Structural And Functional Integration:

Why all imaging requires you to be a structural imager

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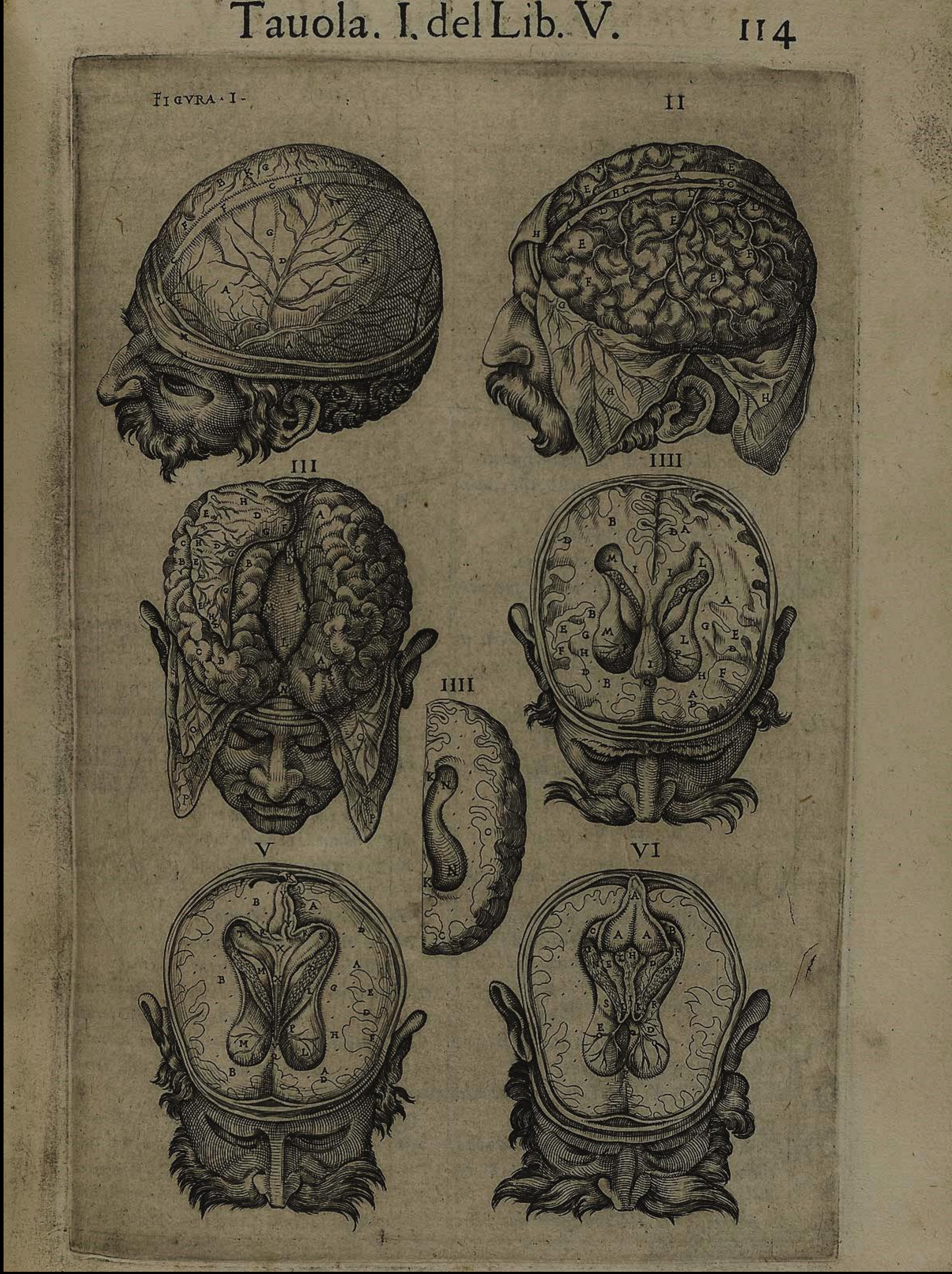
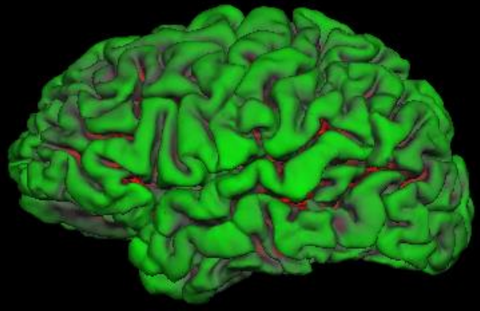
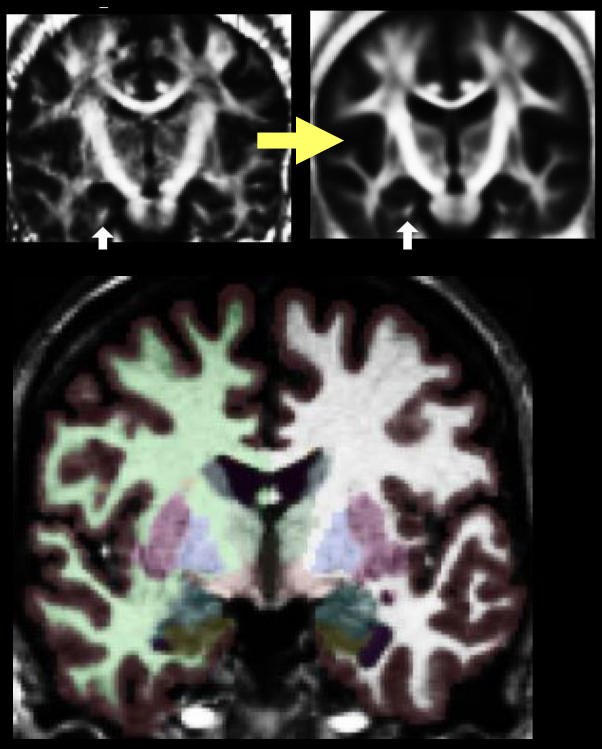


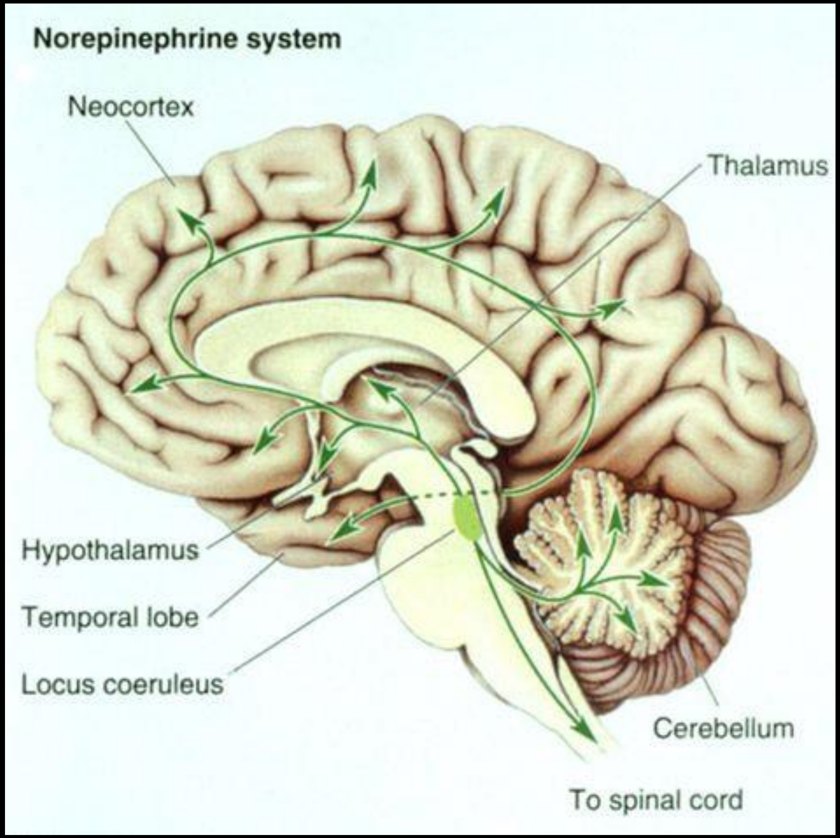
Structural Information is Critical for Functional (or other) research

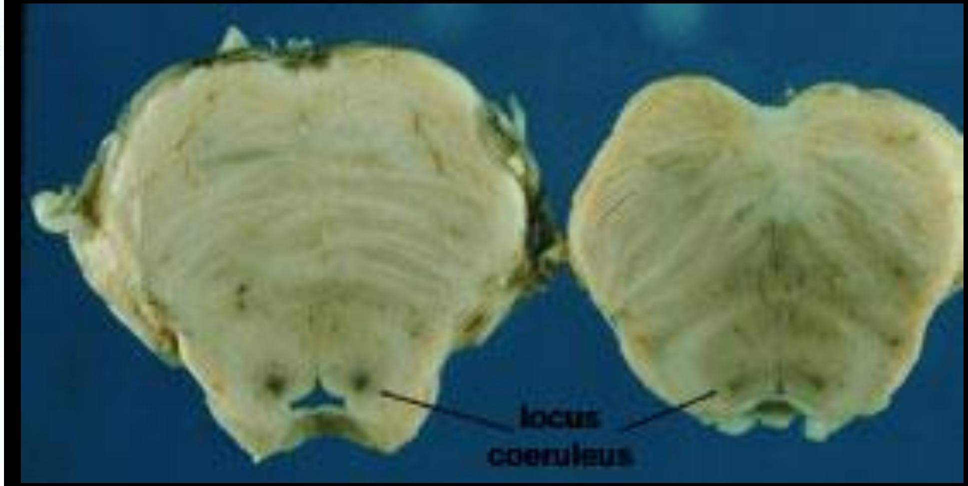
- Functional analysis is potentially critically flawed or severely limited without structural information.
- Structural data is necessary for:
  - visualization of functional data (view data on an easy to interpret representation of the brain)
  - spatial normalization of functional data (match anatomical locations across subjects)
  - region of interest analysis of functional data (sample data from a specific area of the brain)
  - Correction of measurement error (e.g. partial volume)
  - integrated functional analysis (e.g. volume analysis/anatomical descriptions)





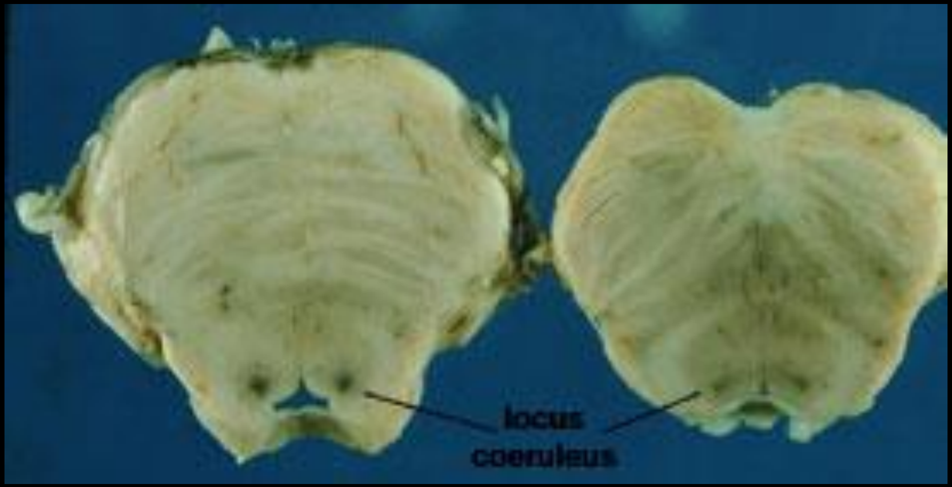
What is the locus coeruleus?





Why Is Structure/Anatomy Critical?

Structure to a large degree dictates what can be done functionally:



- How big are your voxels?
- How much smoothing?
- Physiological contamination?
- How big is your effect?

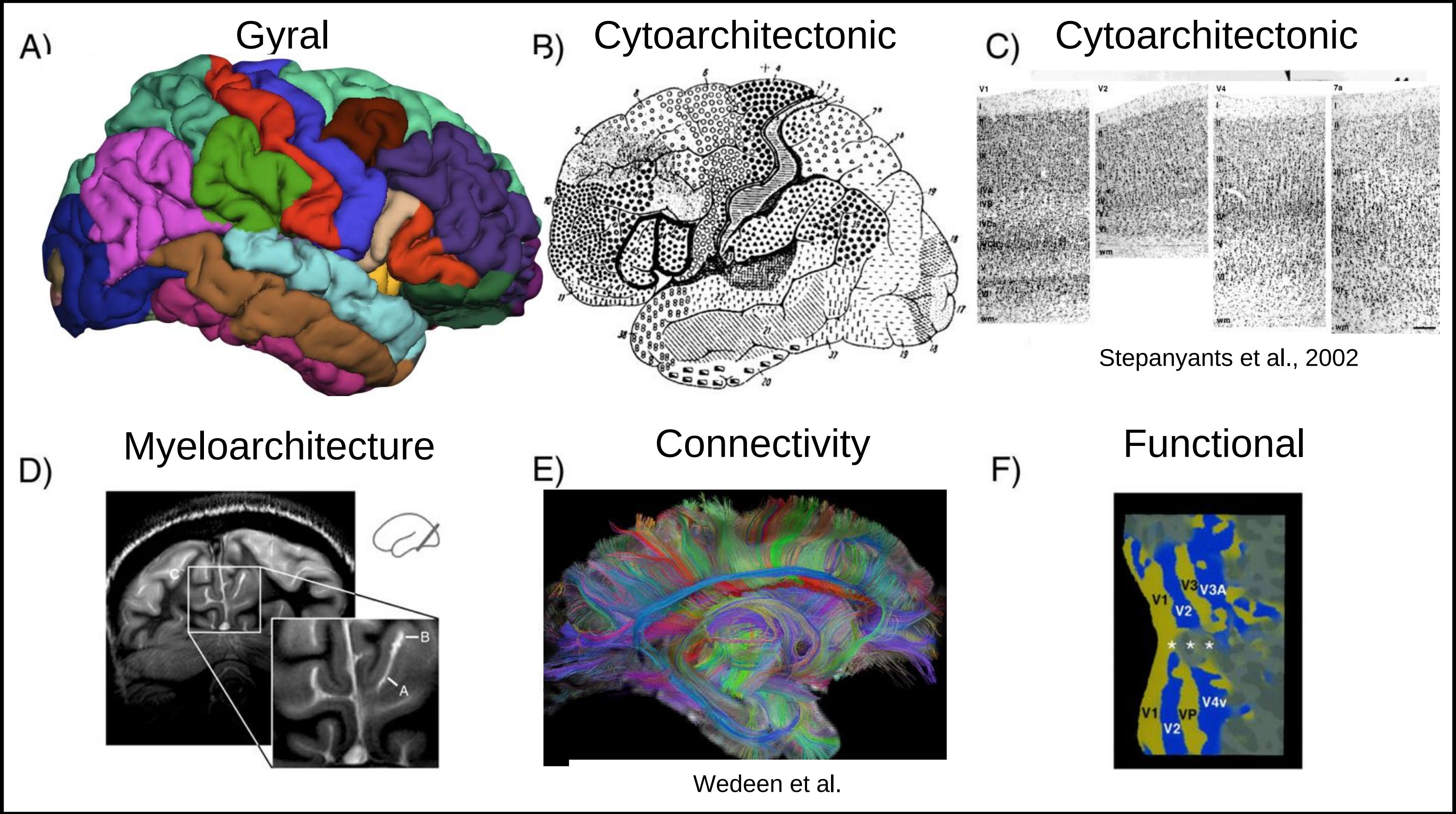
Why Is Structure/Anatomy Critical?

