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

A) Gyral
B) Cytoarchitectonic
C) Cytoarchitectonic
D) Myeloarchitecture
E) Connectivity
F) Functional

Modified from Devlin and Poldrack, *Neuroimage*, 2007

Stepanyants et al., 2002

Wedeen et al.
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
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

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  Folded  Semi-inflated  Inflated

High quality structural data

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
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

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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

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 subject 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

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Tohka, 2014
Tissue class probability maps

Tohka, 2014
Partial Volume in Functional Voxels

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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

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Park and Friston, 2013