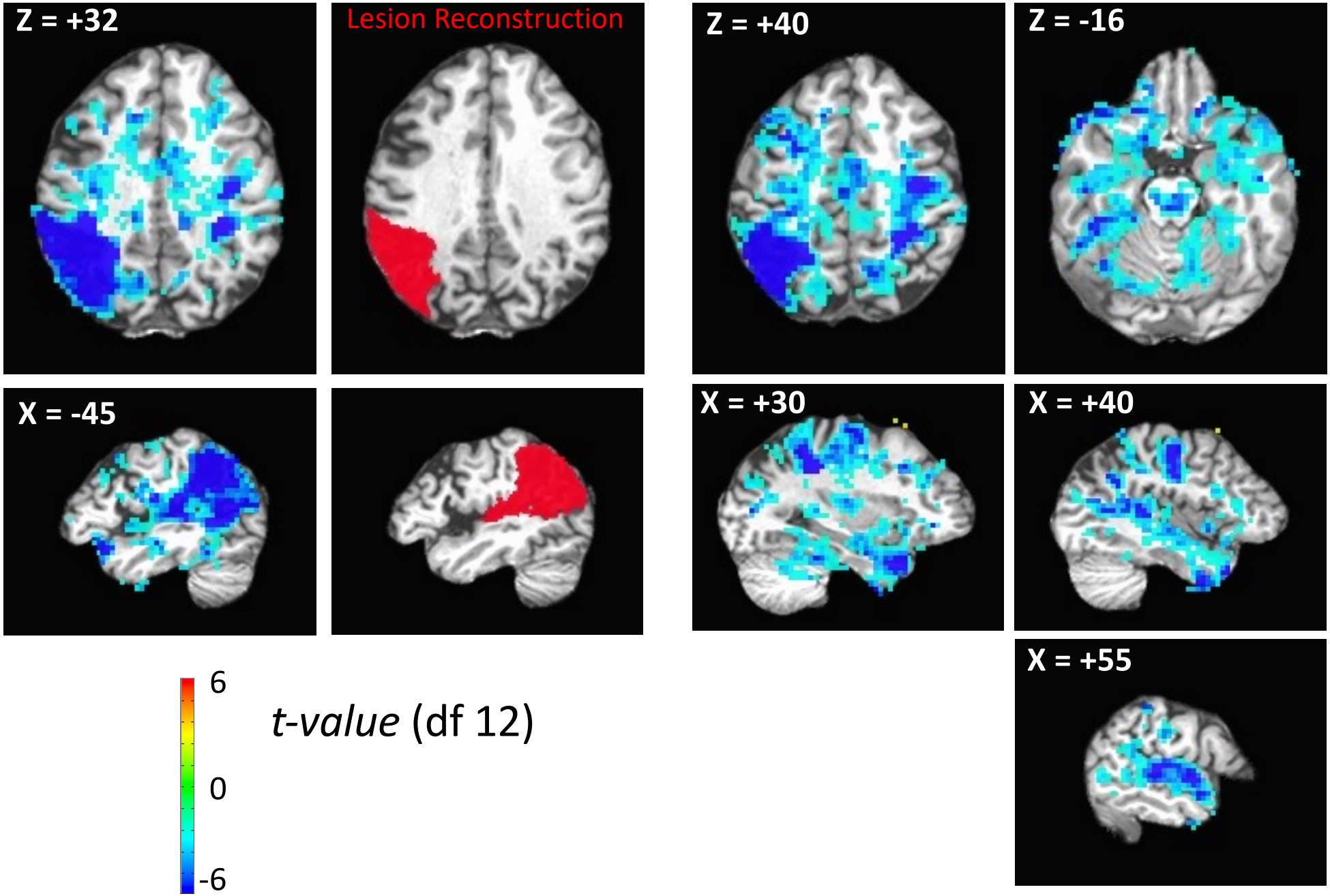
Example Patient < Penn Controls (p<.05, corrected)





t-value (df 12)

Example Patient < Penn Controls (p<.05, corrected)



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- fMRI Connectivity can be used to map large scale brain organization
- Individual variation in cognitive abilities (e.g. verbal, visual) and in patient symptoms is also reflected in connectivity measures
- Each of these phenomena demonstrates not only *reliability* of resting-state correlations, but ***validity*** - and they are most likely based in real neural covariation