- Accurate localization of functional results
  - Precision of localization is key to any interesting functional study
  - Don’t just say ‘dorsolateral prefrontal cortex’
  - Know your limitations (small structures, big voxels; ventricular borders, etc.)
- Understanding the contributions of structural changes to fMRI results in health and disease
  - Are functional changes associated with tissue degeneration within a brain structure?
  - Controlling for group biases/confounds due to structural changes
- Clinical procedures
  - Structural measurements are useful clinically, independent of functional integration (volume/lesion studies)
  - Localization of vital regions of the brain to *avoid* in neurosurgical procedures

Why is integration of anatomical and functional data difficult?

- Various levels of neuroanatomy: gyral, functional, cytoarchitectonic, neurochemical, gene expression, etc.
- Accurate models of the brain are difficult to create
- Differences in distortions/geometry across imaging domains
  - Distortion correction (acquisition/processing)
- Biological variability in anatomy across individuals

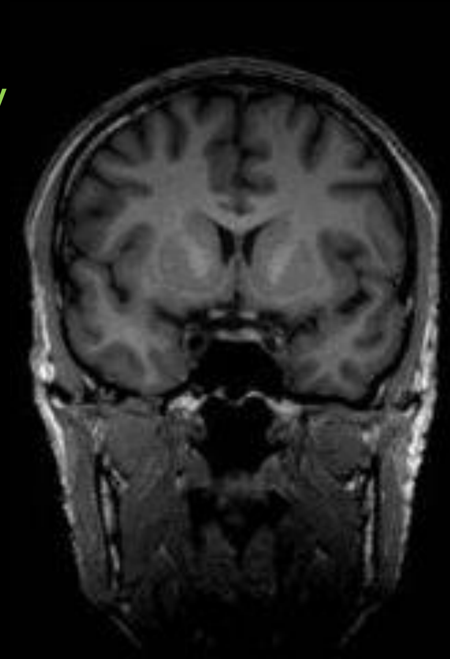
Levels of Anatomy

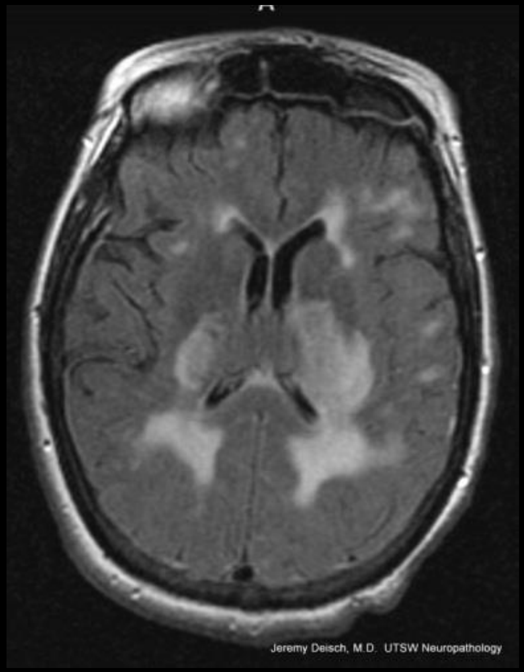


Modified from Devlin and Poldrack, *Neuroimage*, 2007

Commonly Used MR Sequences

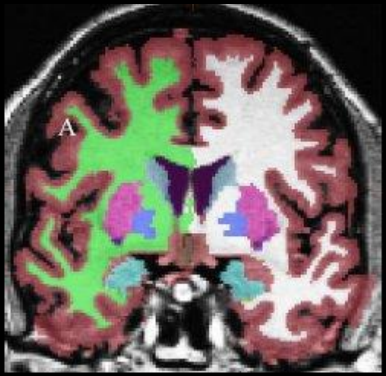
- Anatomy/structure AND pathology
- T1-weighted imaging: Good contrast for gray matter/white matter; useful in segmentation of cortex and deep/subcortical gray matter
- T2/FLAIR imaging: Good contrast for segmentation of altered brain tissue such as white matter signal abnormalities (WMSA; hyperintensities; hypointense on T1, but less sensitive)
- Diffusion imaging: Good contrast for anatomy of white matter fascicles (bundles) projecting across neural regions/microstructural properties

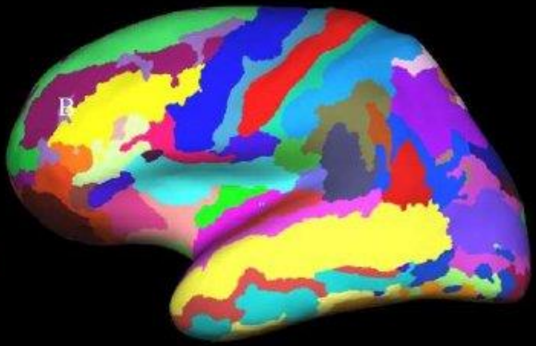


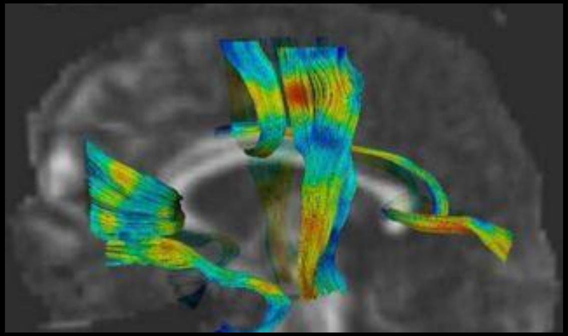


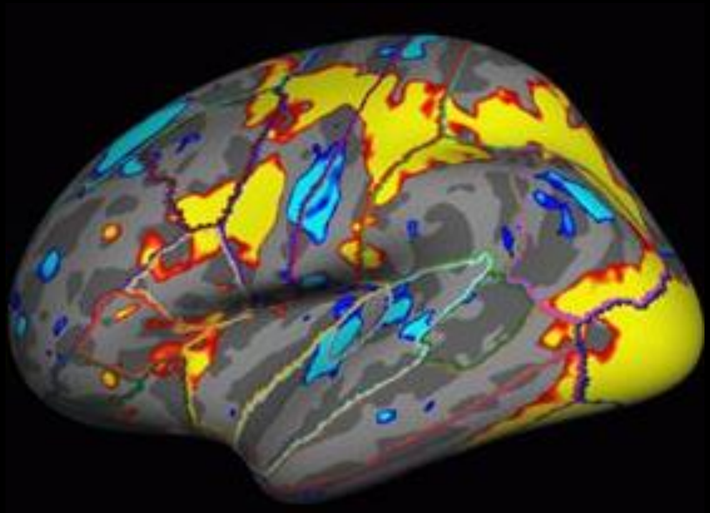
Types of ‘anatomical’ information extracted from MRI data

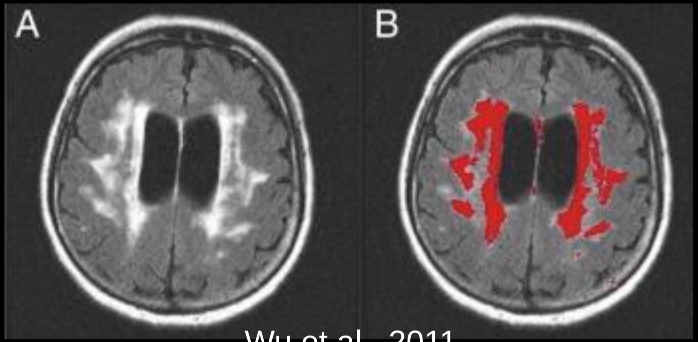
- Segmentations (extraction of specific structures) brain, cortex, white matter, deep brain structures
- Cortical surface models
- Cortical parcellation (division of the cortex)
- White matter fascicles
- Lesions
- fMRI regions of activation





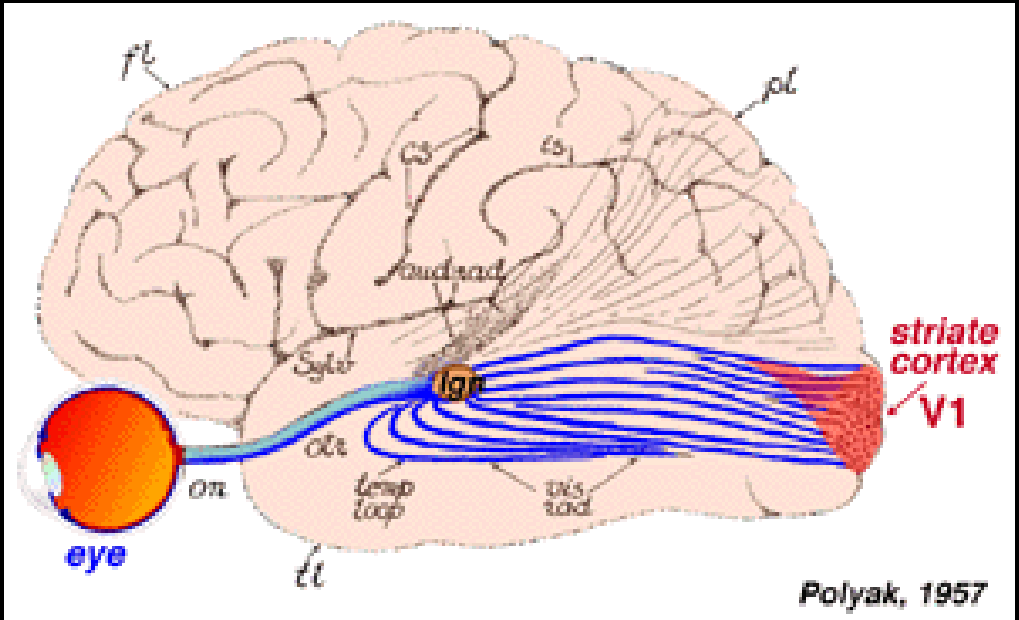


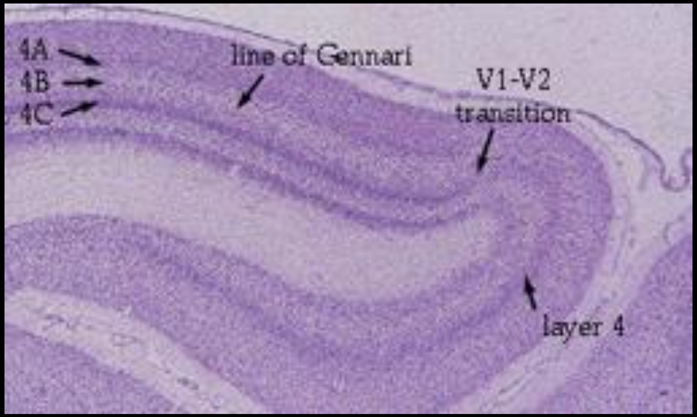


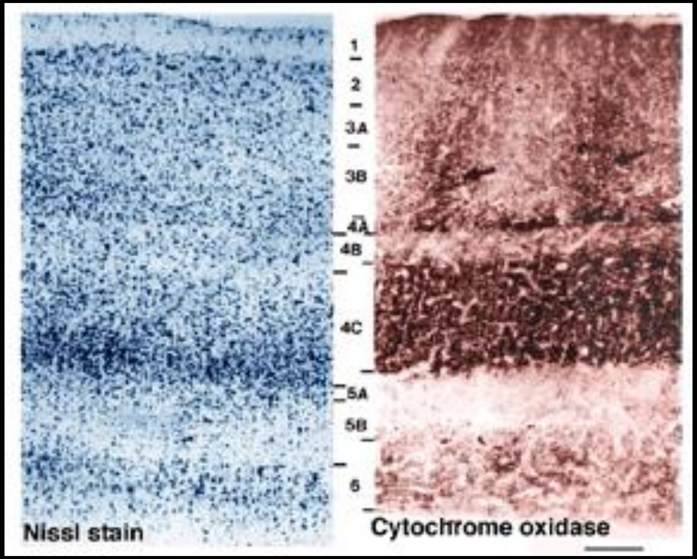


Wu et al., 2011

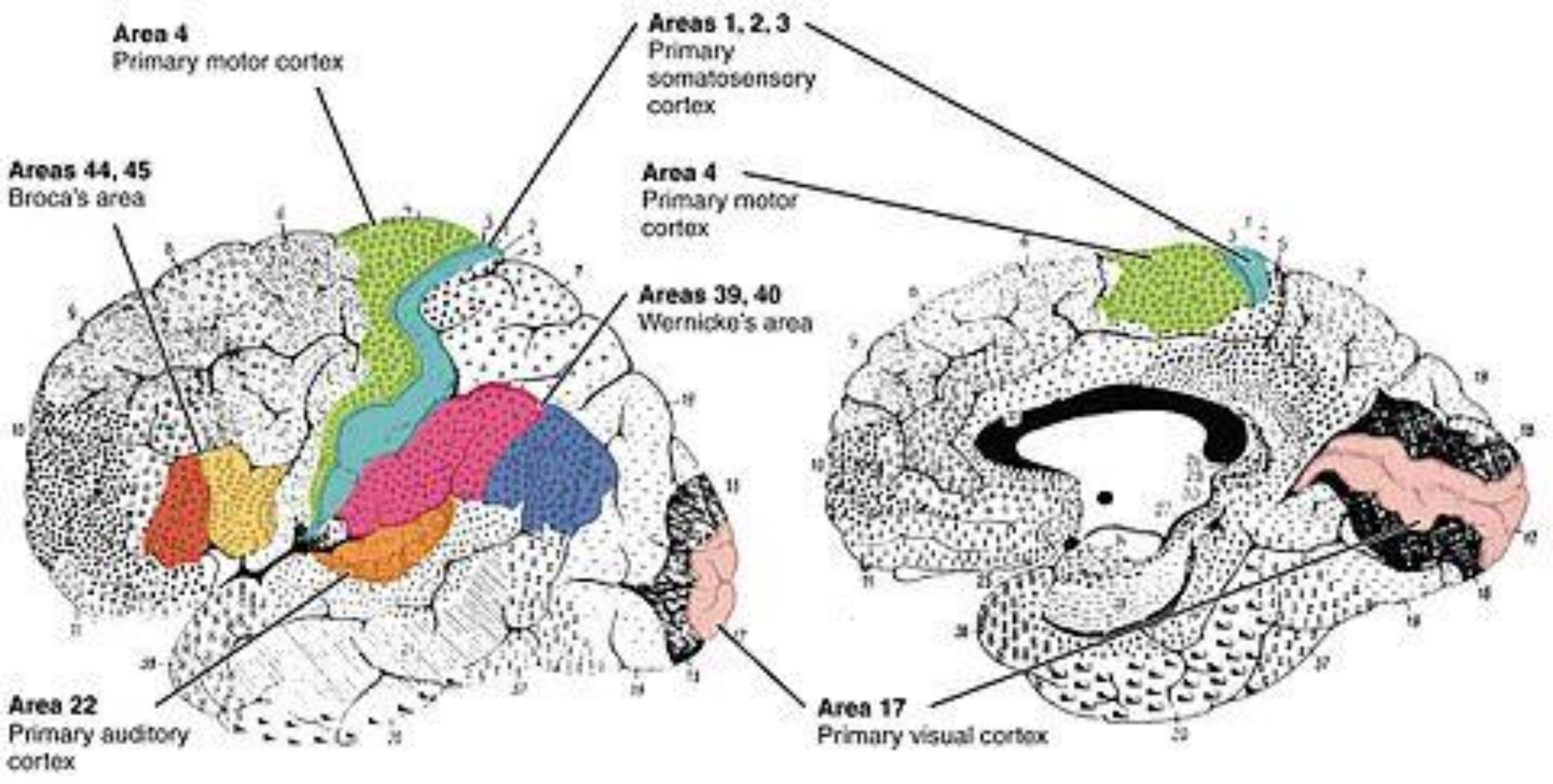
How is Structure Related to Function?







Brodmann: Primary Visual Cortex



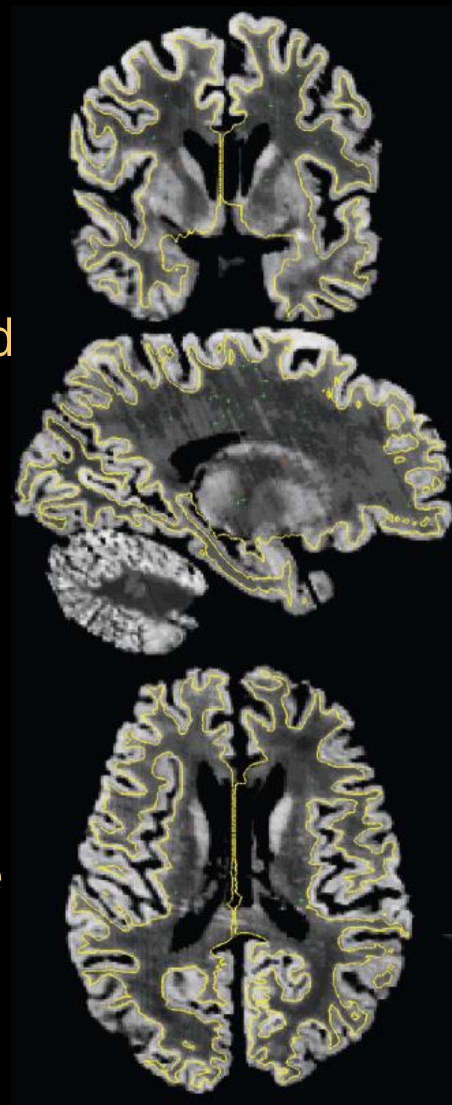
Brodmann's cytotechtonic map (1909): Lateral surface

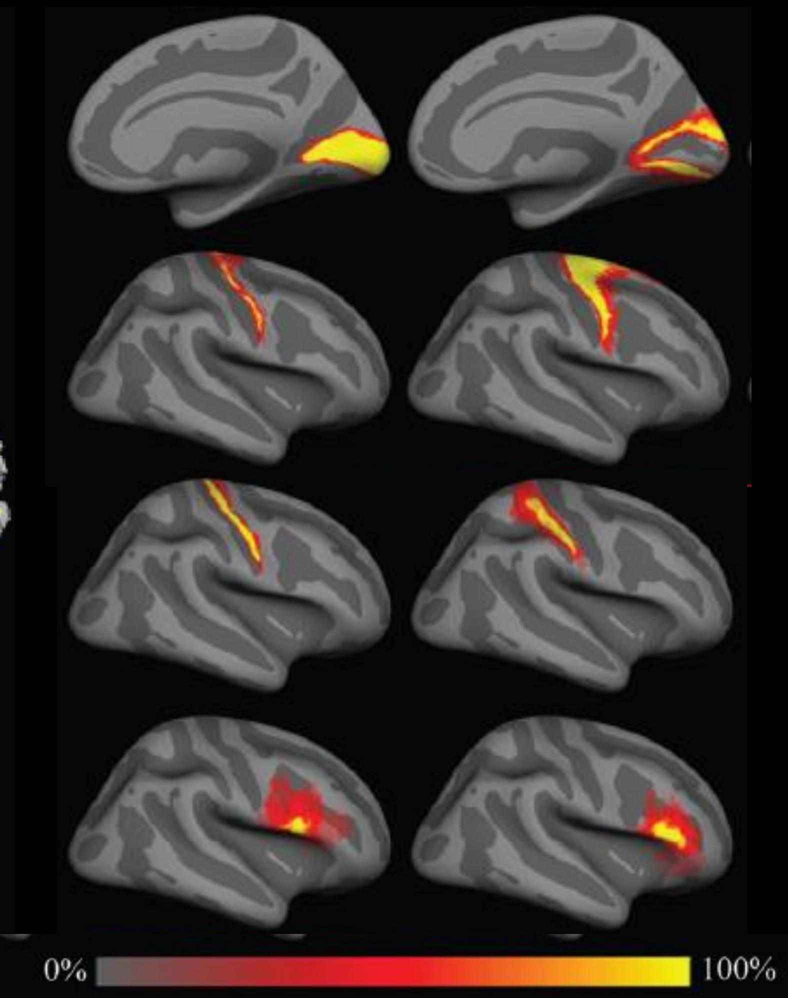
Brodmann's cytotechtonic map (1909): Medial surface

How is Structure Related to Function?

(Can folds predict cytoarchitecture?)

- *Ex vivo* imaging for creation of surface models
- Cytoarchitectonic borders defined with histology and mapped to surface models
- Cytoarchitecture showed good correspondence with folds, particularly in primary/secondary areas
- Some limitations of MR for defining microanatomy can be overcome by good macroanatomy





Fischl et al., *Cerebral Cortex,* 2008

How is Structure Related to Function?

(Can connectivity predict function?)

- Cortical connectivity can be used to segment the nuclei of the thalamus
- Connectivity based segmentation of thalamic nuclei validated through correspondence to functionally distinct regions
- Several ways to define anatomy with imaging

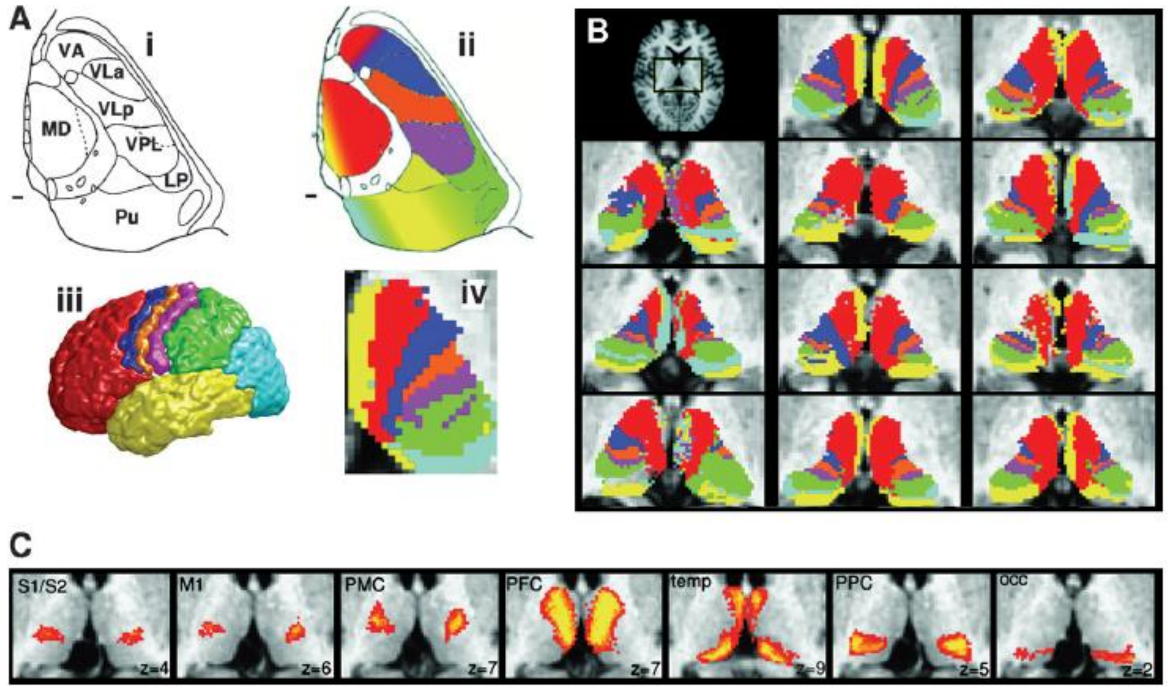
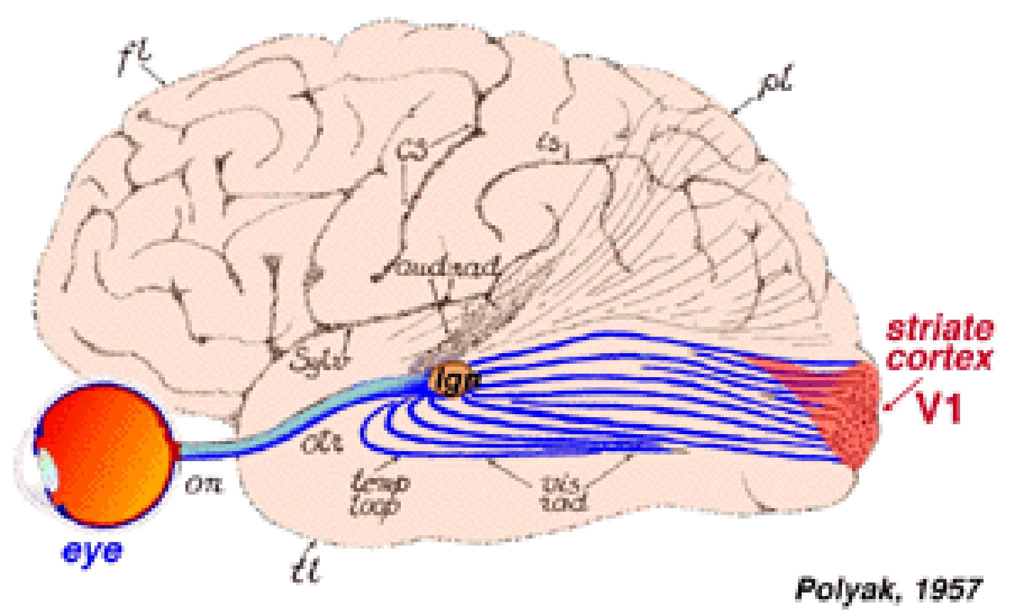


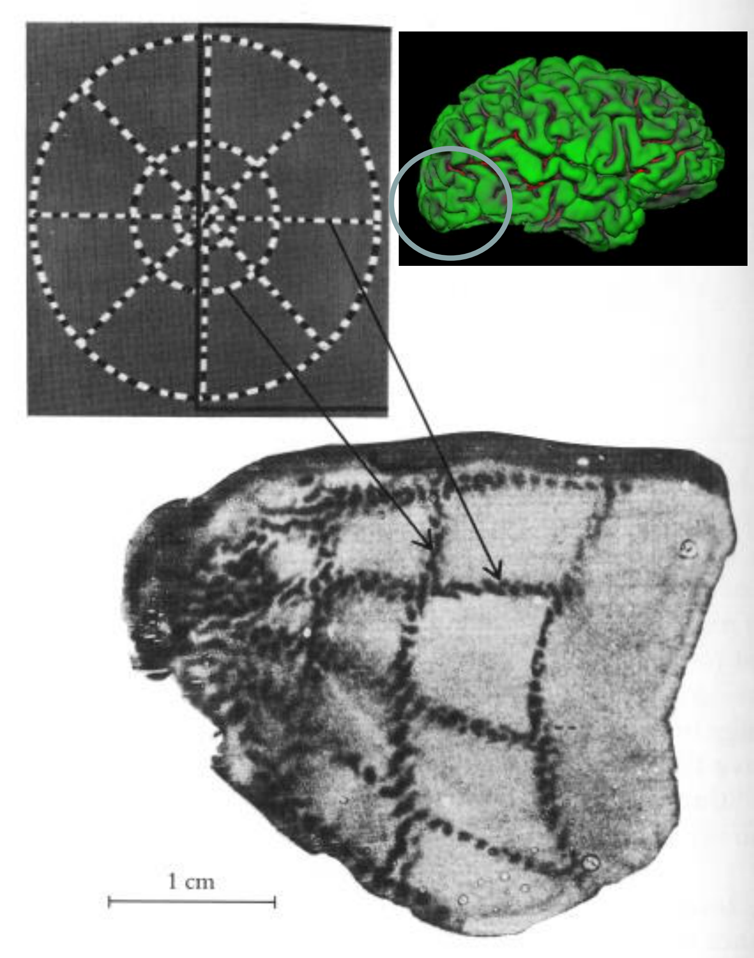
Figure 1. Individual variation of connectivity-based thalamic segmentation. (*A*) Segmentation of the human thalamus. (*i*) Axial thalamic section from a cytoarchitectonic atlas (Morel *et al.*, 1997). (*ii*) In the same atlas section, major nuclei have been coloured according to their major cortical connection site (as in iii). (*iii*) Cortical subdivisions. Red = PFC; blue = PMC; orange = M1; magenta = S1/S2; green = PPC; cyan = occipital; yellow = temporal. (*iv*) Connectivity-based parcellation of the thalamus in a single subject for an axial slice at the same level as the section in *A* and *B*. Voxels are coloured according to the cortical region with which they show the highest connection probability (as in *iii*). (*B*) Connectivity-based segmentation of the thalamus in eleven subjects. Top left panel indicates location of axial thalamic slices. Each subsequent panel represents data from an individual subject. Thalamic voxels colour coded as in *Aiii*. (*C*) Group probability maps. Axial images showing overlap of thalamic sub-regions across subjects in voxels showing >25% probability of connection to selected cortical mask (indicated in top left of each image) using a colour scale running from red (4/11 subjects) to yellow (11/11 subjects). Slices are taken at the average *Z*-coordinate (given in bottom right of each image) across the left and right hemispheres for the centre of gravity of that cluster.

Johansen-Berg et al., *Cerebral Cortex*, 2005

Retinotopy

- Presentation of spoke image to macaque
- Measure metabolism using 2DG technique on flattened visual cortex

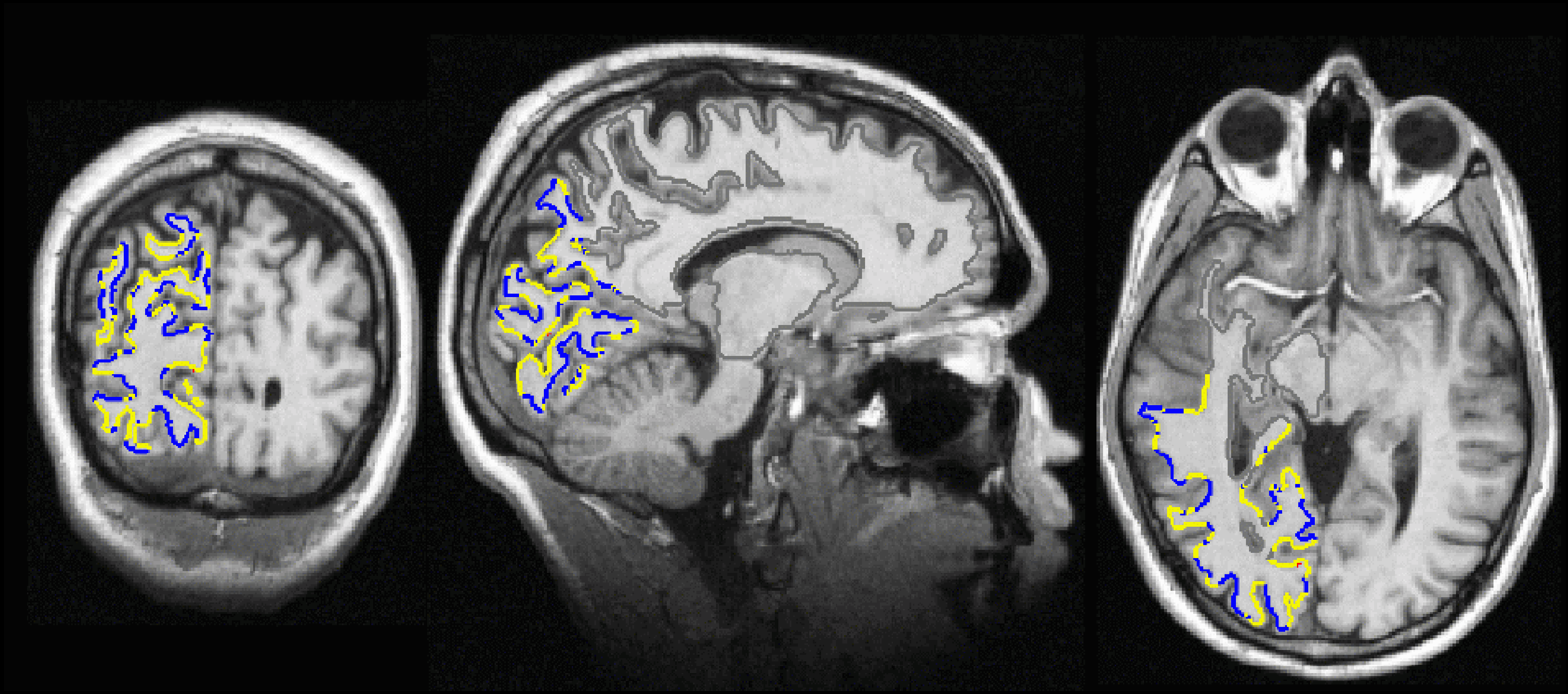




Tootell, 1982

Slice Based Visual Organization

Spatial organization of the fMRI response to visual stimuli in occipital cortex

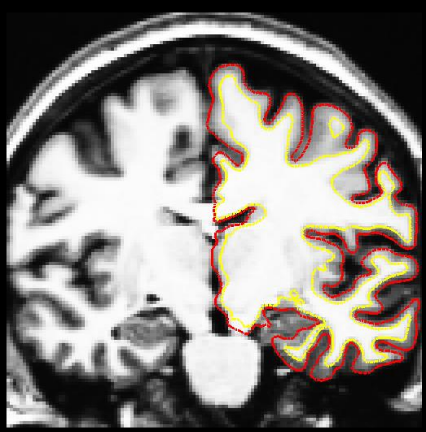


Fischl et al.

Cortical Surface Model, Inflated, Flattened

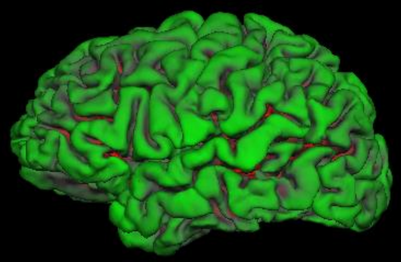
- Model created of the cortical mantle, computationally manipulated for inflation, cutting and flattening

Surface Boundaries

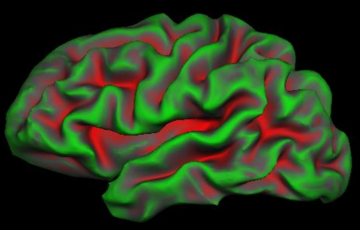


High quality structural data

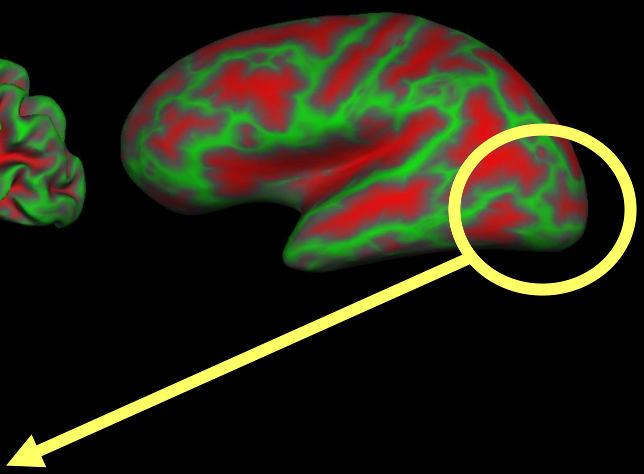
Folded



Semi-inflated



Inflated



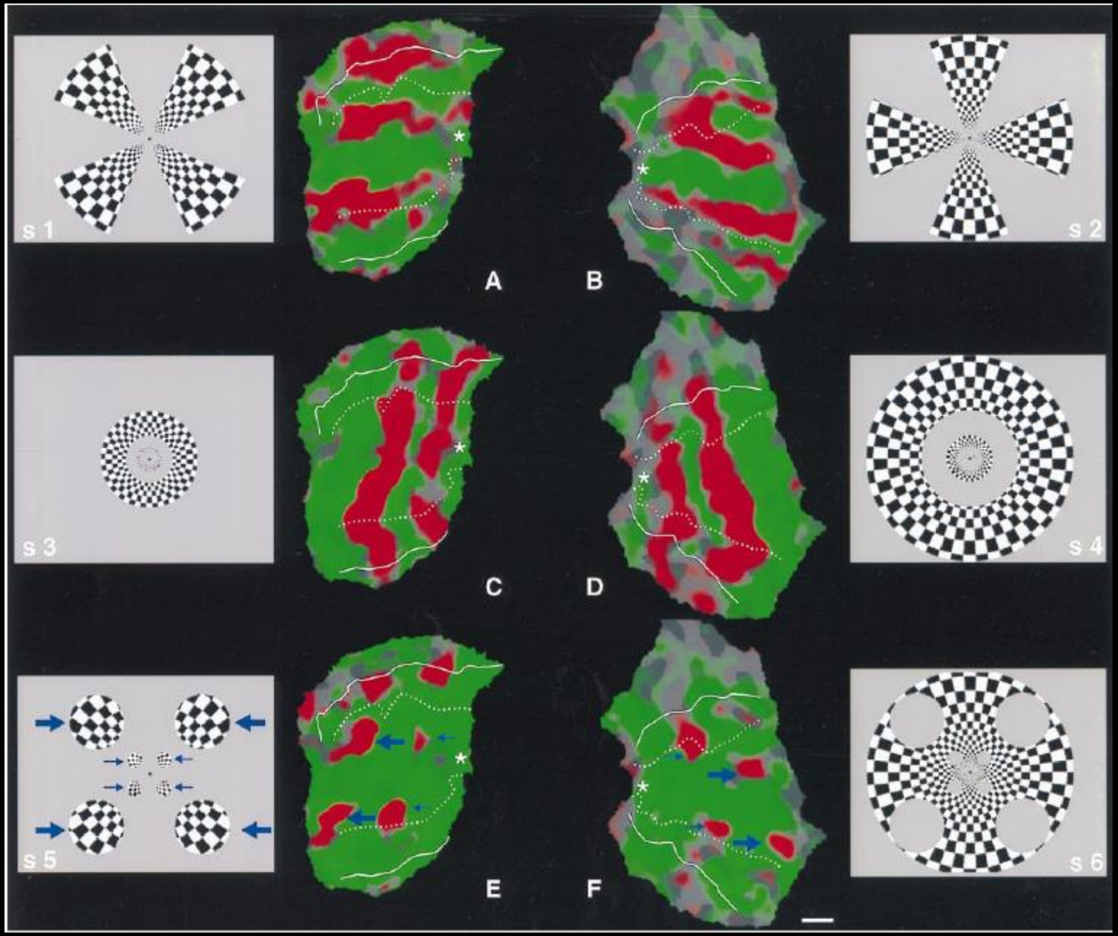
Cut and flattened
for visualization

Occipital Flat Patch Retinotopy

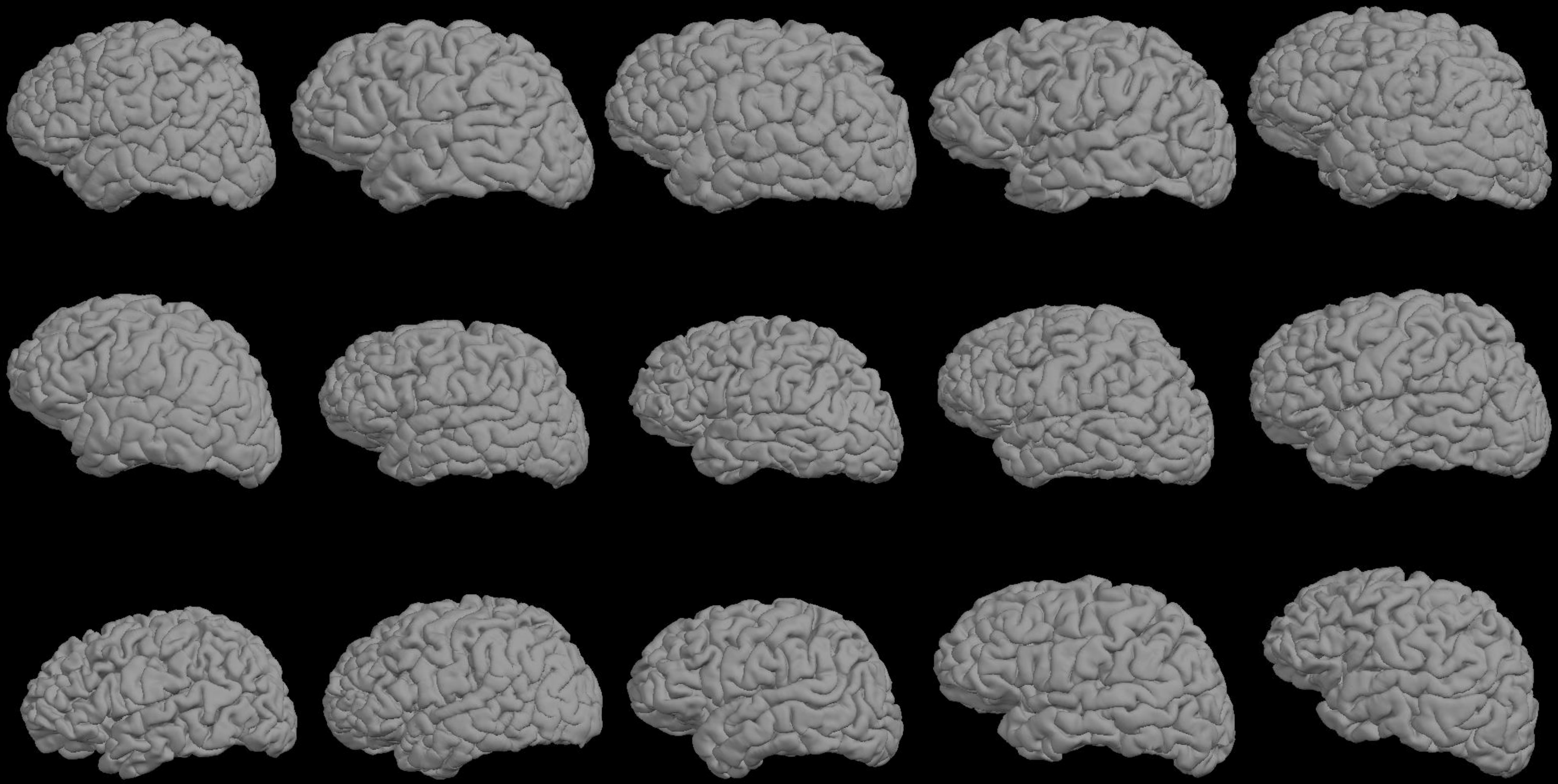
- Different patterns presented to the visual field create different patterns of activity in occipital cortex
- “M-G-H”

Tootell et al., *PNAS,* 1998

Flat Patch of Occipital Cortex



Variability in Cortical Anatomy



Fischl, Sereno, Dale, Neuroimage, 1999; Fischl et al., Human Brain Mapping, 1999

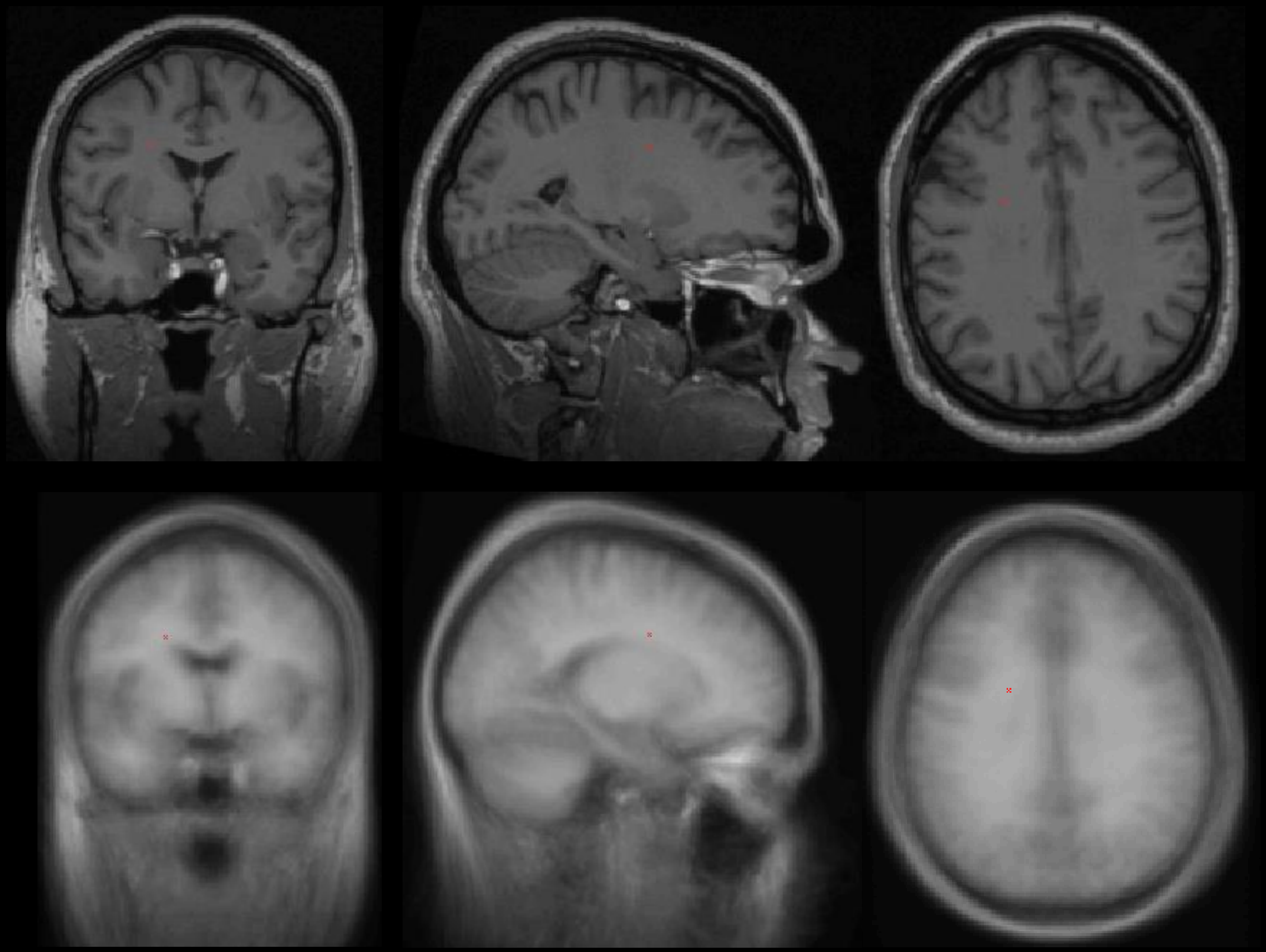
Various (imperfect) ways deal with anatomical variability

- Automated spatial normalization (typically whole-brain matching)
  - 'Best guess': morph structure from participant 1 to participant 2
  - What are the anatomical features?
- Individual labeling of regions/structures
  - Hippocampus may differ in shape and size, but has clear boundaries within individuals
- Functional localizer

Spatial Normalization: Affine/linear averaging

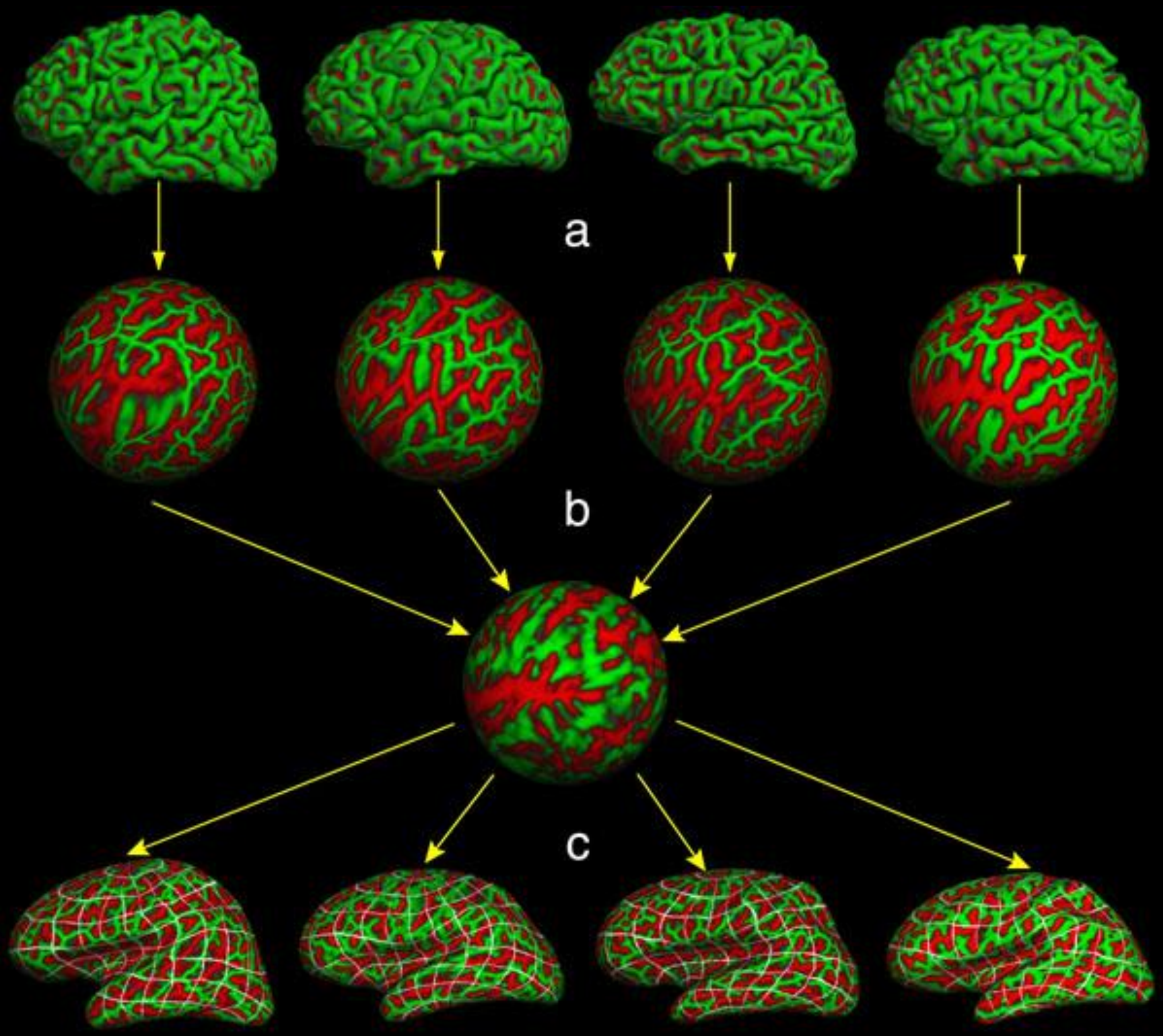
Single subject

Average of 40



Fischl et al.

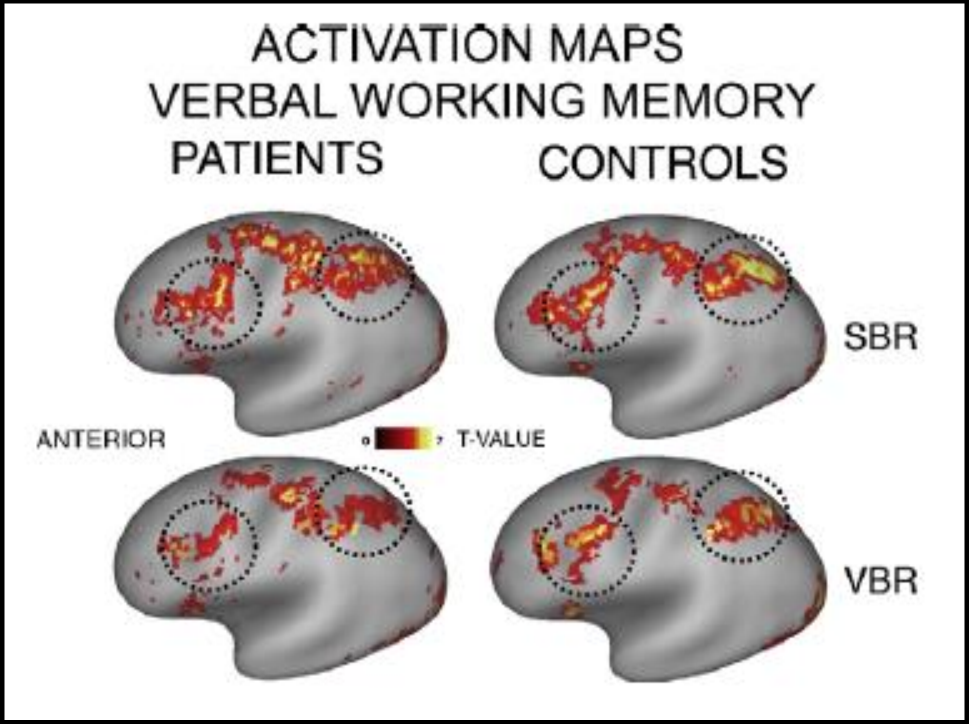
A Surface-Based Coordinate System



Fischl et al., Neuroimage, 1999; Fischl et al., Human Brain Mapping, 1999

Spherical Versus Volumetric Normalization

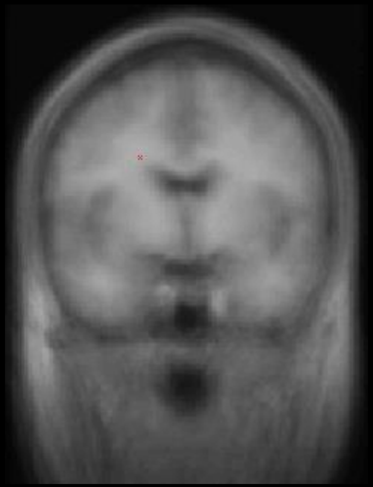
- Activations stronger in maps created from surface based averaging
- This demonstrates validity to the idea that function is somewhat predicted by structure (greater statistical power)
- Suggests that some limitations due to variability in anatomy can be overcome with good anatomical models/procedures

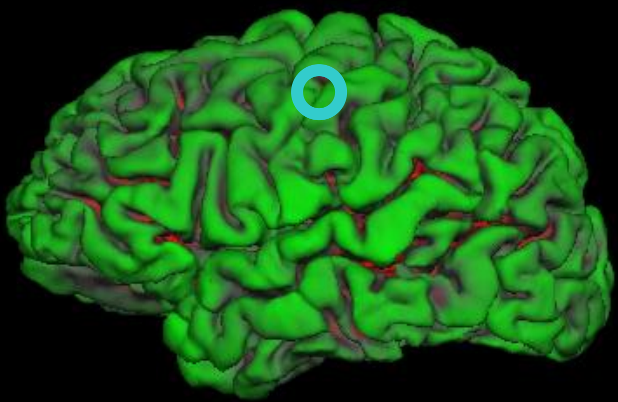


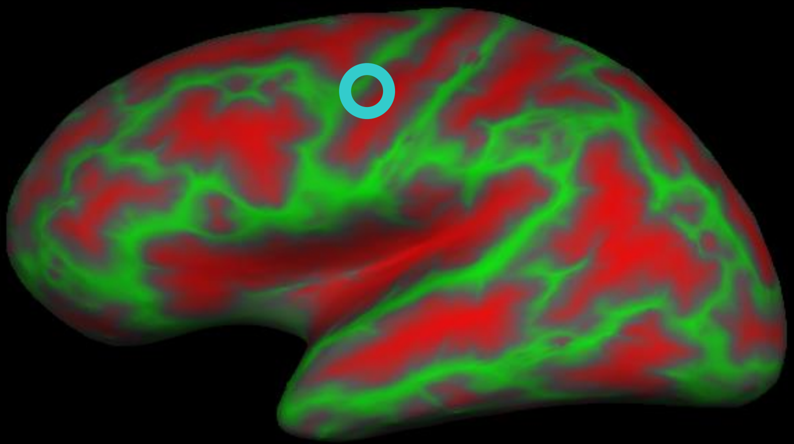
Anticevic et al., Neuroimage, 2008; See also Dasai et al., Neuroimage, 2005

Surface Smoothing

Limit smoothing to regions in close proximity on cortical surface





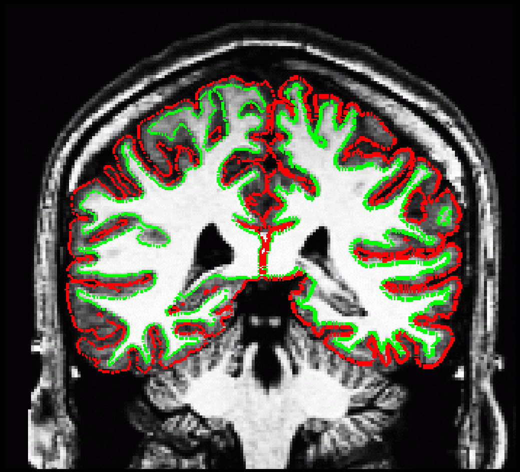


3D Spatial Smoothing: Combines information across gyral/sulcal boundaries

Surface Smoothing: Constrains the type of information included

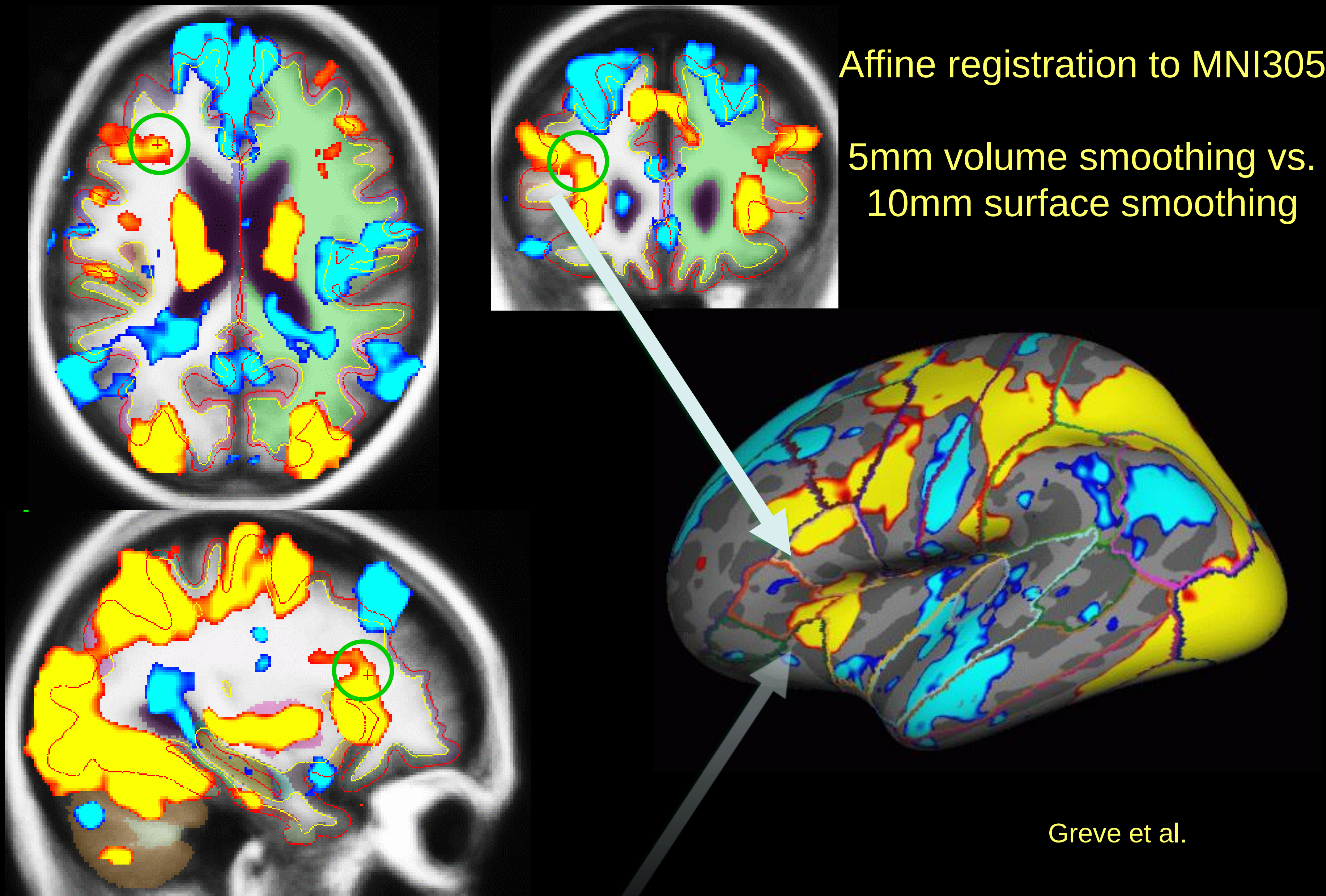
Spatial Smoothing

- 5 mm apart in 3D
- 25 mm apart on surface!
- Kernel much larger
- Averaging with other tissue types (WM, CSF)
- Averaging with other functional areas



Greve et al.

Good anatomy makes better function!



Affine registration to MNI305

5mm volume smoothing vs.
10mm surface smoothing

Greve et al.

Once you have a result, high quality atlases are important in localization

- General neuroanatomy
- Structures of Interest (hippocampus, cerebellum)
- ‘Talairach’ atlas commonly used: not really an atlas of neuroanatomy
- Anatomy should be confirmed for each given individual in a study (automated procedures for labeling individual anatomy exist)
- Template anatomy (using regional labels based on an atlas) can be confounded
  - Registration to the template
  - Disease associated changes

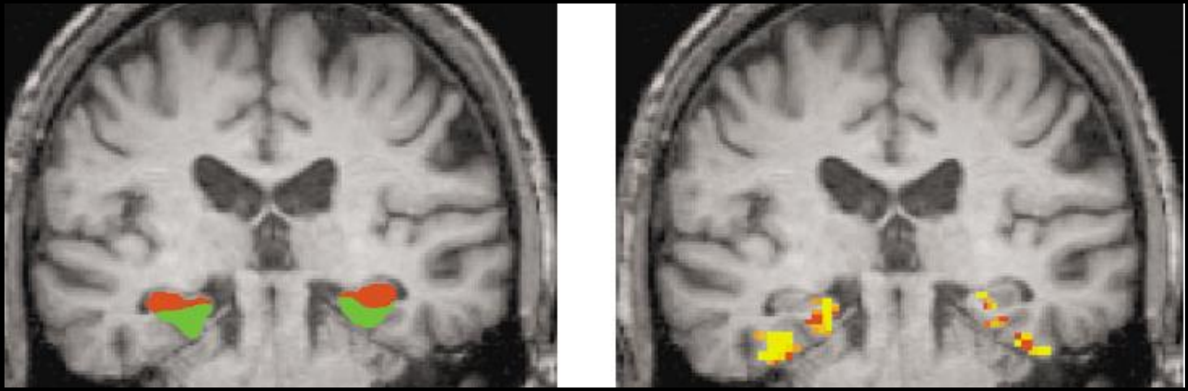
Region of Interest (ROI)

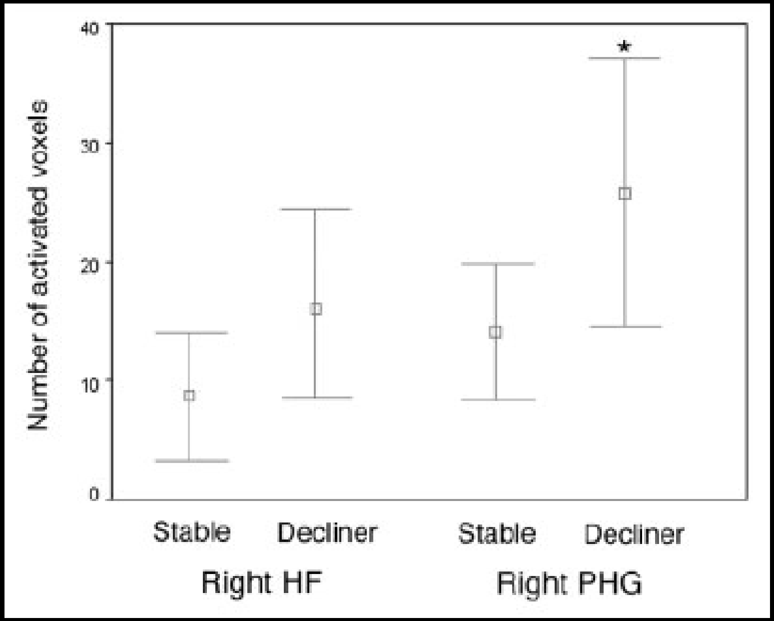
- ROI analysis is typically a *secondary* step
- Why ROI over maps?
  - Focused data exploration: plot data by condition for each individual/group
  - Control for statistical error by limiting measurements to *a priori* hypothesized regions
  - Limit testing to a defined region
  - Avoid circularity
  - Examine the association between the anatomical structure and function

See Poldrack, 2007

Hyperactivation in MTL in Preclinical Alzheimer's Disease

- Define a region based on *a priori* hypothesis/group results
- Demonstrated greater activation in individuals that subsequently declined in clinical status
- Result remained when statistically controlling for atrophy
- This type of structural control contributes to the validity and interpretation of the results



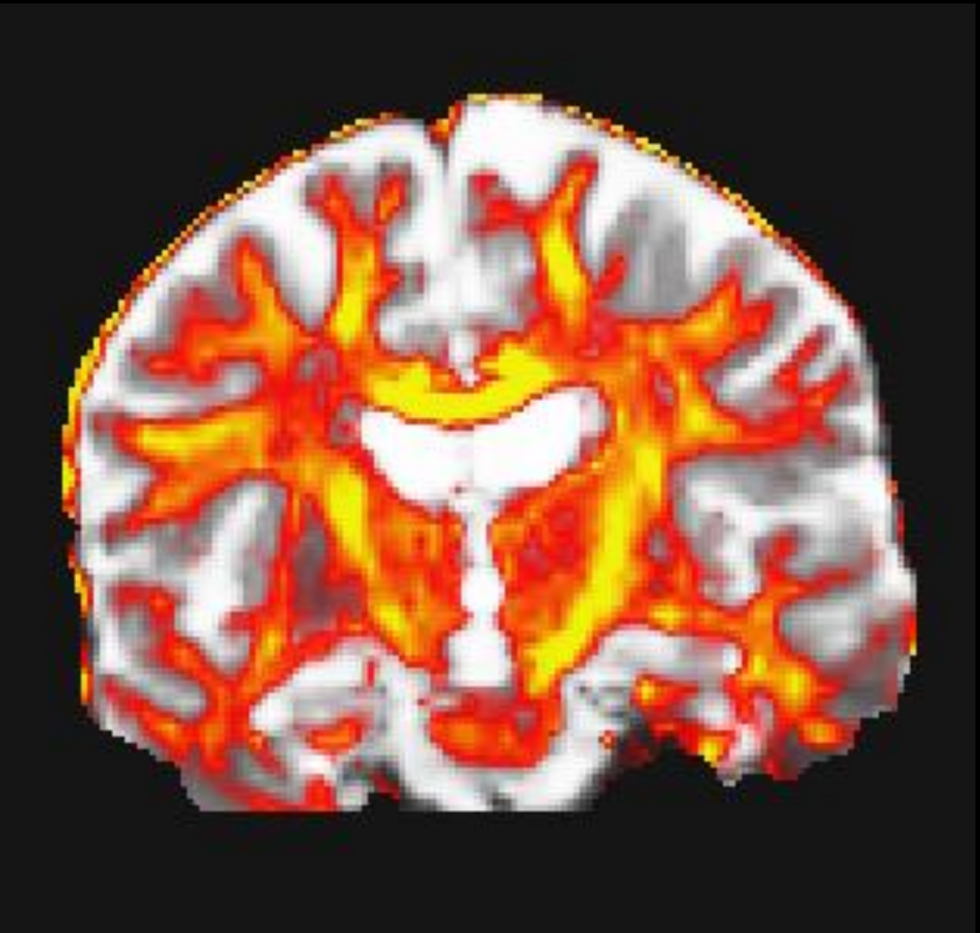


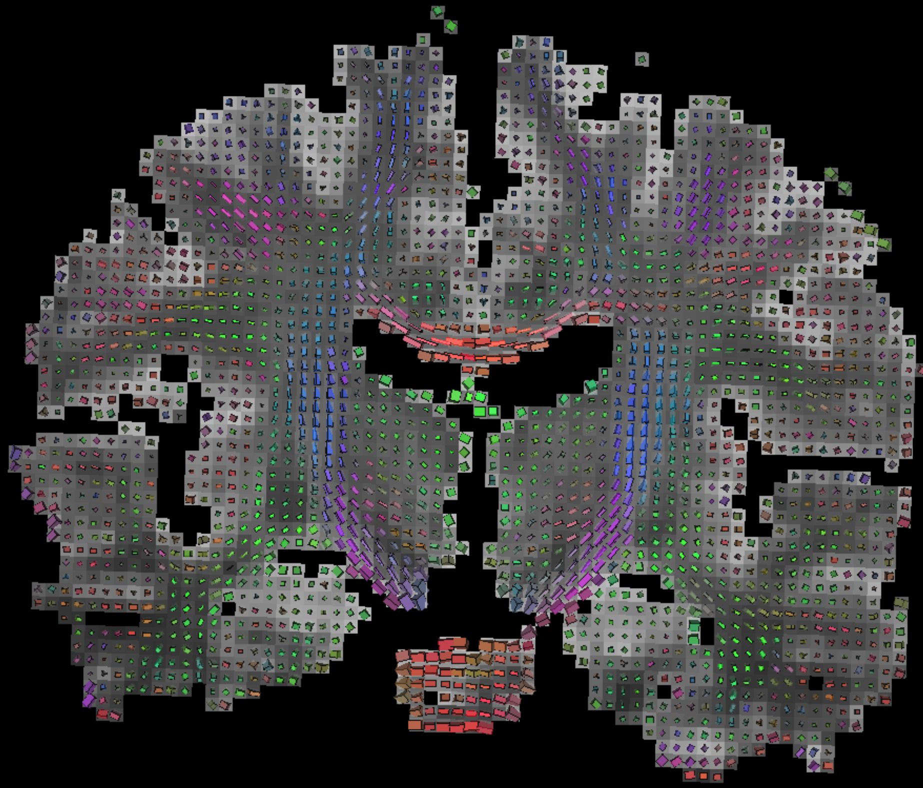
Dickerson et al., *Annals of Neurology*, 2004

Using Diffusion To Define Structure
(tissue properties/microstructure)

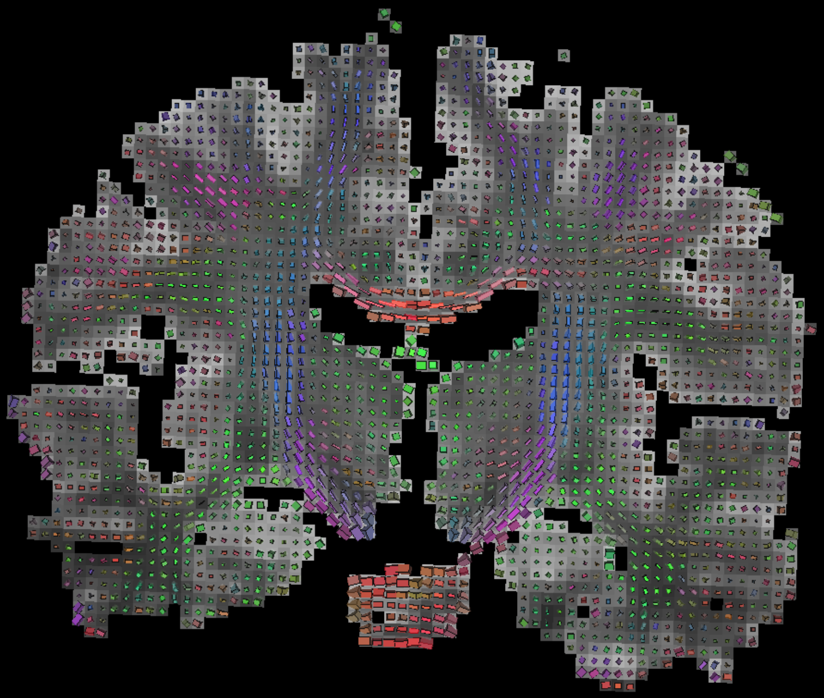
Tissue Integrity:
Fractional Anisotropy (FA); Diffusivity

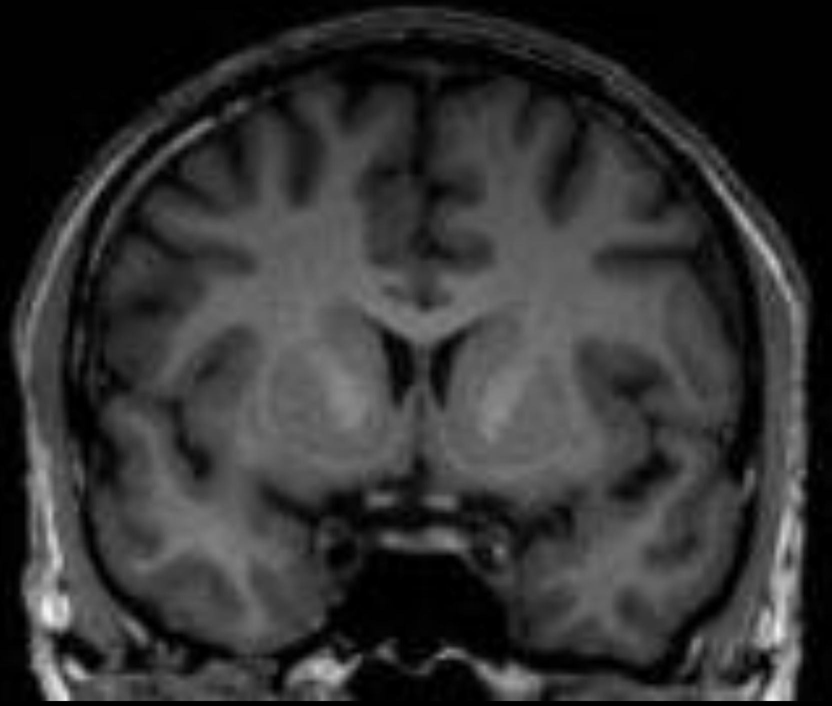
Tissue anatomy:
Tensormap; Tractography





Diffusion Properties can be used to Align White Matter Regions Across Individuals



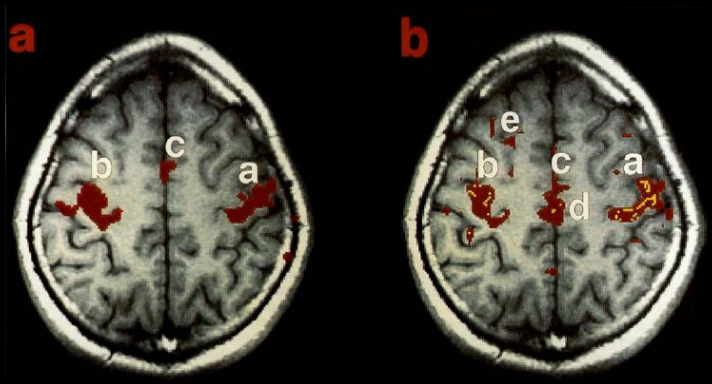


Diffusion Tractography
'Structural Connectivity'

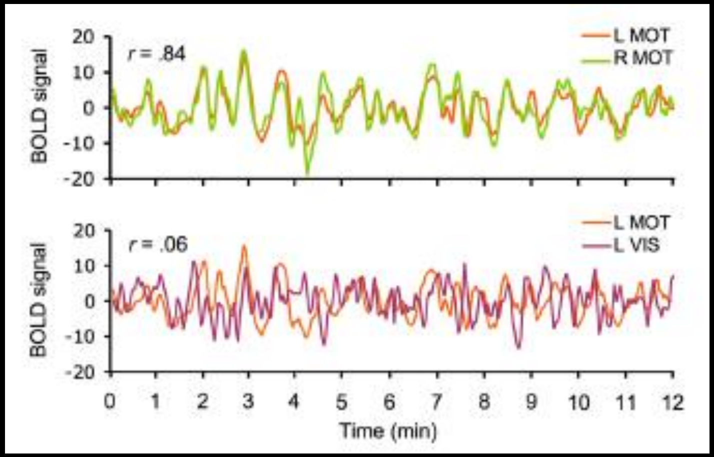
Is structural/connective integrity, determined by diffusion imaging, an important factor in functional activation?

‘Functional Connectivity’

- Correlated activity in specific ‘networks’ of the brain
- First demonstration of intrinsic activity correlations (Biswal et al., 1995)
- Lack of correlation between motor and visual cortex



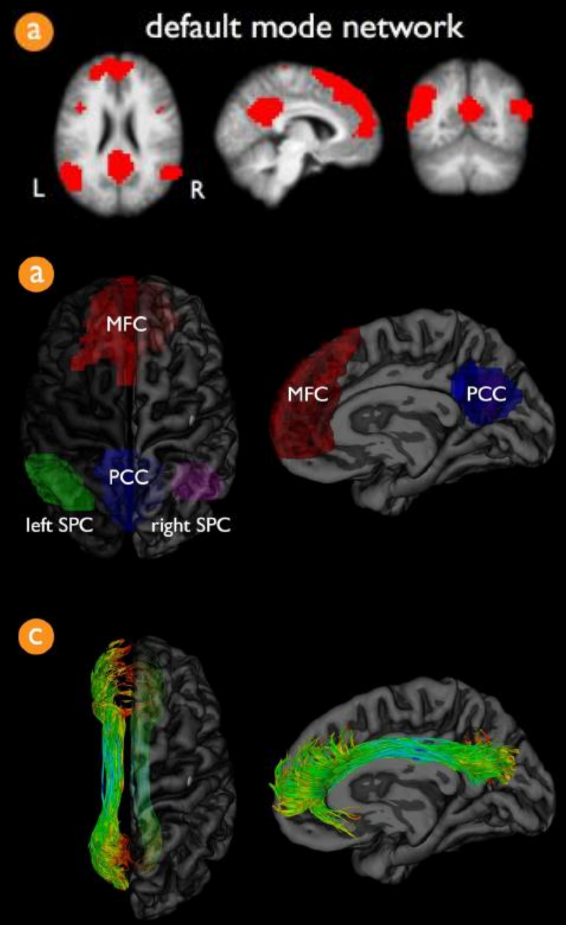
Biswal et al., 1995



Van Dijk et al., 2010

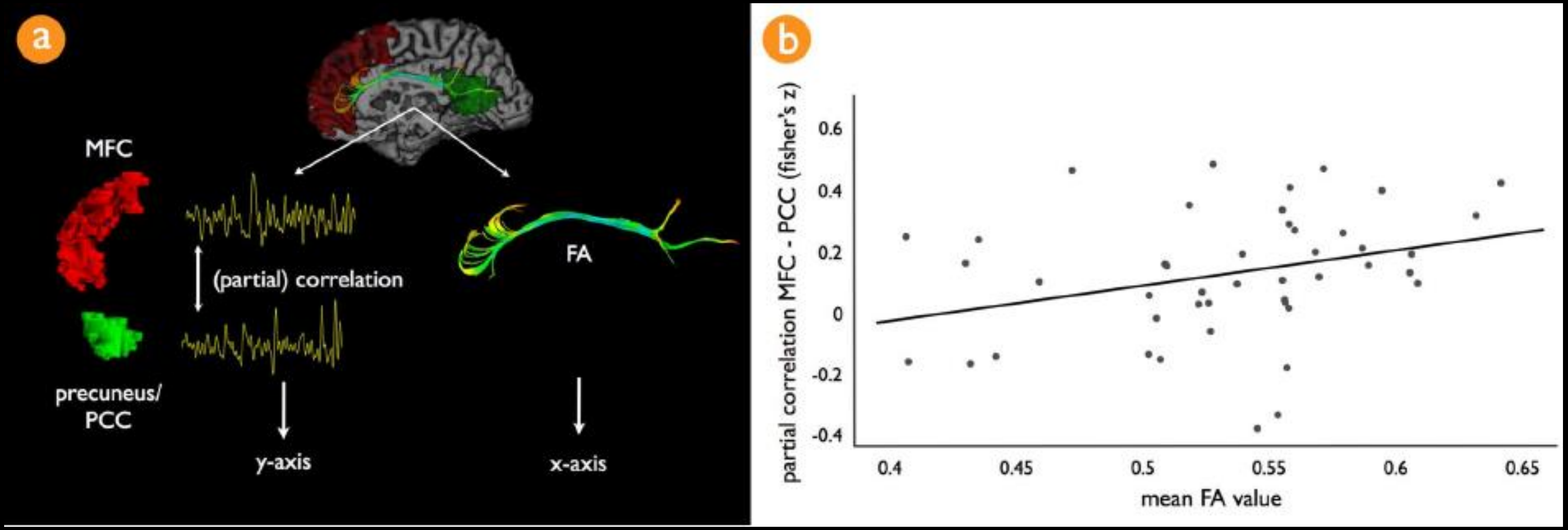
Connectivity of Default Mode Network

- Consistent functional maps across individuals of regional BOLD covariation
- Functional regions then used as seeds in diffusion tractography to map connectivity across regions



Van den Heuvel et al., Journal of Neuroscience, 2008;
See also Skudlarski et al., Neuroimage, 2008

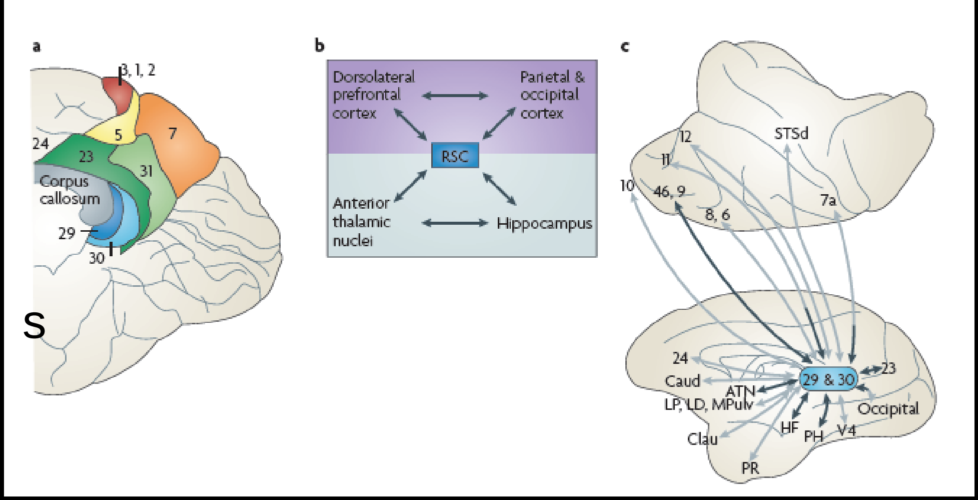
Integrity of the pathway is associated with correlation in activation across regions



Van den Heuvel et al., Journal of Neuroscience, 2008

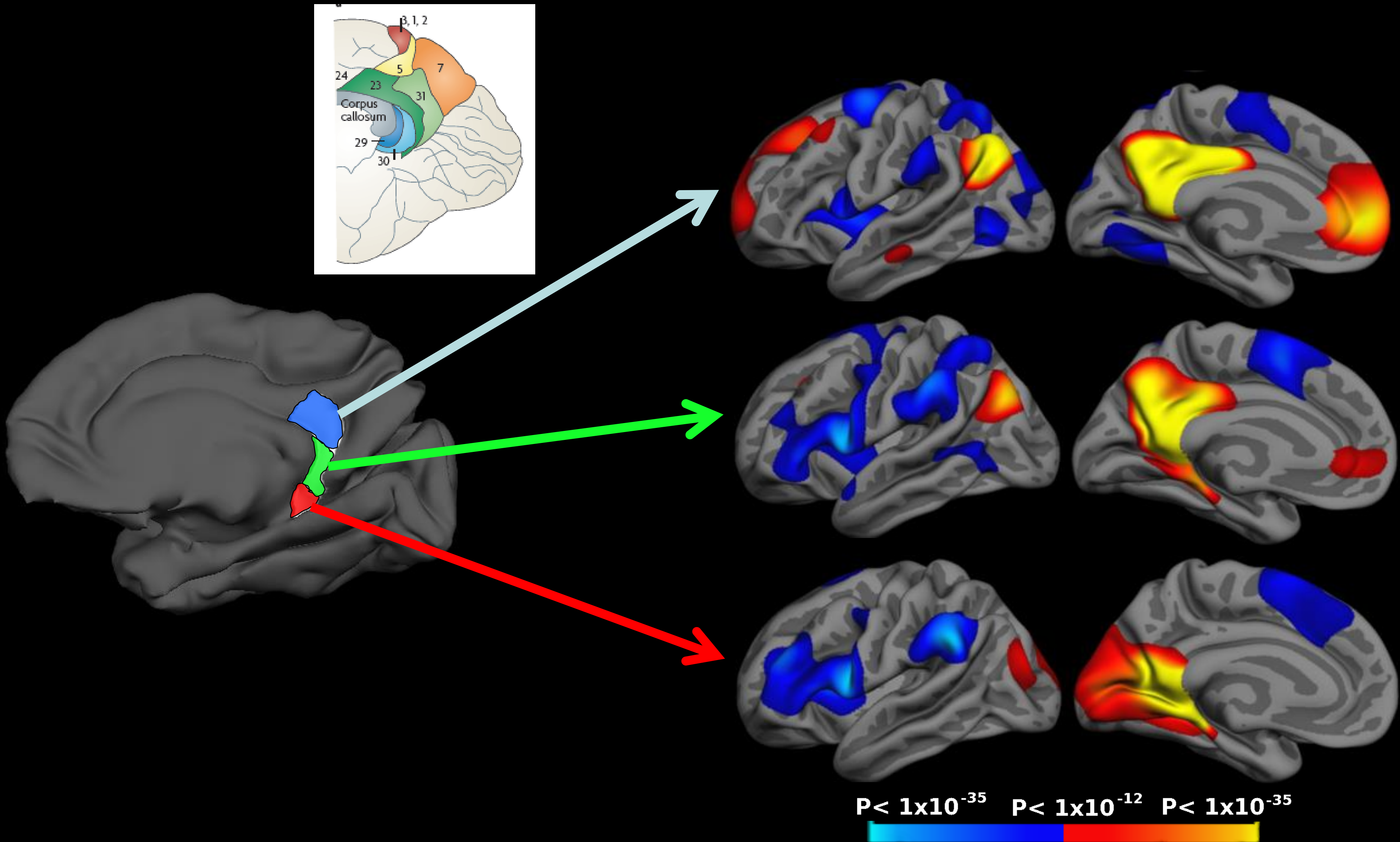
Retrosplenial Cortex/PCC is a Typical Seed Area for fcMRI

- Seeds are typically placed in atlas or Talairach space
- This is a highly variable structural region
- Seed placement can be inaccurate due to subejct variability/misregistration
- Seed placement can be inaccurate due to atrophy in clinical populations
- Anatomy must be carefully considered

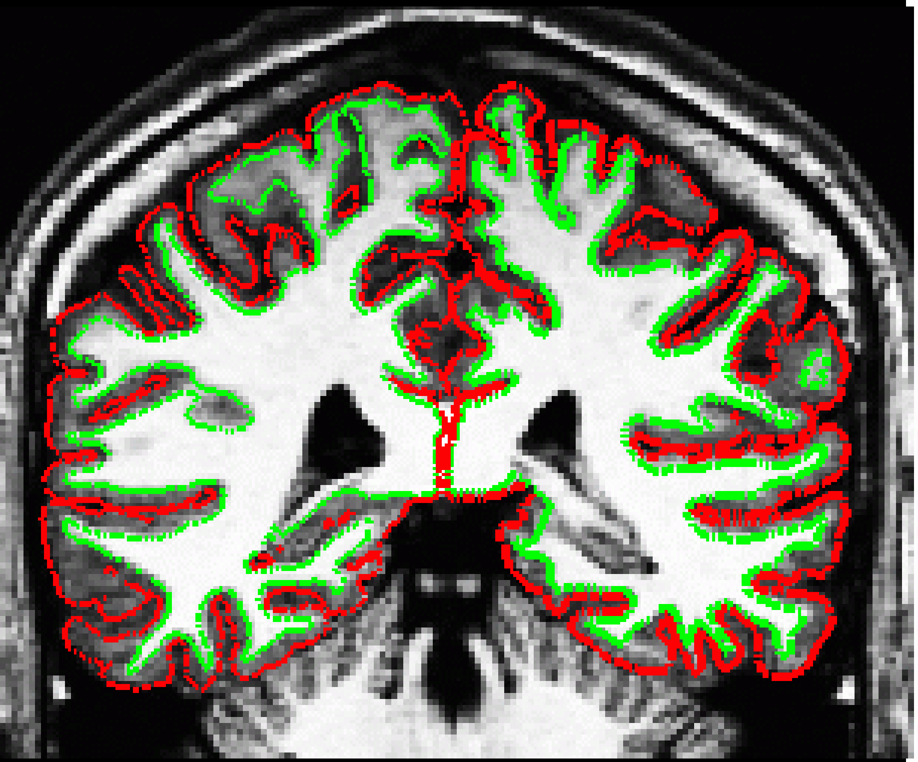


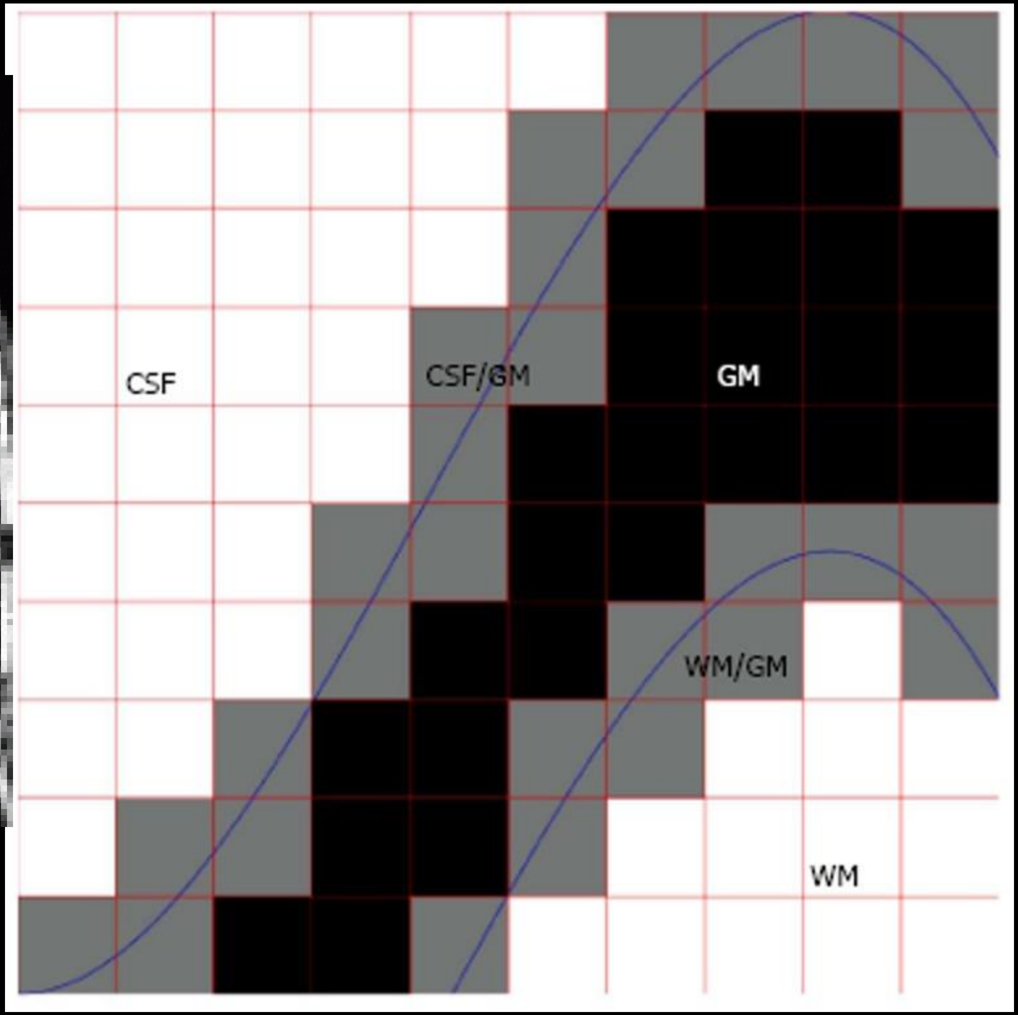
Vann et al., 2009

Mean Connectivity Maps



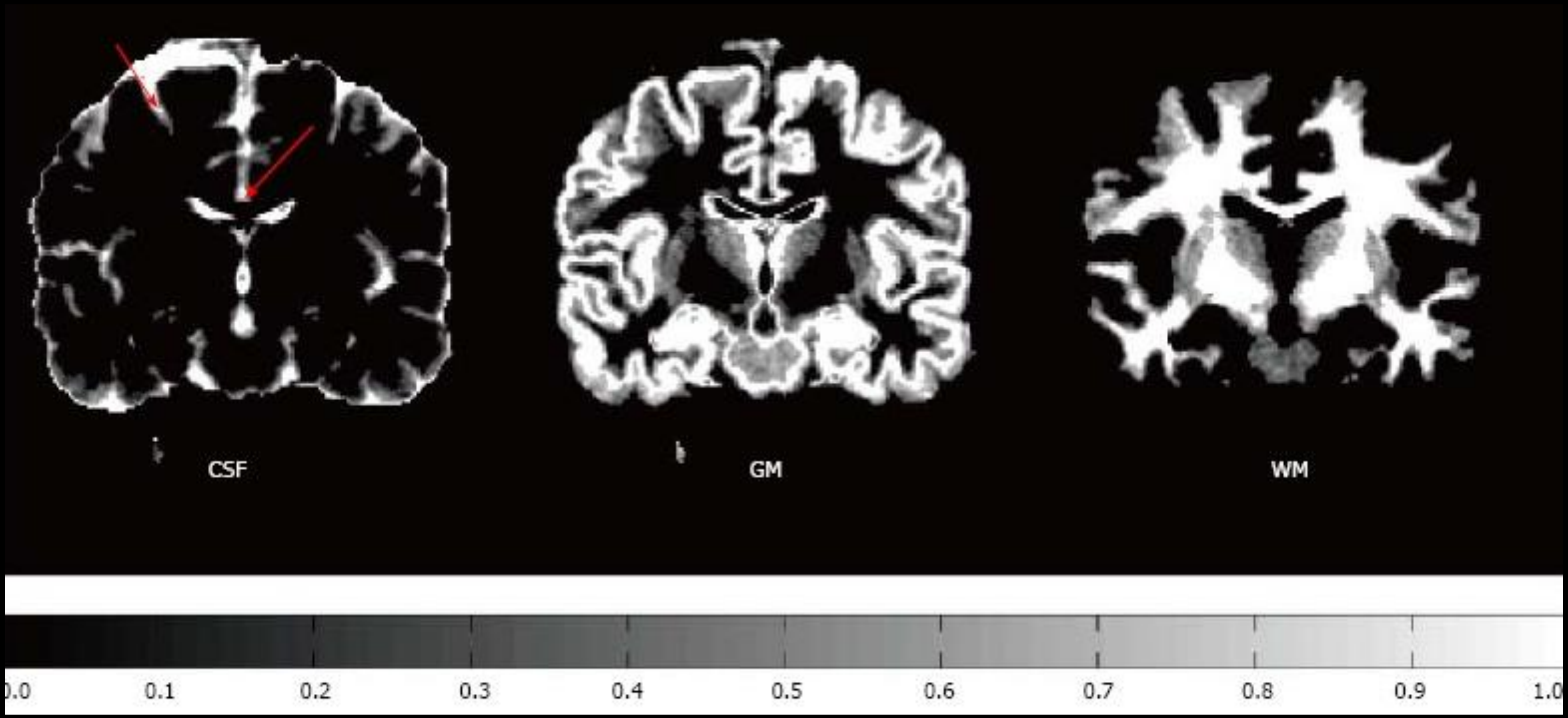
Partial Volume Contamination





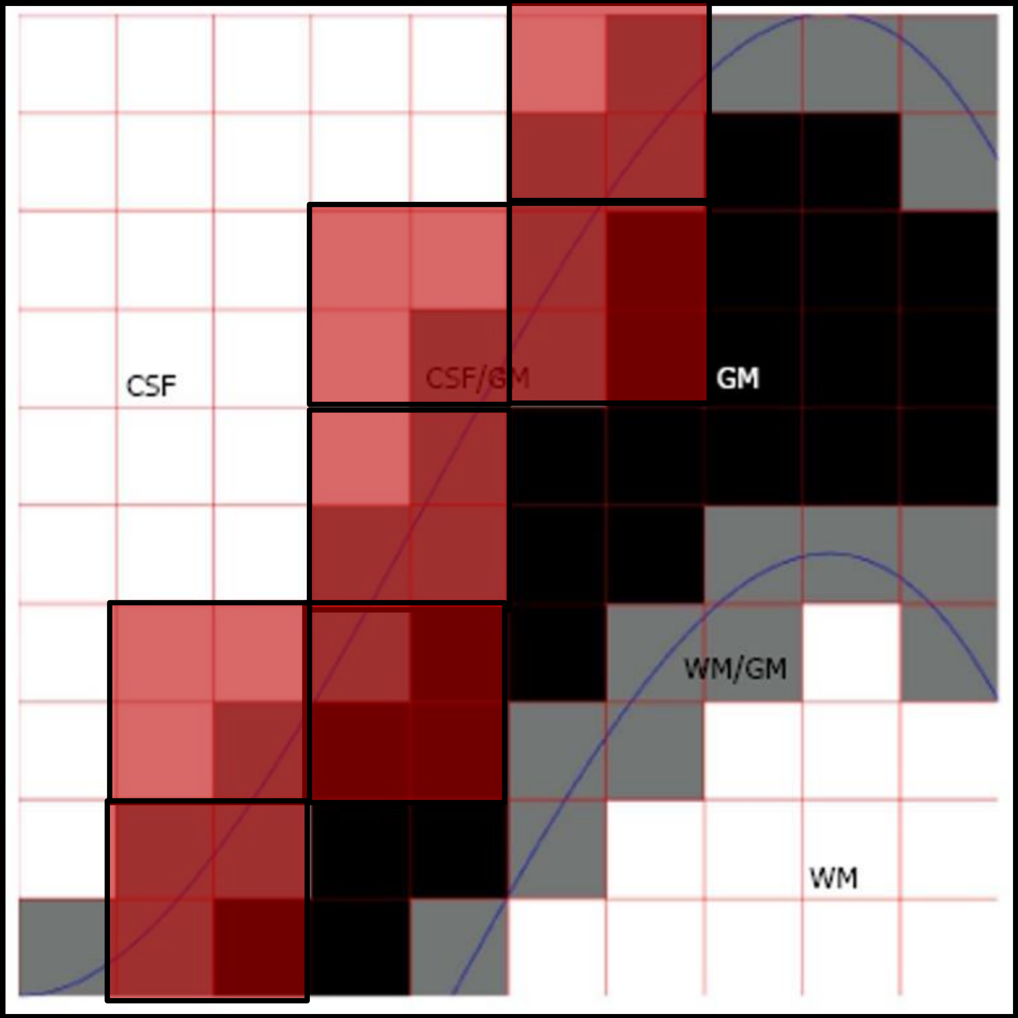
Tohka, 2014

Tissue class probability maps

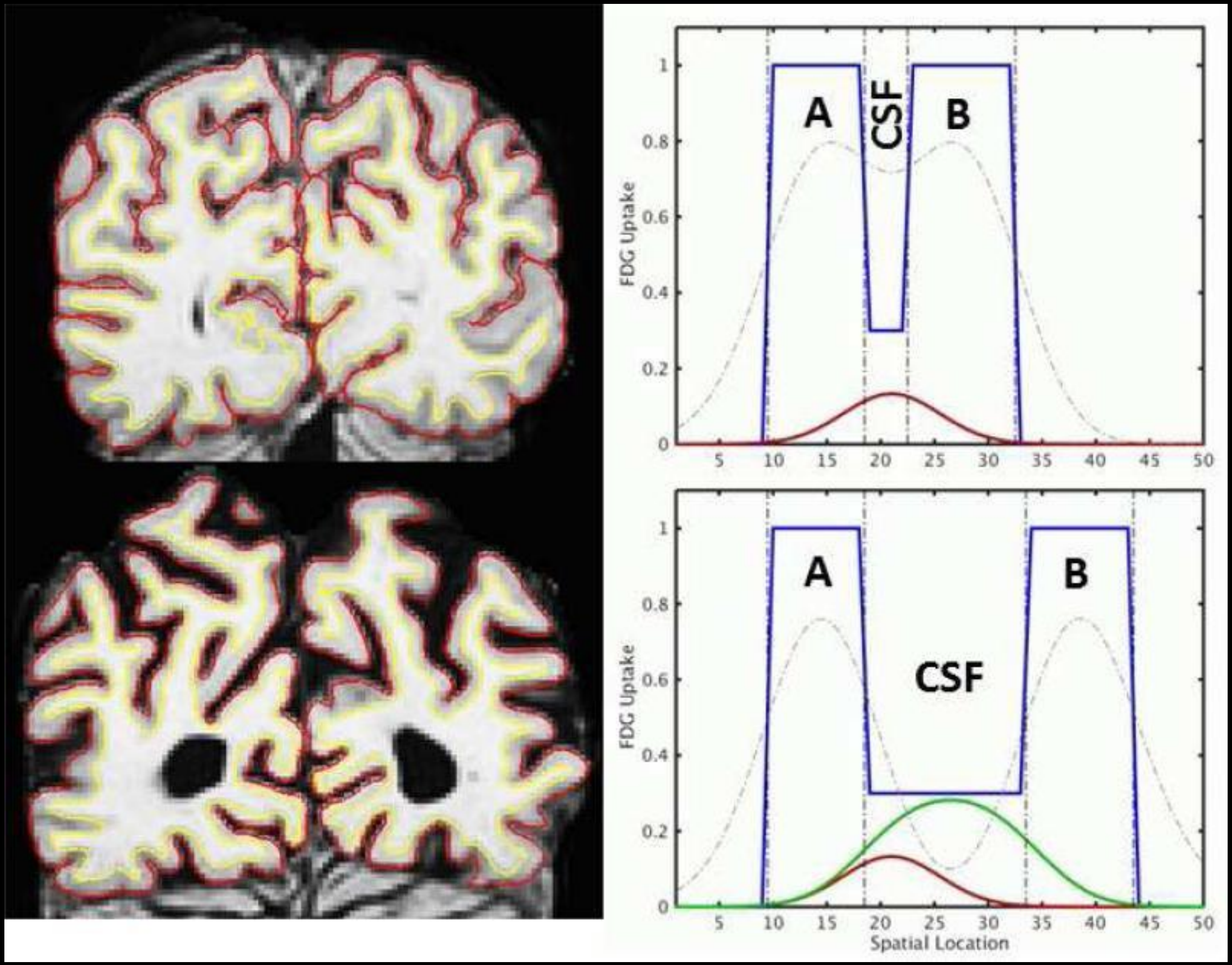


Tohka, 2014

Partial Volume in Functional Voxels



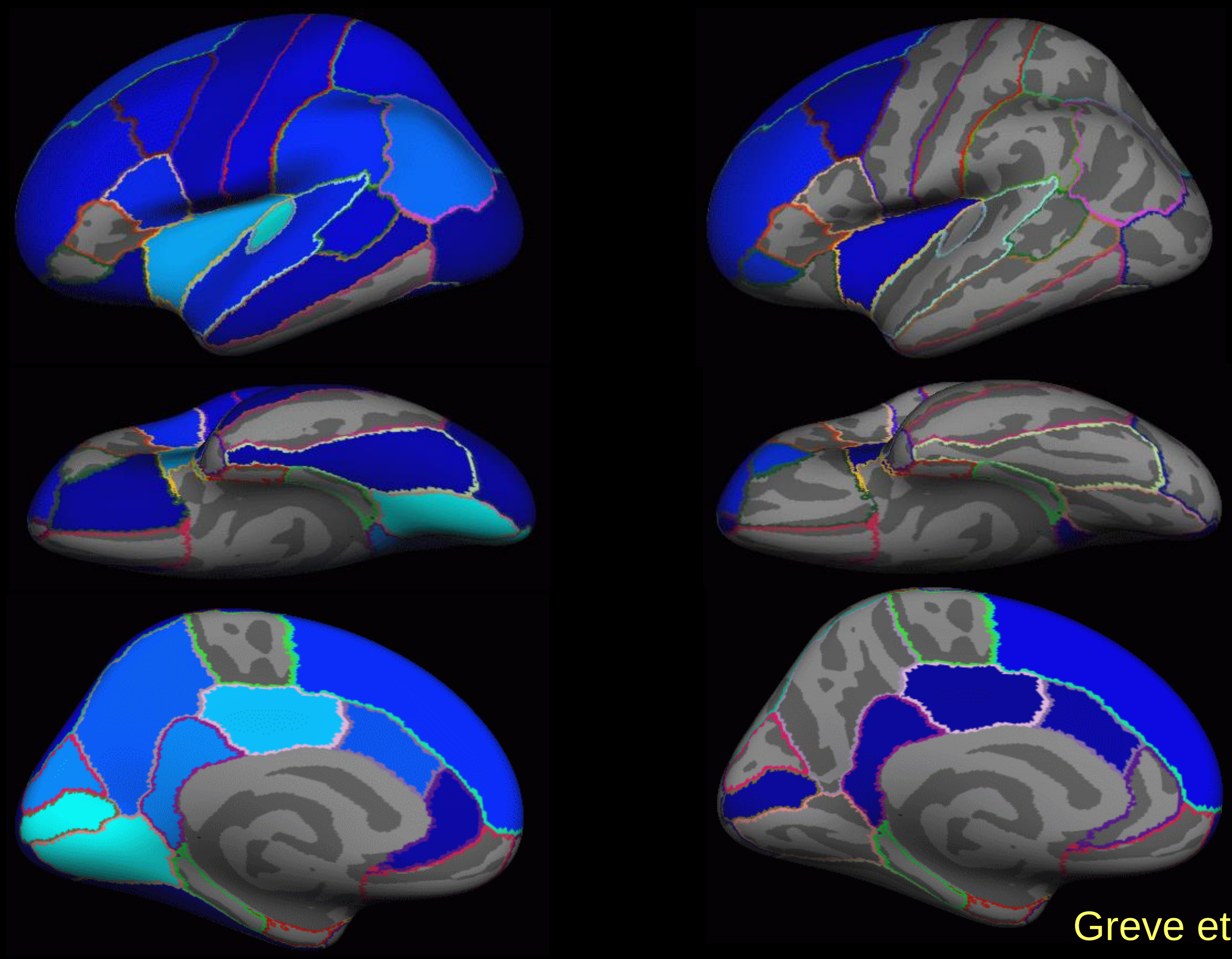
Differential Partial Volume Between Groups



Greve et al, 2016

Effects of Age on FDG

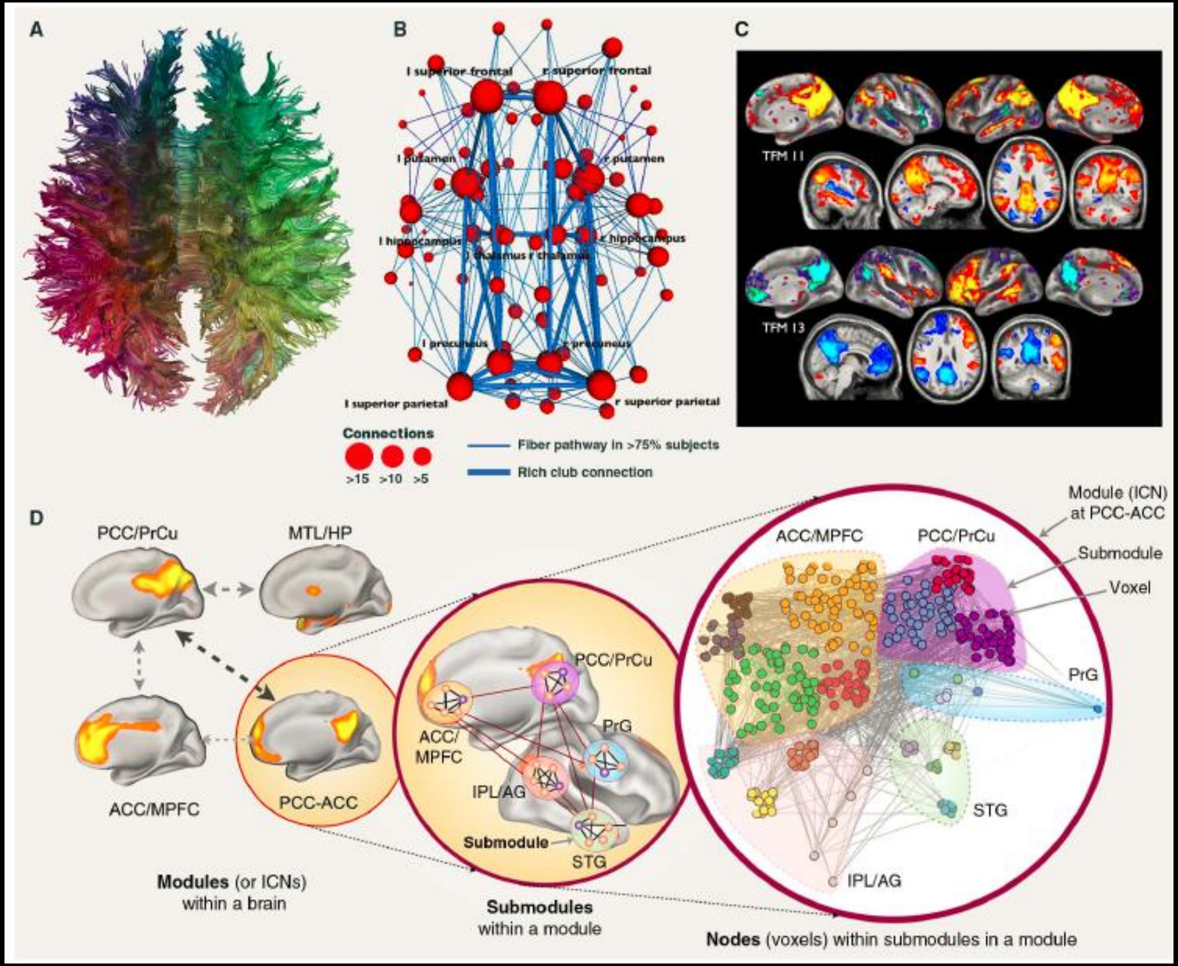
Without PVC With PVC



Greve et al, 2016

Convergence of Structural and Functional Brain Networks

- How does complex structure relate to complex function?
- Network theory and theoretical neuroscience can be used for modeling these properties



Salat:StructFunct:HST.583:2017

Park and Friston, 2013

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